



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 standard deviation | 68.2 ± 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 | |
| Ethnicity 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 occurrences (all) | 9 / 89 (10.11%) 9 | | |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Non-cardiac chest pain subjects affected / exposed occurrences (all) | 14 / 89 (15.73%) 16 5 / 89 (5.62%) 6 | | |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) | 52 / 89 (58.43%) 184 44 / 89 (49.44%) 70 29 / 89 (32.58%) 57 8 / 89 (8.99%) 8 7 / 89 (7.87%) 7 6 / 89 (6.74%) 7 | | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) | 20 / 89 (22.47%) 22 10 / 89 (11.24%) 10 | | |

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

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