Clinical trial results:
An Exploratory Multicenter, Open-label, Single Arm Study of the Safety and Tolerability of Pirfenidone (Esbriet®) in Combination with Nintedanib (Ofev®) in Patients with Idiopathic Pulmonary Fibrosis

Summary

EudraCT number	2015-003280-11
Trial protocol	DE ES DK NL IT
Global end of trial date	16 May 2017

Results information

Result version number	v1 (current)
This version publication date	30 May 2018
First version publication date	30 May 2018

Trial information

Trial identification

Sponsor protocol code	MA29895

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02598193
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.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	16 May 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This 1-arm study is to investigate the safety and tolerability of adding nintedanib to treatment with pirfenidone in subjects with idiopathic pulmonary fibrosis.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 January 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	Canada: 4
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Netherlands: 8
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	United States: 45
Worldwide total number of subjects	89
EEA total number of subjects	40

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)	23
From 65 to 84 years	66
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects with idiopathic pulmonary fibrosis were recruited for this study.

Pre-assignment

Screening details:

At the start of Screening, subjects will have been on pirfenidone for at least 16 weeks and on a stable dose (1602–2403 mg/d) for at least 28 days. A total of 109 subjects were screened, 20 subjects were screen failures and 89 were enrolled at 36 study centers in 8 countries.

Period 1

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

Arms

Arm title	Experimental: Pirfenidone+Nintedanib

Arm description:

Subjects with idiopathic pulmonary fibrosis (IPF) received pirfenidone at 1602-2403 milligrams per day (mg/day) dose and nintedanib at the 200-300 mg/day dose up to 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Pirfenidone
Investigational medicinal product code	
Other name	Esbriet
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Three 267 milligrams (mg) capsules orally administered three times a day for 24 weeks (total dose, 2403 mg/day)

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

Dosage and administration details:

Dose of 150 mg orally administered as capsule twice daily for 24 weeks

Number of subjects in period 1	Experimental: Pirfenidone+Nintedanib
Started	89
Completed	73
Not completed	16
Consent withdrawn by subject	1
Listen in active lung transplant list	1
Adverse event	13

Does not want to take nintedanib	1

Baseline characteristics

Reporting groups	
Reporting group title	Experimental: Pirfenidone+Nintedanib
Reporting group description:	
Subjects with idiopathic pulmonary fibrosis (IPF) received pirfenidone at 1602-2403 milligrams per day (mg/day) dose and nintedanib at the 200-300 mg/day dose up to 24 weeks.	

Reporting group values	Experimental: Pirfenidone+Nintedanib	Total	
Number of subjects	89	89	
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	68.2		
standard deviation	± 6.82	-	
Gender Categorical Units: Subjects			
Female	18	18	
Male	71	71	
Race Units: Subjects			
White	84	84	
Black or African American	3	3	
Asian	1	1	
Asian/White	1	1	
Ethinicity Units: Subjects			
Hispanic or Latino	9	9	
Not Hispanic or Latino	74	74	
Missing	6	6	

End points

End points reporting groups

Reporting group title	Experimental: Pirfenidone+Nintedanib

Reporting group description:

Subjects with idiopathic pulmonary fibrosis (IPF) received pirfenidone at 1602-2403 milligrams per day (mg/day) dose and nintedanib at the 200-300 mg/day dose up to 24 weeks.

Primary: Percentage of Subjects Who Complete 24 Weeks of Combination Treatment on Pirfenidone at a Dose of 1602-2403 mg/day and Nintedanib at a Dose of 200-300 mg/day

End point title	Percentage of Subjects Who Complete 24 Weeks of Combination Treatment on Pirfenidone at a Dose of 1602-2403 mg/day and Nintedanib at a Dose of 200-300 mg/day[1]

End point description:

Safety population included all subjects who had received at least one dose of investigational medicinal product on or after Day 1.

End point type	Primary

End point timeframe:

Week 24

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: Only descriptive statistics was planned to be reported in the endpoint.

End point values	Experimental: Pirfenidone+Nintedanib			
Subject group type	Reporting group			
Number of subjects analysed	89			
Units: percentage of subjects				
number (confidence interval 95%)	77.5 (67.4 to 85.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Adverse Events and Serious Adverse Events

End point title	Percentage of Subjects with Adverse Events and Serious Adverse Events

End point description:

An adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events. Safety population included all subjects who had received at least one dose of investigational medicinal product on or after Day 1.

End point type	Secondary

End point timeframe:

Baseline up to Week 28

End point values	Experimental: Pirfenidone+Nintedanib			
Subject group type	Reporting group			
Number of subjects analysed	89			
Units: percentage of subjects				
number (not applicable)				
Adverse Event	98.9			
Serious Adverse Event	18.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Discontinue Pirfenidone, Nintedanib, or Both Study Treatments Because of Adverse Events Before the Week 24 Visit

End point title	Percentage of Subjects Who Discontinue Pirfenidone, Nintedanib, or Both Study Treatments Because of Adverse Events Before the Week 24 Visit

End point description:

Safety population included all subjects who had received at least one dose of investigational medicinal product on or after Day 1.

End point type	Secondary

End point timeframe:

Baseline up to Week 24

End point values	Experimental: Pirfenidone+Nintedanib			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: percentage of subjects				
number (confidence interval 95%)	14.6 (8.0 to 23.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total Number of Subject Days of Combination Treatment With Pirfenidone and Nintedanib

End point title	Total Number of Subject Days of Combination Treatment With Pirfenidone and Nintedanib

End point description:

Safety population included all subjects who had received at least one dose of investigational medicinal product on or after Day 1.

End point type	Secondary

End point timeframe:

Baseline up to Week 24

End point values	Experimental: Pirfenidone+Nintedanib			
Subject group type	Reporting group			
Number of subjects analysed	89			
Units: subject days	13330			

Statistical analyses

No statistical analyses for this end point

Secondary: Total Number of Days From the Initiation of Combination Treatment to Discontinuation of Pirfenidone, Nintedanib, or Both Study Treatments

End point title	Total Number of Days From the Initiation of Combination Treatment to Discontinuation of Pirfenidone, Nintedanib, or Both Study Treatments

End point description:

Safety population included all participants who had received at least one dose of investigational medicinal product on or after Day 1.

End point type	Secondary

End point timeframe:

Baseline up to Week 24

End point values	Experimental: Pirfenidone+Nintedanib			
Subject group type	Reporting group			
Number of subjects analysed	89			
Units: Number of Days				
arithmetic mean (standard deviation)	149.8 (± 43.93)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to Week 28

Adverse event reporting additional description:

Safety population included all subjects who received at least one dose of investigational medicinal product on or after Day 1.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Experimental: Pirfenidone+Nintedanib

Reporting group description:

Subjects with IPF will receive pirfenidone at 1602-2403 milligrams per day (mg/day) dose and nintedanib at the 200-300 mg/day dose up to 24 weeks.

Serious adverse events	Experimental: Pirfenidone+Nintedanib		
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 89 (17.98%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostate cancer			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			

Deep vein thrombosis			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	3 / 89 (3.37%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Idiopathic pulmonary fibrosis			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumomediastinum			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Lumbar spinal stenosis			

subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cholecystitis infective			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tracheobronchitis			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Experimental: Pirfenidone+Nintedanib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	83 / 89 (93.26%)		
Investigations			
Weight decreased			
subjects affected / exposed	6 / 89 (6.74%)		
occurrences (all)	6		
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 89 (14.61%)		
occurrences (all)	22		

Dizziness			
subjects affected / exposed	9 / 89 (10.11%)		
occurrences (all)	9		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	14 / 89 (15.73%)		
occurrences (all)	16		
Non-cardiac chest pain			
subjects affected / exposed	5 / 89 (5.62%)		
occurrences (all)	6		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	52 / 89 (58.43%)		
occurrences (all)	184		
Nausea			
subjects affected / exposed	44 / 89 (49.44%)		
occurrences (all)	70		
Vomiting			
subjects affected / exposed	29 / 89 (32.58%)		
occurrences (all)	57		
Dyspepsia			
subjects affected / exposed	8 / 89 (8.99%)		
occurrences (all)	8		
Gastrooesophageal reflux disease			
subjects affected / exposed	7 / 89 (7.87%)		
occurrences (all)	7		
Abdominal pain upper			
subjects affected / exposed	6 / 89 (6.74%)		
occurrences (all)	7		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	20 / 89 (22.47%)		
occurrences (all)	22		
Dyspnoea			
subjects affected / exposed	10 / 89 (11.24%)		
occurrences (all)	10		

Infections and infestations Viral upper respiratory tract infection subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	 9 / 89 (10.11%) 13 8 / 89 (8.99%) 9		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 14 / 89 (15.73%) 14		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 October 2015	1) Study assessments have been changed to decrease the number of 12-lead electrocardiograms (ECGs) because no abnormalities in the ECGs potentially caused by pirfenidone were detected. 2) Clarification has been added on subjects to sign informed consent form prior to washout or discontinuation of prohibited medication. 3) Screening period has been changed to clarify that subjects stop commercial Esbriet and switch to pirfenidone provided as study drug based on feedback received during feasibility testing that there is an obligation in some countries to supply subjects with study medication once eligibility is confirmed. 4) Changes have been made to reflect that collection of unused pirfenidone need to be done, and dosing adherence, AEs and concomitant medications need to be reviewed, which is necessary as subject receives study drug from Screening Day to Day 21. 5) Relevant sections have been changed to clarify the allowance of down-titration for both study medication used in this trial.
21 June 2016	1) Excluded subjects with clinical evidence of active infection only if, according to the investigator, the infection would interfere with the study conduct, measurement of pulmonary function, or impact the course of IPF. 2) Excluded all subjects with any degree of hepatic impairment, based on an updated United States Package Insert (USPI) for nintedanib. 3) Excluded all subjects with hypersensitivity to peanuts or soy, and added soy products and soy lecithin-containing products as prohibited foods. 4) The requirement for a urine pregnancy test at Baseline was removed, as a serum pregnancy test was already required at Baseline. 5) Revised the Schedule of Assessments to include collection of Forced expiratory volume at 1 second (FEV1) at Screening and Baseline and to include the King's Brief Interstitial Lung Disease (KBILD) questionnaire at the Early Discontinuation Visit. 6) Schedule of Assessment was revised to include monthly urine pregnancy testing for women of childbearing potential, based on a request by the Health Authorities in Germany. 7) The option for blood samples for laboratory tests to be drawn by a home nursing agency was added. 8) Clarified the timing for providing informed consent prior to entering the Washout Period, and clarified the procedure for tapering (down titration) of prohibited medications during the Washout Period. 9) Revised the assessment of laboratory parameters to specify c-reactive protein (CRP) as a separate measurement, and to remove hemoglobin A1c. 10) Added a third independent data monitoring committee (iDMC) meeting when approximately 75% of the total subject group had either completed 24 weeks of combination treatment or had permanently discontinued study treatments.
21 June 2016	11) Added a Biomarker Study to the protocol for the purpose of assessing the pharmacodynamic effect of nintedanib on pirfenidone- or IPC-related biomarkers. 12) Revised the Safety Population definition. 13) Corrected the confidence intervals (CIs) from 80% to 95% for reporting the number and proportion of subjects who completed 24 weeks on pirfenidone at a dose of 1602 to 2403 mg/day and nintedanib at a dose of 200 to 300 mg/day, and the number and proportion of subjects who discontinued combination treatment because of an AE. 14) Updated the embryo-fetal toxicity of nintedanib and updated the pirfenidone pregnancy wording. 15) Updated the impact on pirfenidone treatment due to a photosensitivity reaction or rash and gastrointestinal side effects. 16) Added hepatic side effects as a safety measure to be analyzed. 17) Revised contraception requirements after the final Follow-up Visit and updated reporting requirements related to hospitalizations, pregnancy, and post-study AEs. 18) Clarified that all adverse event of special interests (AESIs) needed to be reported within 24 hours after learning of the event.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported