Clinical trial results:
A 24-week, double-blind, randomised, parallel-group study evaluating the efficacy and safety of oral nintedanib co-administered with oral sildenafil, compared to treatment with nintedanib alone, in patients with idiopathic pulmonary fibrosis (IPF) and advanced lung function impairment.

Summary

EudraCT number	2015-002619-14
Trial protocol	DE ES BE GB FR IT
Global end of trial date	13 April 2018

Results information

Result version number	v1
This version publication date	20 April 2019
First version publication date	20 April 2019

Trial information

Trial identification

Sponsor protocol code	1199.36

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02802345
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	Scientific contact QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Scientific contact QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 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	04 June 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 December 2017
Global end of trial reached?	Yes
Global end of trial date	13 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess the efficacy and safety of concomitant treatment with nintedanib and sildenafil in patients with idiopathic pulmonary fibrosis (IPF) with advanced lung function impairment.

Protection of trial subjects:

Only patients that met all the study inclusion and none of the exclusion criteria were to be randomized in the study. All patients were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all patients was adhered to throughout the trial conduct.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 July 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 9
Country: Number of subjects enrolled	Belgium: 17
Country: Number of subjects enrolled	Canada: 23
Country: Number of subjects enrolled	France: 42
Country: Number of subjects enrolled	Germany: 39
Country: Number of subjects enrolled	India: 28
Country: Number of subjects enrolled	Italy: 44
Country: Number of subjects enrolled	Japan: 29
Country: Number of subjects enrolled	Korea, Republic of: 42
Country: Number of subjects enrolled	Mexico: 34
Country: Number of subjects enrolled	Spain: 25
Country: Number of subjects enrolled	United Kingdom: 22
Country: Number of subjects enrolled	United States: 52
Worldwide total number of subjects	406
EEA total number of subjects	189

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)	88
From 65 to 84 years	306
85 years and over	12

Subject disposition

Recruitment

Recruitment details:

Randomised, double-blind, parallel design comparison of nintedanib 150 milligram (mg) twice daily (bid) and sildenafil 20 mg three times a day (tid) to nintedanib 150 mg bid and placebo matching sildenafil tid administered orally over 24 weeks.

Pre-assignment

Screening details:

All patients were screened for eligibility to participate in the trial. Patients attended specialist sites to ensure that all patients met all inclusion/exclusion criteria. Patients were not to be randomized to trial if any one of the specific entry criteria were not met.

Period 1

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

Blinding implementation details:

It was a double-blind trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Nintedanib+placebo

Arm description:

Patients administered 150 milligram (mg) Nintedanib soft gelatine capsule orally twice daily (bid), with a possibility of dose reduction to 100 mg capsule bid along with placebo matching to Sildenafil for 24 weeks.

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

Dosage and administration details:

Patients administered 150 milligram (mg) Nintedanib soft gelatine capsule orally twice daily (bid), with a possibility of dose reduction to 100 mg capsule bid along with placebo matching to Sildenafil for 24 weeks.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Patients administered 150 milligram (mg) Nintedanib soft gelatine capsule orally twice daily (bid), with a possibility of dose reduction to 100 mg capsule bid along with placebo matching to Sildenafil for 24 weeks.

Arm title	Nintedanib+sildenafil

Arm description:

Patients administered 150 milligram (mg) Nintedanib soft gelatine capsule orally twice daily (bid), with a possibility of dose reduction to 100 mg capsule bid along with 20 mg thrice daily (tid) Sildenafil for 24 weeks.

Arm type	Experimental

Investigational medicinal product name	Sildenafil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Patients administered 150 milligram (mg) Nintedanib soft gelatine capsule orally twice daily (bid), with a possibility of dose reduction to 100 mg capsule bid along with 20 mg thrice daily (tid) Sildenafil for 24 weeks.

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

Dosage and administration details:

Patients administered 150 milligram (mg) Nintedanib soft gelatine capsule orally twice daily (bid), with a possibility of dose reduction to 100 mg capsule bid along with 20 mg thrice daily (tid) Sildenafil for 24 weeks.

Number of subjects in period 1[1]	Nintedanib+placebo	Nintedanib+sildenafil
Started	136	137
Completed	104	108
Not completed	32	29
Adverse event, serious fatal	8	6
Consent withdrawn by subject	3	3
Adverse event, non-fatal	20	14
Other than listed	1	5
Protocol deviation	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one dose of the trial medication.

Baseline characteristics

Reporting groups	
Reporting group title	Nintedanib+placebo
Reporting group description:	
Patients administered 150 milligram (mg) Nintedanib soft gelatine capsule orally twice daily (bid), with a possibility of dose reduction to 100 mg capsule bid along with placebo matching to Sildenafil for 24 weeks.	
Reporting group title	Nintedanib+sildenafil
Reporting group description:	
Patients administered 150 milligram (mg) Nintedanib soft gelatine capsule orally twice daily (bid), with a possibility of dose reduction to 100 mg capsule bid along with 20 mg thrice daily (tid) Sildenafil for 24 weeks.	

Reporting group values	Nintedanib+placebo	Nintedanib+sildenafil	Total
Number of subjects	136	137	273
Age categorical			
Units: Subjects			
Age Continuous			
Treated Set (TS): TS included all patients who were randomised to a treatment group and received at least one dose of randomised study medication.			
Units: years			
arithmetic mean	70.0	70.3	
standard deviation	± 7.9	± 8.6	-
Sex: Female, Male			
TS			
Units: Subjects			
Male	106	110	216
Female	30	27	57
Race (NIH/OMB)			
TS			
Units: Subjects			
American Indian or Alaska Native	2	3	5
Asian	39	30	69
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	95	103	198
More than one race	0	1	1
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
TS			
Units: Subjects			
Hispanic or Latino	15	23	38
Not Hispanic or Latino	121	114	235
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Nintedanib+placebo
Reporting group description:	
Patients administered 150 milligram (mg) Nintedanib soft gelatine capsule orally twice daily (bid), with a possibility of dose reduction to 100 mg capsule bid along with placebo matching to Sildenafil for 24 weeks.	
Reporting group title	Nintedanib+sildenafil
Reporting group description:	
Patients administered 150 milligram (mg) Nintedanib soft gelatine capsule orally twice daily (bid), with a possibility of dose reduction to 100 mg capsule bid along with 20 mg thrice daily (tid) Sildenafil for 24 weeks.	

Primary: Change from baseline in St George's Respiratory Questionnaire (SGRQ) total score at Week 12

End point title	Change from baseline in St George's Respiratory Questionnaire (SGRQ) total score at Week 12
End point description:	
The SGRQ is a 50-item questionnaire developed to measure health status (quality of life). Scores are calculated for three domains: Symptoms, Activity and Impacts (Psycho-social) as well as a total score. A minimum change in score of 4 units was established as clinically relevant after patient and clinician testing. Scores range from 0 to 100, with higher scores indicating more limitations. The mean and standard error presented are actually adjusted mean for change from baseline and its standard error. Treated Set (TS): TS included all patients who were randomised to a treatment group and received at least one dose of randomised study medication.	
End point type	Primary
End point timeframe:	
Baseline and week 12	

End point values	Nintedanib+placebo	Nintedanib+sildenafil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133[1]	132[2]		
Units: Unit on scale				
arithmetic mean (standard error)	-0.77 (± 1.009)	-1.28 (± 1.013)		

Notes:

[1] - TS

[2] - TS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Mixed Model for Repeated Measures (MMRM) included fixed effects for treatment, visit, presence of any echocardiographic signs, baseline SGRQ total score as covariate, treatment−by−visit and baseline SGRQ total score−by−visit interaction terms using an unstructured covariance matrix. No imputation was planned. Data collected after Visit 5 (planned 12 weeks after start of study treatment) were not used for analysis. Roger- Kenward approximation was used to estimate denominator degrees of freedom.	
Comparison groups	Nintedanib+sildenafil v Nintedanib+placebo

Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.7191
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	Adjusted mean difference
Point estimate	-0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.33
upper limit	2.3
Variability estimate	Standard error of the mean
Dispersion value	1.431

Notes:

[3] - Adjusted mean is based on all analyzed patients in model (not only patients with a measurement at baseline and 12 weeks). H0: There is no difference in mean change from baseline in SGRQ total score at Week 12 between treatment with nintedanib co-administered with sildenafil and treatment with nintedanib alone. Ha: There is a difference in mean change from baseline in SGRQ total score at Week 12 between treatment with nintedanib coadministered with sildenafil and treatment with nintedanib alone.

Secondary: Change from baseline in dyspnoea using the University of California San Diego Shortness of Breath Questionnaire (UCSD SOBQ) at Week 12

End point title	Change from baseline in dyspnoea using the University of California San Diego Shortness of Breath Questionnaire (UCSD SOBQ) at Week 12

End point description:

The UCSD SOBQ is a 24-item questionnaire developed to measure breathlessness on a scale between zero and five where 0 is not at all breathless and 5 is maximally breathless or too breathless to do the activity. The mean and standard error presented for descriptive statistics are actually adjusted mean for change from baseline and its standard error. TS.

End point type	Secondary

End point timeframe:

Baseline and week 12

End point values	Nintedanib+placebo	Nintedanib+sildenafil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122[4]	120[5]		
Units: Unit on scale				
arithmetic mean (standard error)	4.40 (± 1.529)	1.46 (± 1.575)		

Notes:

[4] - TS

[5] - TS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

MMRM included fixed effects for treatment, visit, presence of any echocardiographic signs, baseline UCSD SOBQ total score as covariate, treatment−by−visit and baseline UCSD SOBQ total score−by−visit interaction terms using an unstructured covariance matrix. No imputation was planned. Data collected after Visit 5 (planned 12 weeks after start of study treatment) were not used for analysis. Roger-

Kenward approximation was used to estimate denominator degrees of freedom.

Comparison groups	Nintedanib+placebo v Nintedanib+sildenafil
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.1823
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	Adjusted mean difference
Point estimate	-2.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.27
upper limit	1.39
Variability estimate	Standard error of the mean
Dispersion value	2.198

Notes:

[6] - Adjusted mean is based on all analyzed patients in the model (not only patients with a measurement at baseline and at 12 weeks).

Secondary: Change from baseline in SGRQ total score at Week 24

End point title	Change from baseline in SGRQ total score at Week 24

End point description:

The SGRQ is a 50-item questionnaire developed to measure health status (quality of life). Scores are calculated for three domains: Symptoms, Activity and Impacts (Psycho-social) as well as a total score. A minimum change in score of 4 units was established as clinically relevant after patient and clinician testing. The mean and standard error presented for descriptive statistics are actually adjusted mean for change from baseline and its standard error. TS

End point type	Secondary

End point timeframe:

Baseline and week 24

End point values	Nintedanib+placebo	Nintedanib+sildenafil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133[7]	132[8]		
Units: Unit on scale				
arithmetic mean (standard error)	2.42 (± 1.158)	0.23 (± 1.148)		

Notes:

[7] - TS

[8] - TS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Mixed Model for Repeated Measures (MMRM) included fixed effects for treatment, visit, presence of any echocardiographic signs, baseline SGRQ total score as covariate, treatment−by−visit and baseline SGRQ total score−by−visit interaction terms using an unstructured covariance matrix. No imputation was planned. Roger- Kenward approximation was used to estimate denominator degrees of freedom.

Comparison groups	Nintedanib+placebo v Nintedanib+sildenafil

Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.1809
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	Adjusted mean difference
Point estimate	-2.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.4
upper limit	1.02
Variability estimate	Standard error of the mean
Dispersion value	1.631

Notes:

[9] - Adjusted mean is based on all analyzed patients in the model (not only patients with a measurement at baseline and at 12 weeks).

Secondary: Change from baseline in dyspnoea using UCSD SOBQ at Week 24

End point title	Change from baseline in dyspnoea using UCSD SOBQ at Week 24

End point description:

The UCSD SOBQ is a 24-item questionnaire developed to to measure breathlessness on a scale between zero and five where 0 is not at all breathless and 5 is maximally breathless or too breathless to do the activity. The mean and standard error presented for descriptive statistics are actually adjusted mean for change from baseline and its standard error. TS

End point type	Secondary

End point timeframe:

Baseline and week 24

End point values	Nintedanib+placebo	Nintedanib+sildenafil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124[10]	123[11]		
Units: Unit on scale				
arithmetic mean (standard error)	6.85 (± 1.791)	4.44 (± 1.779)		

Notes:

[10] - TS

[11] - TS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Mixed Model for Repeated Measures (MMRM) included fixed effects for treatment, visit, presence of any echocardiographic signs, baseline UCSD SOBQ total score as covariate, treatment−by−visit and baseline UCSD SOBQ total score−by−visit interaction terms using an unstructured covariance matrix. No imputation was planned. The Roger- Kenward approximation was used to estimate denominator degrees of freedom.

Comparison groups	Nintedanib+placebo v Nintedanib+sildenafil

Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.3421
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	Adjusted mean difference
Point estimate	-2.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.39
upper limit	2.58
Variability estimate	Standard error of the mean
Dispersion value	2.529

Notes:

[12] - Adjusted mean is based on all analyzed patients in the model (not only patients with a measurement at baseline and at 12 weeks).

Secondary: Percentage of patients with on-treatment serious adverse events (SAE) from baseline to Week 24

End point title	Percentage of patients with on-treatment serious adverse events (SAE) from baseline to Week 24

End point description:

Percentage of patients with on-treatment serious adverse events (SAE) from baseline to Week 24 is presented. TS

End point type	Secondary

End point timeframe:

Baseline and week 24

End point values	Nintedanib+placebo	Nintedanib+sildenafil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136[13]	137[14]		
Units: Percentage of participants (%)				
number (not applicable)	32.4	27.0		

Notes:

[13] - TS

[14] - TS

Statistical analyses

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Risk difference, Comparison of treatment groups is calculated by Cochran−Mantel−Haenszel test adjusting for the categorical covariate presence of any echocardiographic signs indicative of right heart dysfunction (yes/no), adjusted Mantel−Haenszel type risk ratios and risk differences with 95% confidence are presented.

Comparison groups	Nintedanib+placebo v Nintedanib+sildenafil

Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.334
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference (%)
Point estimate	-5.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.25
upper limit	5.52

Notes:

[15] - Within strata confidence limits are calculated according to Wald. Percentage difference = (% of Nintedanib+sildenafil) - (% of Nintedanib+placebo).

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Relative risk, Comparison of treatment groups is calculated by Cochran−Mantel−Haenszel test adjusting for the categorical covariate presence of any echocardiographic signs indicative of right heart dysfunction (yes/no), adjusted Mantel−Haenszel type risk ratios and risk differences with 95% confidence are presented.

Comparison groups	Nintedanib+placebo v Nintedanib+sildenafil
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority[16]
Parameter estimate	Percentage ratio (%)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	1.2

Notes:

[16] - Within strata confidence limits are calculated according to Wald. Percentage ratio = (% of Nintedanib+sildenafil) / (% of Nintedanib+placebo).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first drug administration to 28 days after the last trial medication administration, 227 days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Nintedanib+sildenafil

Reporting group description:

Patients administered 150 milligram (mg) soft gelatine capsule orally twice daily (bid), with a possibility of dose reduction to 100 mg capsule bid along with 20 mg thrice daily (tid) Sildenafil for 24 weeks.

Reporting group title	Nintedanib+placebo

Reporting group description:

Patients administered 150 milligram (mg) soft gelatine capsule orally twice daily (bid), with a possibility of dose reduction to 100 mg capsule bid along with placebo matching to Sildenafil for 24 weeks.

Serious adverse events	Nintedanib+sildenafil	Nintedanib+placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	37 / 137 (27.01%)	44 / 136 (32.35%)	
number of deaths (all causes)	12	12	
number of deaths resulting from adverse events	1	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung adenocarcinoma			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm malignant			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine carcinoma of the skin			
subjects affected / exposed	1 / 137 (0.73%)	0 / 136 (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 / 137 (0.73%)	0 / 136 (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 / 137 (0.73%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 137 (0.73%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 137 (0.73%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Oedema			
subjects affected / exposed	1 / 137 (0.73%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sudden death			
subjects affected / exposed	1 / 137 (0.73%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	1 / 1	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 137 (0.73%)	2 / 136 (1.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Asthma			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	5 / 137 (3.65%)	2 / 136 (1.47%)	
occurrences causally related to treatment / all	1 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Idiopathic pulmonary fibrosis			
subjects affected / exposed	8 / 137 (5.84%)	9 / 136 (6.62%)	
occurrences causally related to treatment / all	2 / 9	0 / 10	
deaths causally related to treatment / all	1 / 3	0 / 3	
Lung disorder			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumothorax			
subjects affected / exposed	2 / 137 (1.46%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax spontaneous			
subjects affected / exposed	1 / 137 (0.73%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary congestion			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 137 (0.00%)	2 / 136 (1.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	1 / 137 (0.73%)	4 / 136 (2.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 137 (1.46%)	3 / 136 (2.21%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 137 (0.73%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 137 (0.73%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Eosinophil count increased			
subjects affected / exposed	1 / 137 (0.73%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eosinophil percentage increased			
subjects affected / exposed	1 / 137 (0.73%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Pelvic fracture			
subjects affected / exposed	1 / 137 (0.73%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 137 (0.73%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 137 (0.73%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic intracranial haemorrhage			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 137 (0.73%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac arrest			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	1 / 137 (0.73%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
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 / 137 (0.73%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocarditis			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	0 / 137 (0.00%)	3 / 136 (2.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemianopia homonymous			

subjects affected / exposed	1 / 137 (0.73%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 137 (0.73%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 137 (0.73%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	1 / 137 (0.73%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 137 (0.73%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastritis			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
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	1 / 137 (0.73%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pancreatitis acute			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
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 / 137 (0.00%)	1 / 136 (0.74%)	
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	0 / 137 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	1 / 137 (0.73%)	0 / 136 (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 / 137 (0.73%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver injury			
subjects affected / exposed	2 / 137 (1.46%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 137 (0.73%)	0 / 136 (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			
Bronchitis			
subjects affected / exposed	1 / 137 (0.73%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cellulitis			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 137 (0.00%)	2 / 136 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
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 / 137 (3.65%)	8 / 136 (5.88%)	
occurrences causally related to treatment / all	0 / 5	1 / 8	
deaths causally related to treatment / all	0 / 1	1 / 3	
Respiratory tract infection			
subjects affected / exposed	0 / 137 (0.00%)	2 / 136 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
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	2 / 137 (1.46%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 2	1 / 1	
Urinary tract infection			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 137 (0.73%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	2 / 137 (1.46%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			
subjects affected / exposed	0 / 137 (0.00%)	1 / 136 (0.74%)	
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	Nintedanib+sildenafil	Nintedanib+placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	118 / 137 (86.13%)	113 / 136 (83.09%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	8 / 137 (5.84%)	8 / 136 (5.88%)	
occurrences (all)	9	9	
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 137 (3.65%)	7 / 136 (5.15%)	
occurrences (all)	6	10	
C-reactive protein increased			
subjects affected / exposed	6 / 137 (4.38%)	7 / 136 (5.15%)	
occurrences (all)	6	9	
Gamma-glutamyltransferase increased			
subjects affected / exposed	7 / 137 (5.11%)	7 / 136 (5.15%)	
occurrences (all)	7	9	
Weight decreased			
subjects affected / exposed	7 / 137 (5.11%)	12 / 136 (8.82%)	
occurrences (all)	7	13	
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 137 (4.38%)	8 / 136 (5.88%)	
occurrences (all)	6	8	
Headache			
subjects affected / exposed	21 / 137 (15.33%)	10 / 136 (7.35%)	
occurrences (all)	24	12	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 137 (4.38%)	7 / 136 (5.15%)	
occurrences (all)	6	8	
Fatigue			
subjects affected / exposed	7 / 137 (5.11%)	6 / 136 (4.41%)	
occurrences (all)	7	6	
Oedema peripheral			

subjects affected / exposed	7 / 137 (5.11%)	6 / 136 (4.41%)	
occurrences (all)	8	6	
Pyrexia			
subjects affected / exposed	6 / 137 (4.38%)	9 / 136 (6.62%)	
occurrences (all)	9	10	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 137 (2.92%)	9 / 136 (6.62%)	
occurrences (all)	4	10	
Abdominal pain upper			
subjects affected / exposed	6 / 137 (4.38%)	7 / 136 (5.15%)	
occurrences (all)	8	8	
Constipation			
subjects affected / exposed	3 / 137 (2.19%)	8 / 136 (5.88%)	
occurrences (all)	3	10	
Diarrhoea			
subjects affected / exposed	79 / 137 (57.66%)	66 / 136 (48.53%)	
occurrences (all)	152	110	
Dyspepsia			
subjects affected / exposed	9 / 137 (6.57%)	4 / 136 (2.94%)	
occurrences (all)	9	4	
Gastrooesophageal reflux disease			
subjects affected / exposed	7 / 137 (5.11%)	5 / 136 (3.68%)	
occurrences (all)	7	9	
Nausea			
subjects affected / exposed	22 / 137 (16.06%)	14 / 136 (10.29%)	
occurrences (all)	30	15	
Vomiting			
subjects affected / exposed	19 / 137 (13.87%)	9 / 136 (6.62%)	
occurrences (all)	32	12	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	20 / 137 (14.60%)	13 / 136 (9.56%)	
occurrences (all)	24	13	
Dyspnoea			

subjects affected / exposed	13 / 137 (9.49%)	11 / 136 (8.09%)	
occurrences (all)	14	11	
Epistaxis			
subjects affected / exposed	11 / 137 (8.03%)	6 / 136 (4.41%)	
occurrences (all)	15	6	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	7 / 137 (5.11%)	2 / 136 (1.47%)	
occurrences (all)	8	2	
Myalgia			
subjects affected / exposed	7 / 137 (5.11%)	3 / 136 (2.21%)	
occurrences (all)	8	3	
Infections and infestations			
Bronchitis			
subjects affected / exposed	12 / 137 (8.76%)	4 / 136 (2.94%)	
occurrences (all)	13	5	
Influenza			
subjects affected / exposed	4 / 137 (2.92%)	7 / 136 (5.15%)	
occurrences (all)	4	7	
Nasopharyngitis			
subjects affected / exposed	9 / 137 (6.57%)	8 / 136 (5.88%)	
occurrences (all)	9	8	
Respiratory tract infection			
subjects affected / exposed	8 / 137 (5.84%)	4 / 136 (2.94%)	
occurrences (all)	9	4	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	19 / 137 (13.87%)	23 / 136 (16.91%)	
occurrences (all)	20	24	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 March 2016	The text describing potential risks of sildenafil treatment was updated. The number of participating sites and the number of patients per site were modified based on a site feasibility assessment. In the exclusion criteria 6, 'partial thromboplastin time' was replaced by 'activated thromboplastin time'. Exclusion criteria 34, concerning patients with chronic liver disease, was added. Measurements of nintedanib metabolites were removed from the planned pharmacokinetic (PK) assessments. The amount of blood needed for biomarker assessments was increased.
18 August 2016	A trade name (INSTAGETM) was assigned to the trial. Pancreatitis and thrombocytopenia were added as risks of nintedanib treatment. major cardiovascular events (MACE) was added to the list of events to be adjudicated. The inclusion and exclusion criteria were modified to allow retesting, within a defined time frame, for the parameters mentioned in the inclusion criterion 5 and the exclusion criteria 4, 9 and 15, in case values at Visit 1 were abnormal. Footnote 1 of the inclusion and exclusion criteria was modified to also allow retesting of blood pressure and lung function tests, in addition to the laboratory parameters. In the exclusion criterion 15, 'systolic blood pressure (SBP) >180 millimeter of mercury (mmHg); diastolic blood pressure (DBP) >100 mmHg' was changed to (SBP >180 mmHg or DBP >100 mmHg). In the exclusion criterion 23 'treatment for pulmonary hypertension' was changed to 'treatment'. Clarifications were added regarding restrictions in concomitant medication use. The method of measuring oxygen saturation was corrected. The definition of acute IPF exacerbation was modified according to the new definition by an international working group. It was clarified that biobanking is an optional procedure, requiring local approval. Details of analyses of further endpoints were added in the statistical methods.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported