Clinical trial results:
The main objective was to assess the safety and tolerability of the combined treatment with nintedanib and pirfenidone in patients with idiopathic pulmonary fibrosis (IPF).

Summary

EudraCT number	2015-000640-42
Trial protocol	FR NL DE IT
Global end of trial date	31 January 2017

Results information

Result version number	v1 (current)
This version publication date	27 December 2017
First version publication date	27 December 2017

Trial information

Trial identification

Sponsor protocol code	1199.222

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com
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	21 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 January 2017
Global end of trial reached?	Yes
Global end of trial date	31 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective was to assess the safety and tolerability of the combined treatment with nintedanib and pirfenidone in patients with idiopathic pulmonary fibrosis (IPF).

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were 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	03 November 2015
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	Canada: 17
Country: Number of subjects enrolled	France: 48
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Netherlands: 28
Country: Number of subjects enrolled	United States: 25
Worldwide total number of subjects	136
EEA total number of subjects	94

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)	29
From 65 to 84 years	107
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

4 weeks of run-in treatment on 150 mg nintedanib twice daily, followed by 12 weeks of randomised treatment with either Nintedanib alone or with the combined treatment of Nintedanib and Pirfenidone.In this study,105 subjects were enrolled & randomized.

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in trial. Subjects attended specialist sites to ensure that they (the subjects) met all implemented inclusion/exclusion criteria. Subjects were not to be randomised to trial drug if any of the specific entry criteria was violated.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This is a Randomised, open-label and parallel-group trial

Arms

Are arms mutually exclusive?	Yes
Arm title	Nintedanib

Arm description:

Patients were orally administered Nintedanib 2x150 mg soft gelatine capsule daily (1 capsule of 150 mg twice daily) with the possibility to reduce to 2x100 mg daily (1 capsule of 100 mg twice daily). One subject randomised to Nintedanib was not treated. Although actual number of subjects started is 52, 51 were reported to ensure consistent reporting with baseline characteristics that includes only treated subjects.

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:

Patients were orally administered Nintedanib 2x150 mg soft gelatine capsule daily (1 capsule of 150 mg twice daily) with
the possibility to reduce to 2x100 mg daily (1 capsule of 100 mg twice daily).

Arm title	Nintedanib + Pirfenidone

Arm description:

Patients were orally administered Nintedanib 2x150 mg soft gelatine capsule daily (1 capsule of 150 mg twice daily) with the possibility to reduce to 2x100 mg daily (1 capsule of 100 mg twice daily) in combination with pirfenidone. The pirfenidone dose was titrated up to 2403 mg daily according to the following schedule: 801 mg (1 capsule of 267 mg 3 times daily) from Visit 3 until the phone call visit ; 1602 mg daily (2 capsules of each 267 mg 3 times daily) after the phone call visit; 2403 mg daily (3 capsules of each 267 mg 3 times daily) starting at Visit 4 after the PK sampling had been performed.The dose of pirfenidone could have been reduced to 1 or 2 capsule(s) 3 times daily.

Arm type	Active comparator
Investigational medicinal product name	Pirfenidone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Patients were administered Pirfenidone in combination with Nintedanib. The pirfenidone dose was titrated up to 2403 mg daily according to the following schedule: 801 mg (1 capsule of 267 mg 3 times daily) from Visit 3 until the phone call visit ; 1602 mg daily (2 capsules of each 267 mg 3 times daily) after the phone call visit; 2403 mg daily (3 capsules of each 267 mg 3 times daily) starting at Visit 4 after the PK sampling had been performed.The dose of pirfenidone could have been reduced to 1 or 2 capsule(s) 3 times daily.

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 were administered Nintedanib 2x150 mg soft gelatine capsule daily (1 capsule of 150 mg twice daily) with the
possibility to reduce to 2x100 mg daily (1 capsule of 100 mg twice daily) in combination with Pirfenidone dose.

Number of subjects in period 1[1]	Nintedanib	Nintedanib + Pirfenidone
Started	51	53
Completed	48	51
Not completed	3	2
Adverse event, non-fatal	2	2
Other than stated	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 the patients who were randomised after successfully completing the screening period and received at least one of the trial medication.

Baseline characteristics

Reporting groups	
Reporting group title	Nintedanib
Reporting group description:	
Patients were orally administered Nintedanib 2x150 mg soft gelatine capsule daily (1 capsule of 150 mg twice daily) with the possibility to reduce to 2x100 mg daily (1 capsule of 100 mg twice daily). One subject randomised to Nintedanib was not treated. Although actual number of subjects started is 52, 51 were reported to ensure consistent reporting with baseline characteristics that includes only treated subjects.	
Reporting group title	Nintedanib + Pirfenidone
Reporting group description:	
Patients were orally administered Nintedanib 2x150 mg soft gelatine capsule daily (1 capsule of 150 mg twice daily) with the possibility to reduce to 2x100 mg daily (1 capsule of 100 mg twice daily) in combination with pirfenidone. The pirfenidone dose was titrated up to 2403 mg daily according to the following schedule: 801 mg (1 capsule of 267 mg 3 times daily) from Visit 3 until the phone call visit ; 1602 mg daily (2 capsules of each 267 mg 3 times daily) after the phone call visit; 2403 mg daily (3 capsules of each 267 mg 3 times daily) starting at Visit 4 after the PK sampling had been performed.The dose of pirfenidone could have been reduced to 1 or 2 capsule(s) 3 times daily.	

Reporting group values	Nintedanib	Nintedanib + Pirfenidone	Total
Number of subjects	51	53	104
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age Continuous			
Treated Set : The treated set (104 patients) consisted of all randomised patients who were dispensed study medication and were documented to have taken at least 1 dose of randomised investigational treatment.			
Units: years			
arithmetic mean	68.9	68.9	
standard deviation	± 6.8	± 6.6	-
Gender, Male/Female Units: Subjects			
Female	7	11	18
Male	44	42	86

End points

End points reporting groups

Reporting group title	Nintedanib

Reporting group description:

Patients were orally administered Nintedanib 2x150 mg soft gelatine capsule daily (1 capsule of 150 mg twice daily) with the possibility to reduce to 2x100 mg daily (1 capsule of 100 mg twice daily). One subject randomised to Nintedanib was not treated. Although actual number of subjects started is 52, 51 were reported to ensure consistent reporting with baseline characteristics that includes only treated subjects.

Reporting group title	Nintedanib + Pirfenidone

Reporting group description:

Patients were orally administered Nintedanib 2x150 mg soft gelatine capsule daily (1 capsule of 150 mg twice daily) with the possibility to reduce to 2x100 mg daily (1 capsule of 100 mg twice daily) in combination with pirfenidone. The pirfenidone dose was titrated up to 2403 mg daily according to the following schedule: 801 mg (1 capsule of 267 mg 3 times daily) from Visit 3 until the phone call visit ; 1602 mg daily (2 capsules of each 267 mg 3 times daily) after the phone call visit; 2403 mg daily (3 capsules of each 267 mg 3 times daily) starting at Visit 4 after the PK sampling had been performed.The dose of pirfenidone could have been reduced to 1 or 2 capsule(s) 3 times daily.

Primary: Percentage of patients with on-treatment gastrointestinal (GI) AEs (SOC GI disorders) from baseline to week 12

End point title	Percentage of patients with on-treatment gastrointestinal (GI) AEs (SOC GI disorders) from baseline to week 12[1]

End point description:

Percentage of patients with on-treatment gastrointestinal (GI) Adverse events (AEs) (SOC GI disorders) from baseline to week 12. On-treatment AEs were defined as AEs with an onset from the first dose of randomised treatment up to the last dose of randomised treatment (inclusive).

End point type	Primary

End point timeframe:

Baseline and week 12

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This endpoint was evaluated only descriptively. Thus, no statistical hypothiesis test were tested.

End point values	Nintedanib	Nintedanib + Pirfenidone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51[2]	53[3]		
Units: percentage of participants				
number (not applicable)	52.9	69.8		

Notes:

[2] - Treated set

[3] - Treated set

Statistical analyses

No statistical analyses for this end point

Secondary: Predose plasma concentrations at steady state (Cpre,ss) of nintedanib at baseline, weeks 2 and 4

End point title	Predose plasma concentrations at steady state (Cpre,ss) of

	nintedanib at baseline, weeks 2 and 4

End point description:

Predose plasma concentrations at steady state (Cpre,ss) of nintedanib at baseline (Visit 3), Week 2 (Visit 4) and Week 4 (Visit 5).

Pharmacokinetic Set (PKS): This analysis set included all patients who had been treated with study medication and who provided evaluable data for at least 1 PK endpoint without important protocol violations relevant to the evaluation of PK.

End point type	Secondary

End point timeframe:

baseline, prior to intake of study medication on week 2 and week 4

End point values	Nintedanib	Nintedanib + Pirfenidone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51[4]	53[5]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
baseline (# of participants analysed= 46; 46)	7.08 (± 56.0)	7.65 (± 72.5)		
Week 2 (# of participants analysed= 41; 35)	7.25 (± 52.7)	8.17 (± 69.8)		
Week 4 (# of participants analysed= 44; 30)	5.92 (± 73.5)	7.13 (± 63.9)		

Notes:

[4] - PKS

[5] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: Predose plasma concentrations at steady state (Cpre,ss) of Pirfenidone

End point title	Predose plasma concentrations at steady state (Cpre,ss) of Pirfenidone[6]

End point description:

Predose plasma concentrations at steady state (Cpre,ss) of Pirfenidone at Week 2 (Visit 4) and Week 4 (Visit 5)

End point type	Secondary

End point timeframe:

Prior to intake of study medication on week 2 and week 4

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Nintedanib + Pirfenidone			
Subject group type	Reporting group			
Number of subjects analysed	53[7]			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Week 2 (# of participants analysed= 32)	1120 (± 122)			
Week 4 (# of participants analysed= 28)	1220 (± 90.7)			

Notes:

[7] - PKS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose administration of the study medication to 28 days after last drug administration; up to 124 days

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Nintedanib + Pirfenidone

Reporting group description:

Patients were orally administered Nintedanib 2x150 mg soft gelatine capsule daily (1 capsule of 150 mg twice daily) with the possibility to reduce to 2x100 mg daily (1 capsule of 100 mg twice daily) in combination with pirfenidone. The pirfenidone dose was titrated up to 2403 mg daily according to the following schedule: 801 mg (1 capsule of 267 mg 3 times daily) from Visit 3 until the phone call visit ; 1602 mg daily (2 capsules of each 267 mg 3 times daily) after the phone call visit; 2403 mg daily (3 capsules of each 267 mg 3 times daily) starting at Visit 4 after the PK sampling had been performed.The dose of pirfenidone could have been reduced to 1 or 2 capsule(s) 3 times daily.

Reporting group title	Nintedanib

Reporting group description:

Patients were orally administered Nintedanib 2x150 mg soft gelatine capsule daily (1 capsule of 150 mg twice daily) with the possibility to reduce to 2x100 mg daily (1 capsule of 100 mg twice daily). One subject randomised to Nintedanib was not treated. Although actual number of subjects started is 52, 51 were reported to ensure consistent reporting with baseline characteristics that includes only treated subjects.

Serious adverse events	Nintedanib + Pirfenidone	Nintedanib	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 53 (3.77%)	5 / 51 (9.80%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 53 (1.89%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Atrial flutter			
subjects affected / exposed	0 / 53 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	0 / 53 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	0 / 53 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 53 (0.00%)	1 / 51 (1.96%)	
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	1 / 53 (1.89%)	0 / 51 (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			
Pneumonia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Nintedanib + Pirfenidone	Nintedanib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 53 (86.79%)	36 / 51 (70.59%)	

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 53 (5.66%)	1 / 51 (1.96%)	
occurrences (all)	3	1	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 53 (5.66%)	1 / 51 (1.96%)	
occurrences (all)	3	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 53 (5.66%)	0 / 51 (0.00%)	
occurrences (all)	3	0	
Weight decreased			
subjects affected / exposed	4 / 53 (7.55%)	3 / 51 (5.88%)	
occurrences (all)	4	3	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 53 (0.00%)	3 / 51 (5.88%)	
occurrences (all)	0	3	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 53 (0.00%)	3 / 51 (5.88%)	
occurrences (all)	0	3	
Dysgeusia			
subjects affected / exposed	3 / 53 (5.66%)	0 / 51 (0.00%)	
occurrences (all)	3	0	
Headache			
subjects affected / exposed	7 / 53 (13.21%)	1 / 51 (1.96%)	
occurrences (all)	7	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 53 (1.89%)	3 / 51 (5.88%)	
occurrences (all)	1	3	
Fatigue			
subjects affected / exposed	10 / 53 (18.87%)	6 / 51 (11.76%)	
occurrences (all)	13	6	
Pyrexia			

subjects affected / exposed	3 / 53 (5.66%)	1 / 51 (1.96%)	
occurrences (all)	3	1	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	4 / 53 (7.55%)	0 / 51 (0.00%)	
occurrences (all)	5	0	
Abdominal pain			
subjects affected / exposed	4 / 53 (7.55%)	3 / 51 (5.88%)	
occurrences (all)	5	3	
Abdominal pain upper			
subjects affected / exposed	7 / 53 (13.21%)	4 / 51 (7.84%)	
occurrences (all)	8	4	
Constipation			
subjects affected / exposed	3 / 53 (5.66%)	1 / 51 (1.96%)	
occurrences (all)	4	1	
Diarrhoea			
subjects affected / exposed	20 / 53 (37.74%)	16 / 51 (31.37%)	
occurrences (all)	34	28	
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 53 (5.66%)	1 / 51 (1.96%)	
occurrences (all)	3	1	
Nausea			
subjects affected / exposed	22 / 53 (41.51%)	6 / 51 (11.76%)	
occurrences (all)	27	7	
Vomiting			
subjects affected / exposed	15 / 53 (28.30%)	6 / 51 (11.76%)	
occurrences (all)	25	7	
Hepatobiliary disorders			
Hepatocellular injury			
subjects affected / exposed	3 / 53 (5.66%)	0 / 51 (0.00%)	
occurrences (all)	3	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 53 (7.55%)	3 / 51 (5.88%)	
occurrences (all)	4	3	
Dyspnoea			

subjects affected / exposed occurrences (all)	2 / 53 (3.77%) 2	8 / 51 (15.69%) 8	
Skin and subcutaneous tissue disorders Photosensitivity reaction subjects affected / exposed occurrences (all)	 3 / 53 (5.66%) 3	 0 / 51 (0.00%) 0	
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	 5 / 53 (9.43%) 5 4 / 53 (7.55%) 4	 2 / 51 (3.92%) 2 2 / 51 (3.92%) 2	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 6 / 53 (11.32%) 7	 5 / 51 (9.80%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 February 2016	The following main changes in the conduct of the trial were introduced by the amendment: 1) The trial clinical monitor responsibility changed. 2) Clarification that all treated patients needed to attend the end-of-treatment and follow-up visits. 3) Clarification that the collection of the vital status was only required for randomised patients. 4) The Exclusion Criterion no. 8 was updated (i.e. inclusion of severe renal impairment based on Cockroft-Gault) to match the summary of product characteristics of pirfenidone. 5) Patients developing signs or symptoms of angioedema were to permanently discontinue pirfenidone; this specification was added to match the summary of product characteristics of pirfenidone. 6) Exclusion Criterion no. 20 was added based on advice from regulatory agencies: patients with underlying chronic liver disease (Child Pugh A, B, or C hepatic impairment)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported