# Clinical trial results:
# A Phase IIb, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Sildenafil Added to Pirfenidone in Subjects With Advanced Idiopathic Pulmonary Fibrosis and Risk of Group 3 Pulmonary Hypertension

## Summary

| | |
|---|---|
| EudraCT number | 2015-005131-40 |
| Trial protocol | ES NL BE DE GR HU CZ IT |
| Global end of trial date | |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 03 September 2020 |
| First version publication date | 03 September 2020 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | MA29957 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02951429 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Hoffmann-La Roche |
| 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 | Medical Communications, Hoffmann-La Roche, +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 | Interim |
| Date of interim/final analysis | 11 November 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 26 September 2019 |
| Global end of trial reached? | No |

Notes:

## General information about the trial

Main objective of the trial:

This Phase IIb, randomized, placebo-controlled, multicenter, international study will evaluate the efficacy, safety, and tolerability of sildenafil or placebo added to pirfenidone (Esbriet) treatment in subjects with advanced IPF and intermediate or high probability of Group 3 pulmonary hypertension (PH) who are on a stable dose of pirfenidone with demonstrated tolerability. Subjects were randomized to receive 1 year of treatment with either oral sildenafil or matching placebo while continuing to take pirfenidone.

Protection of trial subjects:

This study was conducted in accordance with the protocol and with the following:

● Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines

● Applicable ICH Good Clinical Practice (GCP) Guidelines

● Applicable laws and regulations

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 13 January 2017 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 11 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Belgium: 23 |
| Country: Number of subjects enrolled | Canada: 8 |
| Country: Number of subjects enrolled | Czech Republic: 2 |
| Country: Number of subjects enrolled | Egypt: 15 |
| Country: Number of subjects enrolled | Germany: 13 |
| Country: Number of subjects enrolled | Greece: 18 |
| Country: Number of subjects enrolled | Hungary: 4 |
| Country: Number of subjects enrolled | Israel: 21 |
| Country: Number of subjects enrolled | Italy: 29 |
| Country: Number of subjects enrolled | Netherlands: 1 |
| Country: Number of subjects enrolled | South Africa: 7 |
| Country: Number of subjects enrolled | Spain: 10 |
| Country: Number of subjects enrolled | Turkey: 26 |

| | |
|---|---|
| Worldwide total number of subjects | 177 |
| EEA total number of subjects | 100 |

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) | 49 |
| From 65 to 84 years | 128 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Written informed consent for participation in the study was obtained before performing any study-specific screening tests or evaluations.

### 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 | Subject, Investigator |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Pirfenidone+Sildenafil |

Arm description:

Participants received pirfenidone along with sildenafil, orally, three times a day for 52 weeks.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Sildenafil |
| Investigational medicinal product code | |
| Other name | RO0280296 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Sildenafil will be given as 20 mg, TID.

| | |
|---|---|
| Investigational medicinal product name | Pirfenidone |
| Investigational medicinal product code | |
| Other name | Esbriet, RO0220912 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Pirfenidone will be given in the range of 1602 to 2403 milligram per day (mg/day), as 3 divided doses.

| | |
|---|---|
| **Arm title** | Pirfenidone+Placebo |

Arm description:

Participants received pirfenidone along with placebo matched to sildenafil, orally, three times a day for 52 weeks.

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo matched with sildenafil.

| | |
|---|---|
| Investigational medicinal product name | Pirfenidone |
| Investigational medicinal product code | |
| Other name | Esbriet, RO0220912 |

| | |
|---|---|
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Pirfenidone will be given in the range of 1602 to 2403 milligram per day (mg/day), as 3 divided doses.

| **Number of subjects in period 1** | Pirfenidone+Sildenafil | Pirfenidone+Placebo |
|---|---|---|
| Started | 88 | 89 |
| Completed | 16 | 6 |
| Not completed | 72 | 83 |
| Adverse event, serious fatal | 28 | 36 |
| Consent withdrawn by subject | 7 | 11 |
| Adverse event, non-fatal | 3 | 7 |
| Progressive Disease | 1 | 1 |
| Unknown | 1 | 3 |
| Lung Transplantation | 9 | 6 |
| Lost to follow-up | - | 1 |
| Participant ongoing in the study | 23 | 17 |
| Lack of efficacy | - | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Pirfenidone+Sildenafil |
| Reporting group description: | |
| Participants received pirfenidone along with sildenafil, orally, three times a day for 52 weeks. | |
| Reporting group title | Pirfenidone+Placebo |
| Reporting group description: | |
| Participants received pirfenidone along with placebo matched to sildenafil, orally, three times a day for 52 weeks. | |

| Reporting group values | Pirfenidone+Sildenafil | Pirfenidone+Placebo | Total |
|---|---|---|---|
| Number of subjects | 88 | 89 | 177 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 27 | 22 | 49 |
| From 65-84 years | 61 | 67 | 128 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 68.2 | 68.9 | |
| standard deviation | ± 7.7 | ± 7.1 | - |
| Sex: Female, Male<br>Units: Participants | | | |
| Female | 19 | 24 | 43 |
| Male | 69 | 65 | 134 |
| Race (NIH/OMB)<br>Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 1 | 0 | 1 |
| Native Hawaiian or Other Pacific Islander | 1 | 0 | 1 |
| Black or African American | 0 | 1 | 1 |
| White | 85 | 88 | 173 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 1 | 0 | 1 |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 2 | 3 | 5 |
| Not Hispanic or Latino | 78 | 79 | 157 |
| Unknown or Not Reported | 8 | 7 | 15 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Pirfenidone+Sildenafil |
| Reporting group description: | |
| Participants received pirfenidone along with sildenafil, orally, three times a day for 52 weeks. | |
| Reporting group title | Pirfenidone+Placebo |
| Reporting group description: | |
| Participants received pirfenidone along with placebo matched to sildenafil, orally, three times a day for 52 weeks. | |

### Primary: Percentage of Subjects With Disease Progression, as Determined by Relevant Decline in 6 Minute Walk Distance (6MWD) of At Least (>=) 15 Percent (%) From Baseline, Respiratory-Related Non-Elective Hospitalization, or Death From Any Cause

| | |
|---|---|
| End point title | Percentage of Subjects With Disease Progression, as Determined by Relevant Decline in 6 Minute Walk Distance (6MWD) of At Least (>=) 15 Percent (%) From Baseline, Respiratory-Related Non-Elective Hospitalization, or Death From Any Cause |
| End point description: | |
| Disease Progression defined as relative decline in 6MWD from baseline (defined as >25% from baseline or 15–25% from baseline associated with worsening oxygen saturation, worsening Borg score, or increased oxygen requirements), respiratory-related non-elective hospitalizations, or all-cause mortality.<br><br>Population: Subjects with data available at week 52. | |
| End point type | Primary |
| End point timeframe: | |
| Baseline up to Week 52 | |

| End point values | Pirfenidone+Sildenafil | Pirfenidone+Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 88 | 89 | | |
| Units: Percentage | | | | |
| number (not applicable) | 72.7 | 69.7 | | |

### Statistical analyses

| | |
|---|---|
| **Statistical analysis title** | Superiority |
| Comparison groups | Pirfenidone+Sildenafil v Pirfenidone+Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 177 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6527 |
| Method | Clopper-Pearson |
| Parameter estimate | Difference (95% CI) |
| Point estimate | 3.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11.3 |
| upper limit | 17.97 |

## Secondary: Time to First Occurrence of Disease Progression

| | |
|---|---|
| End point title | Time to First Occurrence of Disease Progression |

End point description:

Disease Progression defined as relative decline in 6MWD from baseline (defined as >25% from baseline or 15–25% from baseline associated with worsening oxygen saturation, worsening Borg score, or increased oxygen requirements), respiratory-related non-elective hospitalizations, or all-cause mortality.

Population: Subjects with data available at week 52.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Baseline up to Week 52

| End point values | Pirfenidone+Sildenafil | Pirfenidone+Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 88 | 89 | | |
| Units: Weeks | | | | |
| median (confidence interval 95%) | 26.00 (20.57 to 38.14) | 25.43 (13.00 to 37.71) | | |

### Statistical analyses

| Statistical analysis title | Superiority |
|---|---|
| Comparison groups | Pirfenidone+Sildenafil v Pirfenidone+Placebo |
| Number of subjects included in analysis | 177 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7568 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.95 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.67 |
| upper limit | 1.34 |

## Secondary: Time to Multiple Occurrence Event

| | |
|---|---|
| End point title | Time to Multiple Occurrence Event |
| End point description:<br>Population: Subjects with data available at week 52. | |
| End point type | Secondary |
| End point timeframe:<br>Baseline up to Week 52 | |

| End point values | Pirfenidone+Sildenafil | Pirfenidone+Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 88 | 89 | | |
| Units: Weeks | | | | |
| median (confidence interval 95%) | 20.57 (13.14 to 26.43) | 13.29 (12.71 to 23.29) | | |

### Statistical analyses

| Statistical analysis title | Superiority |
|---|---|
| Comparison groups | Pirfenidone+Sildenafil v Pirfenidone+Placebo |
| Number of subjects included in analysis | 177 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.376 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.89 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.68 |
| upper limit | 1.15 |

## Secondary: Percentage of Subjects With Decline From Baseline in 6MWD of >= 15%

| | |
|---|---|
| End point title | Percentage of Subjects With Decline From Baseline in 6MWD of >= 15% |

| | |
|---|---|
| End point description: | |
| Population: Subjects with data available at week 52 to calculate a change from baseline. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to Week 52 | |

| **End point values** | Pirfenidone+Sildenafil | Pirfenidone+Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 88 | 89 | | |
| Units: Percentage | | | | |
| number (not applicable) | 53.4 | 50.6 | | |

**Statistical analyses**

| **Statistical analysis title** | Superiority |
|---|---|
| Comparison groups | Pirfenidone+Sildenafil v Pirfenidone+Placebo |
| Number of subjects included in analysis | 177 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7046 |
| Method | Clopper-Pearson |
| Parameter estimate | Difference (95% CI) |
| Point estimate | 2.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.13 |
| upper limit | 17.84 |

## Secondary: Time to First Occurrence of Relevant ≥15% Decline from Baseline in 6MWD

| End point title | Time to First Occurrence of Relevant ≥15% Decline from Baseline in 6MWD |
|---|---|
| End point description: | |
| Population: Subjects with data available at week 52 to calculate a change from baseline. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to Week 52 | |

| End point values | Pirfenidone+Sildenafil | Pirfenidone+Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 88 | 89 | | |
| Units: Weeks | | | | |
| median (confidence interval 95%) | 39.00 (27.86 to 52.14) | 38.71 (25.14 to 52.57) | | |

**Statistical analyses**

| Statistical analysis title | Superiority |
|---|---|
| Comparison groups | Pirfenidone+Sildenafil v Pirfenidone+Placebo |
| Number of subjects included in analysis | 177 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.755 |
| Method | Clopper-Pearson |
| Parameter estimate | Difference (95% CI) |
| Point estimate | 0.94 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.62 |
| upper limit | 1.41 |

**Secondary: Time to Respiratory-Related Non-Elective Hospitalization**

| End point title | Time to Respiratory-Related Non-Elective Hospitalization |
|---|---|
| End point description:<br>9999 = non-calculable<br>Population: Subjects with data available at week 52 to calculate a change from baseline. | |
| End point type | Secondary |
| End point timeframe:<br>Baseline up to Week 52 | |

| End point values | Pirfenidone+Sildenafil | Pirfenidone+Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 88 | 89 | | |
| Units: Weeks | | | | |
| median (confidence interval 95%) | 54.29 (36.29 to 9999) | 9999 (42.14 to 9999) | | |

**Statistical analyses**

| **Statistical analysis title** | Superiority |
|---|---|
| Comparison groups | Pirfenidone+Sildenafil v Pirfenidone+Placebo |
| Number of subjects included in analysis | 177 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9174 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.65 |
| upper limit | 1.61 |

**Secondary: Time to All-Cause Non-Elective Hospitalization**

| End point title | Time to All-Cause Non-Elective Hospitalization |
|---|---|

End point description:

9999 = non calculable. KM-curves ends at 52 weeks and the upper CI is higher than 52 weeks and thus based on the data cannot be presented.

Population: Subjects with data available at week 52.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline up to Week 52

| **End point values** | Pirfenidone+Sildenafil | Pirfenidone+Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 88 | 89 | | |
| Units: Weeks | | | | |
| median (confidence interval 95%) | 45.57 (28.00 to 9999) | 49.86 (32.00 to 9999) | | |

**Statistical analyses**

| **Statistical analysis title** | Superiority |
|---|---|
| Comparison groups | Pirfenidone+Sildenafil v Pirfenidone+Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 177 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7748 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7 |
| upper limit | 1.62 |

## Secondary: Time to Death From Any Cause

| | |
|---|---|
| End point title | Time to Death From Any Cause |

End point description:

9999 = non-calculable

Population: Subjects with data available at week 52.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Baseline up to Week 52

| End point values | Pirfenidone+Sildenafil | Pirfenidone+Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 88 | 89 | | |
| Units: Weeks | | | | |
| median (confidence interval 95%) | 9999 (54.43 to 9999) | 9999 (9999 to 9999) | | |

### Statistical analyses

| Statistical analysis title | Superiority |
|---|---|
| Comparison groups | Pirfenidone+Sildenafil v Pirfenidone+Placebo |
| Number of subjects included in analysis | 177 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4258 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.76 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.38 |
| upper limit | 1.5 |

## Secondary: Percentage of Participants With Lung Transplantation

| End point title | Percentage of Participants With Lung Transplantation |
|---|---|
| End point description:<br>Population: Subjects with data available at week 52. | |
| End point type | Secondary |
| End point timeframe:<br>Baseline up to Week 52 | |

| End point values | Pirfenidone+Sildenafil | Pirfenidone+Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 88 | 89 | | |
| Units: Percentage | | | | |
| number (not applicable) | 10.2 | 6.7 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Respiratory-Related Death

| End point title | Time to Respiratory-Related Death |
|---|---|
| End point description:<br>9999 = non-calculable<br><br>Population: Subjects with data available at week 52. | |
| End point type | Secondary |
| End point timeframe:<br>Baseline up to Week 52 | |

| End point values | Pirfenidone+Sildenafil | Pirfenidone+Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 88 | 89 | | |
| Units: Weeks | | | | |
| median (confidence interval 95%) | 9999 (54.43 to 9999) | 9999 (9999 to 9999) | | |

**Statistical analyses**

| **Statistical analysis title** | Superiority |
|---|---|
| Comparison groups | Pirfenidone+Sildenafil v Pirfenidone+Placebo |
| Number of subjects included in analysis | 177 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3161 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.67 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.31 |
| upper limit | 1.46 |

**Secondary: Change From Baseline to Week 52 in Transthoracic Echocardiography (ECHO) Parameter: Peak Tricuspid Regurgitation Velocity**

| End point title | Change From Baseline to Week 52 in Transthoracic Echocardiography (ECHO) Parameter: Peak Tricuspid Regurgitation Velocity |
|---|---|
| End point description: | |
| Population: Subjects with data available at week 52 to calculate a change from baseline. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 52 | |

| **End point values** | Pirfenidone+Sildenafil | Pirfenidone+Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 38 | 29 | | |
| Units: m/s | | | | |
| arithmetic mean (standard deviation) | -0.014 (± 0.6326) | 0.103 (± 0.6699) | | |

**Statistical analyses**

No statistical analyses for this end point

## Secondary: Change From Baseline to Week 52 in Transthoracic Echocardiography (ECHO) Parameter: Pulmonary Artery Pressure (PAPs)

| End point title | Change From Baseline to Week 52 in Transthoracic Echocardiography (ECHO) Parameter: Pulmonary Artery Pressure (PAPs) |
|---|---|
| End point description: | |
| Population: Subjects with data available at week 52 to calculate a change from baseline. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 52 | |

| End point values | Pirfenidone+Sildenafil | Pirfenidone+Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 41 | 30 | | |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | 2.0 (± 15.65) | 3.6 (± 22.38) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline to Week 52 in Transthoracic Echocardiography (ECHO) Parameter: Tricuspid Annular Plane Systolic Excursion (TAPSE)

| End point title | Change From Baseline to Week 52 in Transthoracic Echocardiography (ECHO) Parameter: Tricuspid Annular Plane Systolic Excursion (TAPSE) |
|---|---|
| End point description: | |
| Population: Subjects with data available at week 52 to calculate a change from baseline. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 52 | |

| End point values | Pirfenidone+Sildenafil | Pirfenidone+Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 27 | | |
| Units: cm | | | | |
| arithmetic mean (standard deviation) | -0.204 (± 0.4170) | -0.146 (± 0.4453) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline to Week 52 in Transthoracic Echocardiography (ECHO) Parameter: Right Ventricle Basal Diameter

| End point title | Change From Baseline to Week 52 in Transthoracic Echocardiography (ECHO) Parameter: Right Ventricle Basal Diameter |
|---|---|

End point description:

Population: Subjects with data available at week 52 to calculate a change from baseline.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, Week 52

| End point values | Pirfenidone+Sildenafil | Pirfenidone+Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 24 | | |
| Units: cm | | | | |
| arithmetic mean (standard deviation) | 0.462 (± 1.2305) | 0.095 (± 1.2875) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline to Week 52 in Transthoracic Echocardiography (ECHO) Parameter: Inferior Vena Cava Diameter

| End point title | Change From Baseline to Week 52 in Transthoracic Echocardiography (ECHO) Parameter: Inferior Vena Cava Diameter |
|---|---|

End point description:

Population: Subjects with data available at week 52 to calculate a change from baseline.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, Week 52

| End point values | Pirfenidone+Sildenafil | Pirfenidone+Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24 | 22 | | |
| Units: cm | | | | |
| arithmetic mean (standard deviation) | -0.05 (± 0.595) | -0.09 (± 0.540) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline to Week 52 in Transthoracic Echocardiography (ECHO) Parameter: Left Ventricular Ejection Fraction (LVEF)

| End point title | Change From Baseline to Week 52 in Transthoracic Echocardiography (ECHO) Parameter: Left Ventricular Ejection Fraction (LVEF) |
|---|---|
| End point description: | |
| Population: Subjects with data available at week 52 to calculate a change from baseline. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 52 | |

| End point values | Pirfenidone+Sildenafil | Pirfenidone+Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 43 | 30 | | |
| Units: Percentage | | | | |
| arithmetic mean (standard deviation) | 1.22 (± 9.166) | -0.85 (± 5.767) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline to Week 52 in Carbon Monoxide Diffusing Capacity/ Pulmonary Diffusing Capacity (DLCO)

| End point title | Change From Baseline to Week 52 in Carbon Monoxide Diffusing Capacity/ Pulmonary Diffusing Capacity (DLCO) |
|---|---|
| End point description: | |
| Population: Subjects with data available at week 52 to calculate a change from baseline. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 52 | |

| End point values | Pirfenidone+Sildenafil | Pirfenidone+Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 43 | 29 | | |
| Units: Percentage predicted | | | | |
| arithmetic mean (standard deviation) | -2.918 (± 6.2296) | -2.440 (± 8.2820) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline to Week 52 in Forced Vital Capacity (FVC)

| End point title | Change From Baseline to Week 52 in Forced Vital Capacity (FVC) |
|---|---|
| End point description: | |
| Population: Subjects with data available at week 52 to calculate a change from baseline. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 52 | |

| End point values | Pirfenidone+Sildenafil | Pirfenidone+Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 33 | | |
| Units: Percentage predicted | | | | |
| arithmetic mean (standard deviation) | -2.761 (± 7.8044) | -1.161 (± 11.1158) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects by World Health Organization (WHO) Functional Class at Week 52

| End point title | Percentage of Subjects by World Health Organization (WHO) Functional Class at Week 52 |
|---|---|
| End point description: | |
| Population: Subjects with data available at week 52 to calculate a change from baseline. | |
| End point type | Secondary |
| End point timeframe: | |
| Week 52 | |

| End point values | Pirfenidone+Sildenafil | Pirfenidone+Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 49 | 36 | | |
| Units: Percentage | | | | |
| number (not applicable) | | | | |
| Class II | 19.3 | 13.5 | | |
| Class III | 33.0 | 24.7 | | |
| Class IV | 3.4 | 1.1 | | |
| Missing | 0 | 1.1 | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in N-terminal Pro-Brain Natriuretic Peptide (NT-proBNP) Level (pg/mL) at Week 52

| End point title | Change from Baseline in N-terminal Pro-Brain Natriuretic Peptide (NT-proBNP) Level (pg/mL) at Week 52 |
|---|---|
| End point description: | |
| Population: Subjects with data available at week 52 to calculate a change from baseline. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 52 | |

| End point values | Pirfenidone+Sildenafil | Pirfenidone+Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 44 | 28 | | |
| Units: pg/mL) | | | | |
| arithmetic mean (standard deviation) | 110.1 (± 612.98) | 605.9 (± 1273.19) | | |

### Statistical analyses

| Statistical analysis title | Superiority |
|---|---|
| Comparison groups | Pirfenidone+Sildenafil v Pirfenidone+Placebo |
| Number of subjects included in analysis | 72 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5646 |
| Method | Linear Mixed Effects Model |
| Parameter estimate | Estimate |
| Point estimate | -206.59 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | -920.03 |
| upper limit | 506.85 |

## Secondary: St. George's Respiratory Questionnaire (SGRQ) Changes from Baseline at Week 52

| End point title | St. George's Respiratory Questionnaire (SGRQ) Changes from Baseline at Week 52 |
|---|---|

End point description:

Population: Subjects with data available at week 52 to calculate a change from baseline.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, Week 52

| End point values | Pirfenidone+Sildenafil | Pirfenidone+Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 41 | 31 | | |
| Units: Points on scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Total score | 6.149 (± 12.3407) | 11.437 (± 12.5187) | | |
| Symptoms component score | 2.498 (± 19.6074) | 8.261 (± 19.5558) | | |
| Activities component score | 3.997 (± 15.4341) | 10.871 (± 14.5246) | | |
| Impacts component score | 8.417 (± 15.0040) | 12.118 (± 15.3487) | | |

### Statistical analyses

| Statistical analysis title | Superiority |
|---|---|
| Comparison groups | Pirfenidone+Sildenafil v Pirfenidone+Placebo |
| Number of subjects included in analysis | 72 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5255 |
| Method | ANCOVA |
| Parameter estimate | Median difference (final values) |
| Point estimate | -3.33 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.98 |
| upper limit | 2.36 |

## Secondary: University of California, San Diego–Shortness of Breath Questionnaire (UCSD-SOBQ) Changes from Baseline at Week 52

| | |
|---|---|
| End point title | University of California, San Diego–Shortness of Breath Questionnaire (UCSD-SOBQ) Changes from Baseline at Week 52 |
| End point description: | |
| Population: Subjects with data available at week 52 to calculate a change from baseline. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 52 | |

| End point values | Pirfenidone+Sildenafil | Pirfenidone+Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 35 | 25 | | |
| Units: Points on scale | | | | |
| arithmetic mean (standard deviation) | 12.5 (± 20.93) | 18.8 (± 19.68) | | |

### Statistical analyses

| Statistical analysis title | Superiority |
|---|---|
| Comparison groups | Pirfenidone+Sildenafil v Pirfenidone+Placebo |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4263 |
| Method | ANCOVA |
| Parameter estimate | Median difference (final values) |
| Point estimate | -6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -18 |
| upper limit | 6 |

## Secondary: Change from Baseline in Distance Walked, 6MWT at Week 52

| End point title | Change from Baseline in Distance Walked, 6MWT at Week 52 |
|---|---|
| End point description: | |
| Population: Subjects with data available at week 52 to calculate a change from baseline. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to Week 52 | |

| **End point values** | Pirfenidone+Sildenafil | Pirfenidone+Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 42 | 30 | | |
| Units: meters | | | | |
| arithmetic mean (standard deviation) | -52.9 (± 121.07) | -40.8 (± 91.26) | | |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Change from Baseline in Oxygen Requirements, 6MWT at Week 52**

| End point title | Change from Baseline in Oxygen Requirements, 6MWT at Week 52 |
|---|---|
| End point description: | |
| Population: Subjects with data available at week 52 to calculate a change from baseline. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to Week 52 | |

| **End point values** | Pirfenidone+Sildenafil | Pirfenidone+Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 42 | 30 | | |
| Units: Liters | | | | |
| arithmetic mean (standard deviation) | 0.6 (± 1.27) | 0.6 (± 1.43) | | |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Change from Baseline in other 6MWT Parameters at Week 52**

| End point title | Change from Baseline in other 6MWT Parameters at Week 52 |
|---|---|

End point description:

Population: Subjects with data available at week 52 to calculate a change from baseline.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline up to Week 52

| **End point values** | Pirfenidone+Sildenafil | Pirfenidone+Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 42 | 30 | | |
| Units: Percentage | | | | |
| arithmetic mean (standard deviation) | | | | |
| SpO2 before the test (at rest) | -0.5 (± 4.63) | -0.8 (± 3.77) | | |
| SpO2 lowest during the test | -3.4 (± 8.93) | 0.3 (± 5.27) | | |
| SpO2 after the test | 0.5 (± 9.97) | -2.3 (± 6.67) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects with Adverse Events

| End point title | Percentage of Subjects with Adverse Events |
|---|---|

End point description:

Population: Subjects with data available at week 52. AEs that started or worsened on or after first intake of randomized treatment until last positive dose + 28 days.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline up to Week 52

| **End point values** | Pirfenidone+Sildenafil | Pirfenidone+Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 88 | 89 | | |
| Units: Percentage | | | | |
| number (not applicable) | 98.9 | 93.3 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Borg scale Result at the End of the Test at Week 52

| End point title | Borg scale Result at the End of the Test at Week 52 |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline up to Week 52

| **End point values** | Pirfenidone+Sildenafil | Pirfenidone+Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 42 | 30 | | |
| Units: Points on Scale | | | | |
| arithmetic mean (standard deviation) | 0.9 (± 3.00) | 0.7 (± 3.24) | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From baseline to primary data cut-off (up to 2 years 7 months). The safety data includes DBP and SFU up to 11-Nov-2019.

Adverse event reporting additional description:

Total # of Deaths (all causes n= 64) represent deaths occurring during Double blind treatment period+4 week FU+additional safety follow up to the database snapshot of 11-Nov-2019.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 22.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Pirfenidone+Placebo |

Reporting group description:

Participants received pirfenidone along with placebo matched to sildenafil, orally, three times a day for 52 weeks.

| | |
|---|---|
| Reporting group title | Pirfenidone+Sildenafil |

Reporting group description:

Participants received pirfenidone along with sildenafil, orally, three times a day for 52 weeks.

| Serious adverse events | Pirfenidone+Placebo | Pirfenidone+Sildenafil | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 55 / 89 (61.80%) | 54 / 88 (61.36%) | |
| number of deaths (all causes) | 36 | 28 | |
| number of deaths resulting from adverse events | 1 | 1 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Bladder neoplasm | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 1 / 88 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 88 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal cancer metastatic | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 88 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Squamous cell carcinoma of lung | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 88 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Cryoglobulinaemia | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 88 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dry gangrene | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 1 / 88 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Extremity necrosis | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 1 / 88 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 1 / 88 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Lung transplant | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 1 / 88 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 3 / 88 (3.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 3 | |
| Inflammation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 89 (0.00%) | 1 / 88 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 2 / 88 (2.27%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Chronic respiratory failure | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 88 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 5 / 89 (5.62%) | 7 / 88 (7.95%) | |
| occurrences causally related to treatment / all | 0 / 5 | 1 / 9 | |
| deaths causally related to treatment / all | 0 / 3 | 1 / 1 | |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 1 / 88 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Idiopathic pulmonary fibrosis | | | |
| subjects affected / exposed | 21 / 89 (23.60%) | 19 / 88 (21.59%) | |
| occurrences causally related to treatment / all | 1 / 31 | 0 / 23 | |
| deaths causally related to treatment / all | 0 / 8 | 0 / 3 | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 1 / 88 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 1 / 88 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 88 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 2 / 89 (2.25%) | 0 / 88 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary fibrosis | | | |
| subjects affected / exposed | 2 / 89 (2.25%) | 4 / 88 (4.55%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 2 / 89 (2.25%) | 1 / 88 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 88 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory acidosis | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 1 / 88 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Respiratory failure | | | |
| subjects affected / exposed | 3 / 89 (3.37%) | 5 / 88 (5.68%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 3 | |
| Injury, poisoning and procedural complications | | | |
| Postoperative respiratory failure | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 1 / 88 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal compression fracture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 89 (0.00%) | 1 / 88 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tibia fracture | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 1 / 88 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 1 / 88 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 4 / 89 (4.49%) | 1 / 88 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 2 / 88 (2.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 1 / 88 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 88 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 1 / 88 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardio-respiratory arrest | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 89 (2.25%) | 0 / 88 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 1 / 88 (1.14%) | |
| 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 | 1 / 89 (1.12%) | 3 / 88 (3.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 1 / 88 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Brain stem infarction | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 88 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 88 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 1 / 88 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 88 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 88 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Eye disorders | | | |
| Blindness transient | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 1 / 88 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 1 / 88 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 1 / 88 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 1 / 88 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 1 / 88 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 1 / 88 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholestasis | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 88 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Renal and urinary disorders | | | |
| Urinary bladder polyp | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 88 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Goitre | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 1 / 88 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 1 / 88 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 1 / 88 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atypical pneumonia | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 88 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 1 / 88 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster disseminated | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 1 / 88 (1.14%) | |
| 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 / 89 (0.00%) | 1 / 88 (1.14%) | |
| 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 | 1 / 89 (1.12%) | 4 / 88 (4.55%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pneumonia | | | |
| subjects affected / exposed | 4 / 89 (4.49%) | 7 / 88 (7.95%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 9 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 88 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pneumonia haemophilus | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 1 / 88 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia viral | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 88 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 1 / 88 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 2 / 88 (2.27%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection viral | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 88 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 88 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 88 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 1 / 88 (1.14%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Cachexia | | | |
| subjects affected / exposed | 1 / 89 (1.12%) | 0 / 88 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fluid overload | | | |
| subjects affected / exposed | 0 / 89 (0.00%) | 1 / 88 (1.14%) | |
| 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 / 89 (0.00%) | 1 / 88 (1.14%) | |
| 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** | Pirfenidone+Placebo | Pirfenidone+Sildenafil | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 58 / 89 (65.17%) | 53 / 88 (60.23%) | |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 3 / 89 (3.37%) | 5 / 88 (5.68%) | |
| occurrences (all) | 3 | 5 | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 9 / 89 (10.11%) | 6 / 88 (6.82%) | |
| occurrences (all) | 10 | 7 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 2 / 89 (2.25%) | 5 / 88 (5.68%) | |
| occurrences (all) | 2 | 5 | |
| Headache | | | |
| subjects affected / exposed | 2 / 89 (2.25%) | 6 / 88 (6.82%) | |
| occurrences (all) | 3 | 7 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 6 / 89 (6.74%) | 8 / 88 (9.09%) | |
| occurrences (all) | 6 | 8 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 5 / 89 (5.62%) | 3 / 88 (3.41%) | |
| occurrences (all) | 5 | 4 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 89 (2.25%) | 11 / 88 (12.50%) | |
| occurrences (all) | 2 | 15 | |
| Vomiting | | | |
| subjects affected / exposed | 3 / 89 (3.37%) | 5 / 88 (5.68%) | |
| occurrences (all) | 3 | 5 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 9 / 89 (10.11%) | 7 / 88 (7.95%) | |
| occurrences (all) | 9 | 9 | |
| Dyspnoea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 17 / 89 (19.10%) | 22 / 88 (25.00%) | |
| occurrences (all) | 18 | 23 | |
| Idiopathic pulmonary fibrosis | | | |
| subjects affected / exposed | 7 / 89 (7.87%) | 8 / 88 (9.09%) | |
| occurrences (all) | 10 | 8 | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 5 / 89 (5.62%) | 3 / 88 (3.41%) | |
| occurrences (all) | 6 | 3 | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 9 / 89 (10.11%) | 6 / 88 (6.82%) | |
| occurrences (all) | 15 | 6 | |
| Influenza | | | |
| subjects affected / exposed | 5 / 89 (5.62%) | 2 / 88 (2.27%) | |
| occurrences (all) | 6 | 2 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 4 / 89 (4.49%) | 9 / 88 (10.23%) | |
| occurrences (all) | 6 | 11 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 89 (2.25%) | 8 / 88 (9.09%) | |
| occurrences (all) | 4 | 9 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 9 / 89 (10.11%) | 6 / 88 (6.82%) | |
| occurrences (all) | 9 | 6 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 01 December 2017 | Protocol MA29957 has been amended to reflect the feedback received after the start of the study from the Steering Committee, sites or ethic committees. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported