



## Clinical trial results:

### Multicenter, International, Double-blind, Two-Arm, Randomized, Placebo-controlled Phase II Trial of Pirfenidone in Patients with Unclassifiable Progressive Fibrosing ILD

#### Summary

|                          |                               |
|--------------------------|-------------------------------|
| EudraCT number           | 2016-002744-17                |
| Trial protocol           | ES DK CZ DE PL PT GR BE GB IT |
| Global end of trial date |                               |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1               |
| This version publication date  | 03 December 2019 |
| First version publication date | 03 December 2019 |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | MA39189 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03099187 |
| 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:

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**Results analysis stage**

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|                                                      |                  |
|------------------------------------------------------|------------------|
| Analysis stage                                       | Interim          |
| Date of interim/final analysis                       | 21 November 2018 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 21 November 2018 |
| Global end of trial reached?                         | No               |

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Notes:

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**General information about the trial**

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Main objective of the trial:

The main objective of the trial was to evaluate the effect of pirfenidone versus (vs.) placebo on lung function parameters.

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                          | 15 May 2017 |
| Long term follow-up planned                               | Yes         |
| Long term follow-up rationale                             | Safety      |
| Long term follow-up duration                              | 12 Months   |
| Independent data monitoring committee (IDMC) involvement? | Yes         |

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Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Australia: 38      |
| Country: Number of subjects enrolled | Belgium: 13        |
| Country: Number of subjects enrolled | Canada: 6          |
| Country: Number of subjects enrolled | Czech Republic: 8  |
| Country: Number of subjects enrolled | Denmark: 11        |
| Country: Number of subjects enrolled | Germany: 19        |
| Country: Number of subjects enrolled | Greece: 13         |
| Country: Number of subjects enrolled | Ireland: 5         |
| Country: Number of subjects enrolled | Israel: 30         |
| Country: Number of subjects enrolled | Italy: 21          |
| Country: Number of subjects enrolled | Poland: 16         |
| Country: Number of subjects enrolled | Portugal: 18       |
| Country: Number of subjects enrolled | Spain: 15          |
| Country: Number of subjects enrolled | United Kingdom: 40 |
| Worldwide total number of subjects   | 253                |
| EEA total number of subjects         | 179                |

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Notes:

| <b>Subjects enrolled per age group</b>    |     |
|-------------------------------------------|-----|
| 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)                      | 85  |
| From 65 to 84 years                       | 165 |
| 85 years and over                         | 3   |

## Subject disposition

### Recruitment

Recruitment details:

A total of 253 subjects were randomized at 65 study centers) in Australia, Europe, the Middle East, and North America. Subjects who were withdrawn from the trial were not replaced.

### Pre-assignment

Screening details:

Subjects were requested to taper and/or discontinue all prohibited medications in the 28 days prior to the start of screening during the washout period.

### 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         |
| <b>Arm title</b>             | Pirfenidone |

Arm description:

Subjects received pirfenidone 267 mg capsule three times a day from Day 1 to 7 followed by 2 capsules three times a day from Day 8 to 14 then 3 capsules three times a day from Day 15 up to Week 24.

|                                        |               |
|----------------------------------------|---------------|
| 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:

Pirfenidone was administered at a daily dose of 2403 mg orally in the form of three 267 mg capsules (801 mg) three times daily with food.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description:

Subjects received matching placebo capsule three times a day from Day 1 to 7 followed by 2 capsules three times a day from Day 8 to 14 then 3 capsules three times a day from Day 15 up to Week 24.

|                                        |                              |
|----------------------------------------|------------------------------|
| Arm type                               | Placebo                      |
| Investigational medicinal product name | Pirfenidone matching placebo |
| Investigational medicinal product code |                              |
| Other name                             |                              |
| Pharmaceutical forms                   | Capsule, hard                |
| Routes of administration               | Oral use                     |

Dosage and administration details:

Pirfenidone matching placebo was administered orally in the form of hard capsules three times daily.

| <b>Number of subjects in period 1</b>  | Pirfenidone | Placebo |
|----------------------------------------|-------------|---------|
| Started                                | 127         | 126     |
| Completed                              | 84          | 92      |
| Not completed                          | 43          | 34      |
| Adverse event, serious fatal           | 4           | 7       |
| Randomization error                    | -           | 2       |
| Physician decision                     | 2           | 2       |
| Consent withdrawn by subject           | 11          | 6       |
| Disease progression                    | -           | 1       |
| Adverse event, non-fatal               | 23          | 9       |
| Symptomatic deterioration              | -           | 1       |
| Lung transplantation                   | 1           | 3       |
| Non-compliance with study drug         | -           | 1       |
| Non-compliance with Protocol procedure | 1           | 2       |
| Lack of efficacy                       | 1           | -       |

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                                       |             |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
| Reporting group title                                                                                                                                                                                 | Pirfenidone |
| Reporting group description:                                                                                                                                                                          |             |
| Subjects received pirfenidone 267 mg capsule three times a day from Day 1 to 7 followed by 2 capsules three times a day from Day 8 to 14 then 3 capsules three times a day from Day 15 up to Week 24. |             |
| Reporting group title                                                                                                                                                                                 | Placebo     |
| Reporting group description:                                                                                                                                                                          |             |
| Subjects received matching placebo capsule three times a day from Day 1 to 7 followed by 2 capsules three times a day from Day 8 to 14 then 3 capsules three times a day from Day 15 up to Week 24.   |             |

| Reporting group values            | Pirfenidone | Placebo | Total |
|-----------------------------------|-------------|---------|-------|
| Number of subjects                | 127         | 126     | 253   |
| Age categorical                   |             |         |       |
| Units: Subjects                   |             |         |       |
| Adults (18-64 years)              | 43          | 42      | 85    |
| From 65-84 years                  | 82          | 83      | 165   |
| 85 years and over                 | 2           | 1       | 3     |
| Age Continuous                    |             |         |       |
| Units: Years                      |             |         |       |
| arithmetic mean                   | 68.0        | 67.7    |       |
| standard deviation                | ± 10.1      | ± 9.2   | -     |
| Sex: Female, Male                 |             |         |       |
| Units: Subjects                   |             |         |       |
| Female                            | 57          | 57      | 114   |
| Male                              | 70          | 69      | 139   |
| Race/Ethnicity, Customized        |             |         |       |
| Units: Subjects                   |             |         |       |
| Hispanic or Latino                | 7           | 9       | 16    |
| Not Hispanic or Latino            | 115         | 112     | 227   |
| Not reported                      | 5           | 5       | 10    |
| Race/Ethnicity, Customized        |             |         |       |
| Units: Subjects                   |             |         |       |
| American Indian or Alaskan Native | 1           | 0       | 1     |
| Asian                             | 5           | 0       | 5     |
| Black or African American         | 1           | 2       | 3     |
| Other                             | 0           | 1       | 1     |
| White                             | 120         | 123     | 243   |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                           |                            |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                     | Pirfenidone                |
| Reporting group description:<br>Subjects received pirfenidone 267 mg capsule three times a day from Day 1 to 7 followed by 2 capsules three times a day from Day 8 to 14 then 3 capsules three times a day from Day 15 up to Week 24.                                                                                                                     |                            |
| Reporting group title                                                                                                                                                                                                                                                                                                                                     | Placebo                    |
| Reporting group description:<br>Subjects received matching placebo capsule three times a day from Day 1 to 7 followed by 2 capsules three times a day from Day 8 to 14 then 3 capsules three times a day from Day 15 up to Week 24.                                                                                                                       |                            |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                | Intent-to-Treat Population |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                 | Intention-to-treat         |
| Subject analysis set description:<br>The intent-to-treat (ITT) population was defined as all randomized subjects. The ITT population was the primary analysis population for all efficacy analyses.                                                                                                                                                       |                            |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                | Safety Population          |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                 | Safety analysis            |
| Subject analysis set description:<br>The safety population was defined as all subjects with at least one intake of pirfenidone or placebo, i.e., at least one record in the drug-log of the double-blind period with a non-zero dose. Subjects in the safety population were assigned to a treatment arm according to the actual treatment they received. |                            |

### Primary: Rate of Decline in Forced Vital Capacity (FVC) Over the 24-week Double-blind Treatment Period

|                                                                                                                                                                                                                                                                                                                                           |                                                                                               |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                           | Rate of Decline in Forced Vital Capacity (FVC) Over the 24-week Double-blind Treatment Period |
| End point description:<br>Rate of decline in FVC was measured in mL by daily handheld spirometer. The intent-to-treat (ITT) population was defined as all randomized subjects. The ITT population was the primary analysis population for all efficacy analyses. Only subjects for whom data were collected are included in the analysis. |                                                                                               |
| End point type                                                                                                                                                                                                                                                                                                                            | Primary                                                                                       |
| End point timeframe:<br>Up to Week 24                                                                                                                                                                                                                                                                                                     |                                                                                               |

| End point values                          | Pirfenidone             | Placebo                |  |  |
|-------------------------------------------|-------------------------|------------------------|--|--|
| Subject group type                        | Reporting group         | Reporting group        |  |  |
| Number of subjects analysed               | 124                     | 123                    |  |  |
| Units: milliliter (mL)                    |                         |                        |  |  |
| arithmetic mean (confidence interval 95%) | -17.9 (-311.7 to 275.9) | 116.6 (-45.9 to 685.2) |  |  |

### Statistical analyses

|                                                                                                                                     |             |
|-------------------------------------------------------------------------------------------------------------------------------------|-------------|
| Statistical analysis title                                                                                                          | Superiority |
| Statistical analysis description:<br>Mean FVC decline comparison between treatment groups using a Student's t-test with a two-sided |             |

significance level of 0.05

|                                         |                           |
|-----------------------------------------|---------------------------|
| Comparison groups                       | Placebo v Pirfenidone     |
| Number of subjects included in analysis | 247                       |
| Analysis specification                  | Pre-specified             |
| Analysis type                           |                           |
| P-value                                 | = 0.6777 <sup>[1]</sup>   |
| Method                                  | t-test, 2-sided           |
| Parameter estimate                      | Difference in Group Means |
| Point estimate                          | -134.6                    |
| Confidence interval                     |                           |
| level                                   | 95 %                      |
| sides                                   | 2-sided                   |
| lower limit                             | -772.4                    |
| upper limit                             | 503.3                     |

Notes:

[1] - p-value is not adjusted for multiplicity and is provided for descriptive purpose only

## Secondary: Change in Percent Predicted FVC

|                                                                                                                                                                                                                                                                                      |                                 |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| End point title                                                                                                                                                                                                                                                                      | Change in Percent Predicted FVC |
| End point description:                                                                                                                                                                                                                                                               |                                 |
| FVC was measured in liter (L) by spirometry. The intent-to-treat (ITT) population was defined as all randomized subjects. The ITT population was the primary analysis population for all efficacy analyses. Only subjects for whom data were collected are included in the analysis. |                                 |
| End point type                                                                                                                                                                                                                                                                       | Secondary                       |
| End point timeframe:                                                                                                                                                                                                                                                                 |                                 |
| Baseline (Day 1) to Week 24                                                                                                                                                                                                                                                          |                                 |

| End point values                     | Pirfenidone        | Placebo            |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 127 <sup>[2]</sup> | 126 <sup>[3]</sup> |  |  |
| Units: Percent predicted (%)         |                    |                    |  |  |
| arithmetic mean (standard deviation) |                    |                    |  |  |
| Baseline (Day 1)                     | 73.95 (± 18.815)   | 73.95 (± 19.974)   |  |  |
| Week 4                               | 74.04 (± 18.929)   | 74.55 (± 21.223)   |  |  |
| Week 8                               | 73.98 (± 19.324)   | 73.50 (± 20.168)   |  |  |
| Week 12                              | 73.96 (± 19.493)   | 73.91 (± 20.856)   |  |  |
| Week 16                              | 74.56 (± 20.299)   | 72.96 (± 22.609)   |  |  |
| Week 20                              | 73.94 (± 21.000)   | 71.99 (± 21.673)   |  |  |
| Week 24                              | 72.95 (± 20.819)   | 73.55 (± 22.383)   |  |  |

Notes:

[2] - Number of subjects analysed was different at each time point; only collected data were analysed.

[3] - Number of subjects analysed was different at each time point; only collected data were analysed.

## Statistical analyses

|                                         |                       |
|-----------------------------------------|-----------------------|
| <b>Statistical analysis title</b>       | Superiority           |
| Comparison groups                       | Pirfenidone v Placebo |
| Number of subjects included in analysis | 253                   |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | superiority           |
| P-value                                 | = 0.0383              |
| Method                                  | rank ANCOVA           |

## Secondary: Change in FVC

|                                                                                                                                                                                                                                                                                                                |               |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|
| End point title                                                                                                                                                                                                                                                                                                | Change in FVC |
| End point description:<br>FVC was measured in liter (L) by spirometry. The intent-to-treat (ITT) population was defined as all randomized subjects. The ITT population was the primary analysis population for all efficacy analyses. Only subjects for whom data were collected are included in the analysis. |               |
| End point type                                                                                                                                                                                                                                                                                                 | Secondary     |
| End point timeframe:<br>Baseline (Day 1) to Week 24                                                                                                                                                                                                                                                            |               |

| End point values                     | Pirfenidone        | Placebo            |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 127 <sup>[4]</sup> | 126 <sup>[5]</sup> |  |  |
| Units: Litre (L)                     |                    |                    |  |  |
| arithmetic mean (standard deviation) |                    |                    |  |  |
| Baseline                             | 2.36 (± 0.793)     | 2.38 (± 0.747)     |  |  |
| Week 4                               | 2.36 (± 0.817)     | 2.37 (± 0.786)     |  |  |
| Week 8                               | 2.37 (± 0.822)     | 2.36 (± 0.816)     |  |  |
| Week 12                              | 2.37 (± 0.820)     | 2.35 (± 0.773)     |  |  |
| Week 16                              | 2.41 (± 0.860)     | 2.32 (± 0.791)     |  |  |
| Week 20                              | 2.40 (± 0.866)     | 2.30 (± 0.796)     |  |  |
| Week 24                              | 2.37 (± 0.863)     | 2.34 (± 0.773)     |  |  |

Notes:

[4] - Number of subjects analysed was different at each time point; only collected data were analysed.

[5] - Number of subjects analysed was different at each time point; only collected data were analysed.

## Statistical analyses

|                                         |                         |
|-----------------------------------------|-------------------------|
| <b>Statistical analysis title</b>       | Superiority             |
| Comparison groups                       | Pirfenidone v Placebo   |
| Number of subjects included in analysis | 253                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | = 0.0018 <sup>[6]</sup> |
| Method                                  | Student's t-test        |
| Parameter estimate                      | Overall Mean Difference |
| Point estimate                          | 95.3                    |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 35.9    |
| upper limit         | 154.6   |

Notes:

[6] - p-value is not adjusted for multiplicity and is provided for descriptive purpose only.

### Secondary: Categorical Change in FVC of >5%

|                 |                                  |
|-----------------|----------------------------------|
| End point title | Categorical Change in FVC of >5% |
|-----------------|----------------------------------|

End point description:

Categorical change in FVC was measured both by daily spirometry as well as by spirometry during clinical visits. Only the site spirometry data were used as the daily spirometry data were not normally distributed. The intent-to-treat (ITT) population was defined as all randomized subjects. The ITT population was the primary analysis population for all efficacy analyses.

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

End point timeframe:

Baseline (Day 1) to Week 24

| End point values            | Pirfenidone     | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 127             | 126             |  |  |
| Units: Subjects             | 47              | 74              |  |  |

### Statistical analyses

|                                         |                         |
|-----------------------------------------|-------------------------|
| Statistical analysis title              | Superiority             |
| Comparison groups                       | Pirfenidone v Placebo   |
| Number of subjects included in analysis | 253                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           |                         |
| P-value                                 | = 0.0006 [7]            |
| Method                                  | Cochran-Mantel-Haenszel |
| Parameter estimate                      | Odds ratio (OR)         |
| Point estimate                          | 0.42                    |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 0.25                    |
| upper limit                             | 0.69                    |

Notes:

[7] - p-values was not adjusted for multiplicity and was provided for descriptive purpose only

### Secondary: Categorical Change in FVC of >10%

|                 |                                   |
|-----------------|-----------------------------------|
| End point title | Categorical Change in FVC of >10% |
|-----------------|-----------------------------------|

End point description:

Categorical change in FVC was measured both by daily spirometry as well as by spirometry during clinical visits. Only the site spirometry data were used as the daily spirometry data were not normally distributed. The intent-to-treat (ITT) population was defined as all randomized subjects. The ITT population was the primary analysis population for all efficacy analyses.

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

End point timeframe:

Baseline (Day 1) to Week 24

| End point values            | Pirfenidone     | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 127             | 126             |  |  |
| Units: Subjects             | 18              | 34              |  |  |

## Statistical analyses

|                                         |                         |
|-----------------------------------------|-------------------------|
| Statistical analysis title              | Superiority             |
| Comparison groups                       | Pirfenidone v Placebo   |
| Number of subjects included in analysis | 253                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           |                         |
| P-value                                 | = 0.0114 <sup>[8]</sup> |
| Method                                  | Cochran-Mantel-Haenszel |
| Parameter estimate                      | Odds ratio (OR)         |
| Point estimate                          | 0.44                    |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 0.23                    |
| upper limit                             | 0.84                    |

Notes:

[8] - p-values was not adjusted for multiplicity and was provided for descriptive purpose only

## Secondary: Change in Percent Predicted Diffusing Capacity of the Lung for Carbon Monoxide (DLco)

|                 |                                                                                       |
|-----------------|---------------------------------------------------------------------------------------|
| End point title | Change in Percent Predicted Diffusing Capacity of the Lung for Carbon Monoxide (DLco) |
|-----------------|---------------------------------------------------------------------------------------|

End point description:

The DLco is a pulmonary function test that measures the capacity for the lung to carry out gas exchange between the inhaled breath and the pulmonary capillary blood vessels and the DLco %-predicted represents the DLco expressed as a percentage of the expected normal valued based on the participant's age, height, gender and ethnicity. The intent-to-treat (ITT) population was defined as all randomized subjects. The ITT population was the primary analysis population for all efficacy analyses. Only subjects for whom data were collected are included in the analysis.

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

End point timeframe:

Baseline (Day 1) to Week 24

| <b>End point values</b>              | Pirfenidone        | Placebo             |  |  |
|--------------------------------------|--------------------|---------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group     |  |  |
| Number of subjects analysed          | 127 <sup>[9]</sup> | 125 <sup>[10]</sup> |  |  |
| Units: Percentage                    |                    |                     |  |  |
| arithmetic mean (standard deviation) |                    |                     |  |  |
| Baseline (Day 1)                     | 46.19 (± 12.403)   | 49.57 (± 13.931)    |  |  |
| Week 12                              | 45.71 (± 12.693)   | 50.19 (± 16.171)    |  |  |
| Week 24                              | 45.45 (± 13.983)   | 48.58 (± 15.337)    |  |  |

Notes:

[9] - Number of subjects analysed was different at each time point; only collected data were analysed.

[10] - Number of subjects analysed was different at each time point; only collected data were analysed.

### Statistical analyses

|                                         |                          |
|-----------------------------------------|--------------------------|
| <b>Statistical analysis title</b>       | Superiority              |
| Comparison groups                       | Pirfenidone v Placebo    |
| Number of subjects included in analysis | 252                      |
| Analysis specification                  | Pre-specified            |
| Analysis type                           |                          |
| P-value                                 | = 0.0385 <sup>[11]</sup> |
| Method                                  | rank ANCOVA              |
| Parameter estimate                      | Odds ratio (OR)          |
| Point estimate                          | 0.25                     |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | 0.07                     |
| upper limit                             | 0.93                     |

Notes:

[11] - p-value was not adjusted for multiplicity and was provided for descriptive purpose only

### Secondary: Change in 6-minute Walk Distance (6MWD)

|                             |                                                                                                                                                                                                                                                                                                                                   |
|-----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title             | Change in 6-minute Walk Distance (6MWD)                                                                                                                                                                                                                                                                                           |
| End point description:      | Comparison of 6-minute walk distance before beginning and after completing study therapy. The intent-to-treat (ITT) population was defined as all randomized subjects. The ITT population was the primary analysis population for all efficacy analyses. Only subjects for whom data were collected are included in the analysis. |
| End point type              | Secondary                                                                                                                                                                                                                                                                                                                         |
| End point timeframe:        |                                                                                                                                                                                                                                                                                                                                   |
| Baseline (Day 1) to Week 24 |                                                                                                                                                                                                                                                                                                                                   |

| End point values                     | Pirfenidone         | Placebo             |  |  |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed          | 127 <sup>[12]</sup> | 126 <sup>[13]</sup> |  |  |
| Units: meter (m)                     |                     |                     |  |  |
| arithmetic mean (standard deviation) |                     |                     |  |  |
| Baseline                             | 391.6 (± 114.93)    | 394.0 (± 108.09)    |  |  |
| Week 12                              | 383.4 (± 123.87)    | 383.3 (± 116.50)    |  |  |
| Week 24                              | 397.1 (± 131.08)    | 369.8 (± 125.25)    |  |  |

Notes:

[12] - Number of subjects analysed was different at each time point; only collected data were analysed.

[13] - Number of subjects analysed was different at each time point; only collected data were analysed.

## Statistical analyses

|                                         |                          |
|-----------------------------------------|--------------------------|
| Statistical analysis title              | Superiority              |
| Comparison groups                       | Pirfenidone v Placebo    |
| Number of subjects included in analysis | 253                      |
| Analysis specification                  | Pre-specified            |
| Analysis type                           |                          |
| P-value                                 | = 0.9198 <sup>[14]</sup> |
| Method                                  | Regression, Logistic     |
| Parameter estimate                      | Odds ratio (OR)          |
| Point estimate                          | 1.03                     |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | 0.59                     |
| upper limit                             | 1.78                     |

Notes:

[14] - p-value was not adjusted for multiplicity and was provided for descriptive purpose only

## Secondary: Change in University of California, San Diego-Shortness of Breath Questionnaire Score

|                 |                                                                                       |
|-----------------|---------------------------------------------------------------------------------------|
| End point title | Change in University of California, San Diego-Shortness of Breath Questionnaire Score |
|-----------------|---------------------------------------------------------------------------------------|

End point description:

University of California, San Diego Shortness of Breath Questionnaire (SOBQ) consists of 24-item on a scale of 0 to 5 with 0=not at all and 5=maximal or unable to do because of breathlessness. The total scores were calculated by summation of the 24 items scores and transformed into 0-100, with 0= poor quality of life , and 100= excellent quality of life. The intent-to-treat (ITT) population was defined as all randomized subjects. The ITT population was the primary analysis population for all efficacy analyses. Only subjects for whom data were collected are included in the analysis.

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

End point timeframe:

Baseline (Day 1) to Week 24

| End point values                     | Pirfenidone         | Placebo             |  |  |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed          | 113 <sup>[15]</sup> | 114 <sup>[16]</sup> |  |  |
| Units: Number                        |                     |                     |  |  |
| arithmetic mean (standard deviation) |                     |                     |  |  |
| Baseline                             | 44.17 (± 25.204)    | 48.89 (± 23.441)    |  |  |
| Week 12                              | 45.86 (± 25.345)    | 51.74 (± 27.029)    |  |  |
| Week 24                              | 50.09 (± 27.737)    | 53.46 (± 29.268)    |  |  |

Notes:

[15] - Number of subjects analysed was different at each time point; only collected data were analysed.

[16] - Number of subjects analysed was different at each time point; only collected data were analysed.

## Statistical analyses

|                                         |                                  |
|-----------------------------------------|----------------------------------|
| Statistical analysis title              | Superiority                      |
| Comparison groups                       | Pirfenidone v Placebo            |
| Number of subjects included in analysis | 227                              |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           |                                  |
| P-value                                 | = 0.7788                         |
| Method                                  | rank ANCOVA                      |
| Parameter estimate                      | Hodges-Lehmann Median Difference |
| Point estimate                          | 0                                |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | -5                               |
| upper limit                             | 5                                |

## Secondary: Change in Score in Leicester Cough Questionnaire Score

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                        |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Change in Score in Leicester Cough Questionnaire Score |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                        |
| <p>The Leicester Cough Questionnaire is a subject-reported questionnaire evaluating the impact of cough on quality of life. The questionnaire comprises 19 items. Each item assesses symptoms, or the impact of symptoms, over the last 2 weeks on a seven-point Likert scale. Scores in three domains (physical, psychological and social) were calculated as a mean for each domain (range 1 to 7). A total score (range 3 to 21) was also calculated by adding the domain scores together. Higher scores indicate better quality of life. The intent-to-treat (ITT) population was defined as all randomized subjects. The ITT population was the primary analysis population for all efficacy analyses. Only subjects for whom data were collected are included in the analysis.</p> |                                                        |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Secondary                                              |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                        |
| Baseline (Day 1) to Week 24                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                        |

| End point values                     | Pirfenidone         | Placebo             |  |  |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed          | 127 <sup>[17]</sup> | 125 <sup>[18]</sup> |  |  |
| Units: Number                        |                     |                     |  |  |
| arithmetic mean (standard deviation) |                     |                     |  |  |
| Baseline                             | 16.13 (± 3.711)     | 15.15 (± 3.928)     |  |  |
| Week 12                              | 16.31 (± 3.966)     | 14.78 (± 3.925)     |  |  |
| Week 24                              | 16.36 (± 3.633)     | 15.16 (± 3.974)     |  |  |

Notes:

[17] - Number of subjects analysed was different at each time point; only collected data were analysed.

[18] - Number of subjects analysed was different at each time point; only collected data were analysed.

## Statistical analyses

|                                         |                                  |
|-----------------------------------------|----------------------------------|
| Statistical analysis title              | Superiority                      |
| Comparison groups                       | Pirfenidone v Placebo            |
| Number of subjects included in analysis | 252                              |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           |                                  |
| P-value                                 | = 0.1872 <sup>[19]</sup>         |
| Method                                  | rank ANCOVA                      |
| Parameter estimate                      | Hodges-Lehmann Median difference |
| Point estimate                          | 0.29                             |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | -0.45                            |
| upper limit                             | 1.04                             |

Notes:

[19] - p-value was not adjusted for multiplicity and was provided for descriptive purpose only

## Secondary: Change in Cough Visual Analog Scale (VAS) Score

|                                                                                                                                                                                                                                                                                                                                                                                              |                                                 |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                              | Change in Cough Visual Analog Scale (VAS) Score |
| End point description:                                                                                                                                                                                                                                                                                                                                                                       |                                                 |
| Cough VAS are 100-mm linear scales on which subjects indicate the severity of their cough; 0 mm represents no cough and 100 mm the worst cough ever. The intent-to-treat (ITT) population was defined as all randomized subjects. The ITT population was the primary analysis population for all efficacy analyses. Only subjects for whom data were collected are included in the analysis. |                                                 |
| End point type                                                                                                                                                                                                                                                                                                                                                                               | Secondary                                       |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                         |                                                 |
| Baseline (Day 1) to Week 24                                                                                                                                                                                                                                                                                                                                                                  |                                                 |

| End point values                     | Pirfenidone         | Placebo             |  |  |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed          | 127 <sup>[20]</sup> | 125 <sup>[21]</sup> |  |  |
| Units: millimeter (mm)               |                     |                     |  |  |
| arithmetic mean (standard deviation) |                     |                     |  |  |
| Baseline                             | 35.60 (± 27.497)    | 37.18 (± 26.270)    |  |  |
| Week 12                              | 33.03 (± 25.469)    | 41.09 (± 26.873)    |  |  |
| Week 24                              | 33.60 (± 27.898)    | 37.81 (± 26.619)    |  |  |

Notes:

[20] - Number of subjects analysed was different at each time point; only collected data were analysed.

[21] - Number of subjects analysed was different at each time point; only collected data were analysed.

## Statistical analyses

|                                         |                                  |
|-----------------------------------------|----------------------------------|
| Statistical analysis title              | Superiority                      |
| Comparison groups                       | Pirfenidone v Placebo            |
| Number of subjects included in analysis | 252                              |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           |                                  |
| P-value                                 | = 0.2995                         |
| Method                                  | rank ANCOVA                      |
| Parameter estimate                      | Hodges-Lehmann Median Difference |
| Point estimate                          | -2                               |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | -10                              |
| upper limit                             | 4                                |

## Secondary: Change in Total and Sub-scores of the Saint George's Respiratory Questionnaire (SGRQ)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                       |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Change in Total and Sub-scores of the Saint George's Respiratory Questionnaire (SGRQ) |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                       |
| SGRQ is a health related quality of life questionnaire consisting of 40 items in three areas: symptoms (respiratory symptoms and severity), activity (activities that cause or are limited by breathlessness) and impacts (social functioning and psychological disturbances due to airway disease). The total score is 0 to 100 with a higher score indicating poorer health status. The intent-to-treat (ITT) population was defined as all randomized subjects. The ITT population was the primary analysis population for all efficacy analyses. Only subjects for whom data were collected are included in the analysis. |                                                                                       |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Secondary                                                                             |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                       |
| Baseline (Day 1) to Week 24                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                       |

| End point values                     | Pirfenidone         | Placebo             |  |  |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed          | 127 <sup>[22]</sup> | 126 <sup>[23]</sup> |  |  |
| Units: Number                        |                     |                     |  |  |
| arithmetic mean (standard deviation) |                     |                     |  |  |
| Symptoms sub-score - Baseline        | 49.28 (± 21.687)    | 53.10 (± 21.450)    |  |  |
| Symptoms sub-score - Week 12         | 46.84 (± 22.851)    | 53.70 (± 22.549)    |  |  |
| Symptoms sub-score - Week 24         | 48.22 (± 22.788)    | 52.54 (± 20.974)    |  |  |
| Activities sub-score - Baseline      | 63.93 (± 20.388)    | 66.96 (± 18.615)    |  |  |
| Activities sub-score - Week 12       | 66.05 (± 20.842)    | 68.62 (± 20.845)    |  |  |
| Activities sub-score - Week 24       | 65.95 (± 22.509)    | 69.65 (± 20.638)    |  |  |
| Impacts sub-score - Baseline         | 37.12 (± 20.484)    | 41.47 (± 20.520)    |  |  |
| Impacts sub-score - Week 12          | 38.04 (± 21.283)    | 41.76 (± 20.459)    |  |  |
| Impacts sub-score - Week 24          | 37.30 (± 21.426)    | 42.57 (± 22.808)    |  |  |
| Total score - Baseline               | 47.37 (± 18.465)    | 51.46 (± 17.699)    |  |  |
| Total score - Week 12                | 48.11 (± 19.507)    | 52.14 (± 18.387)    |  |  |
| Total score - Week 24                | 47.95 (± 19.886)    | 52.44 (± 19.420)    |  |  |

Notes:

[22] - Number of subjects analysed was different at each time point; only collected data were analysed.

[23] - Number of subjects analysed was different at each time point; only collected data were analysed.

## Statistical analyses

| Statistical analysis title              | Superiority                      |
|-----------------------------------------|----------------------------------|
| Comparison groups                       | Pirfenidone v Placebo            |
| Number of subjects included in analysis | 253                              |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           |                                  |
| P-value                                 | = 0.163                          |
| Method                                  | rank ANCOVA                      |
| Parameter estimate                      | Hodges-Lehmann Median Difference |
| Point estimate                          | -1.86                            |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | -5.06                            |
| upper limit                             | 1.38                             |

## Secondary: Number of Subjects with Non-elective Hospitalization, Both Respiratory and all Cause

|                 |                                                                                      |
|-----------------|--------------------------------------------------------------------------------------|
| End point title | Number of Subjects with Non-elective Hospitalization, Both Respiratory and all Cause |
|-----------------|--------------------------------------------------------------------------------------|

End point description:

Subjects with non-elective hospitalization are reported. The intent-to-treat (ITT) population was defined as all randomized subjects. The ITT population was the primary analysis population for all efficacy analyses.

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

End point timeframe:

Baseline (Day 1) to Week 24

| End point values                    | Pirfenidone     | Placebo         |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 127             | 126             |  |  |
| Units: Subjects                     |                 |                 |  |  |
| All-cause hospitalization           | 16              | 14              |  |  |
| Respiratory-related hospitalization | 5               | 6               |  |  |

## Statistical analyses

|                                         |                       |
|-----------------------------------------|-----------------------|
| Statistical analysis title              | Superiority           |
| Comparison groups                       | Pirfenidone v Placebo |
| Number of subjects included in analysis | 253                   |
| Analysis specification                  | Pre-specified         |
| Analysis type                           |                       |
| P-value                                 | = 0.5922              |
| Method                                  | Logrank               |
| Parameter estimate                      | Hazard ratio (HR)     |
| Point estimate                          | 1.22                  |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | 0.59                  |
| upper limit                             | 2.49                  |

## Secondary: Percentage of Subjects with Investigator-reported Acute Exacerbations

|                 |                                                                       |
|-----------------|-----------------------------------------------------------------------|
| End point title | Percentage of Subjects with Investigator-reported Acute Exacerbations |
|-----------------|-----------------------------------------------------------------------|

End point description:

Percentage of subjects with acute exacerbation are reported. The intent-to-treat (ITT) population was defined as all randomized subjects. The ITT population was the primary analysis population for all efficacy analyses

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

End point timeframe:

Baseline (Day 1) to Week 24

| End point values            | Pirfenidone     | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 127             | 126             |  |  |
| Units: Percentage           |                 |                 |  |  |
| number (not applicable)     | 3.9             | 5.6             |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time to First Investigator-reported Acute Exacerbations

|                                                                                                                                                                                                                                                                                                                                                                                     |                                                         |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                     | Time to First Investigator-reported Acute Exacerbations |
| End point description:<br>Time to first investigator reported acute exacerbations from start of treatment are reported. The intent-to-treat (ITT) population was defined as all randomized subjects. The ITT population was the primary analysis population for all efficacy analyses. 9999=not estimable; The end point could not be analysed due to the limited number of events. |                                                         |
| End point type                                                                                                                                                                                                                                                                                                                                                                      | Secondary                                               |
| End point timeframe:<br>Baseline (Day 1) to Week 24                                                                                                                                                                                                                                                                                                                                 |                                                         |

| End point values                 | Pirfenidone         | Placebo             |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 127                 | 126                 |  |  |
| Units: Weeks                     |                     |                     |  |  |
| median (confidence interval 95%) | 9999 (9999 to 9999) | 9999 (9999 to 9999) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Progression-free Survival (PFS)

|                                                                                                                                                                                                                                                                                                                                                        |                                 |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                        | Progression-free Survival (PFS) |
| End point description:<br>PFS is defined as the time to the first occurrence of a >10% absolute decline in percent predicted FVC, a >50 m decline of 6MWD, or death. The intent-to-treat (ITT) population was defined as all randomized subjects. The ITT population was the primary analysis population for all efficacy analyses. 9999=not estimable |                                 |
| End point type                                                                                                                                                                                                                                                                                                                                         | Secondary                       |

End point timeframe:  
Baseline (Day 1) to Week 24

| End point values                 | Pirfenidone           | Placebo               |  |  |
|----------------------------------|-----------------------|-----------------------|--|--|
| Subject group type               | Reporting group       | Reporting group       |  |  |
| Number of subjects analysed      | 127                   | 126                   |  |  |
| Units: Week                      |                       |                       |  |  |
| median (confidence interval 95%) | 25.14 (24.71 to 9999) | 24.71 (24.14 to 9999) |  |  |

### Statistical analyses

| Statistical analysis title              | Superiority             |
|-----------------------------------------|-------------------------|
| Comparison groups                       | Pirfenidone v Placebo   |
| Number of subjects included in analysis | 253                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           |                         |
| P-value                                 | = 0.366                 |
| Method                                  | Logrank                 |
| Parameter estimate                      | Cox proportional hazard |
| Point estimate                          | 0.84                    |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 0.56                    |
| upper limit                             | 1.24                    |

### Secondary: Progression-free Survival (PFS)

|                                                                                                                                                                                                                                                                                                                                               |                                 |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                               | Progression-free Survival (PFS) |
| End point description:                                                                                                                                                                                                                                                                                                                        |                                 |
| PFS is defined as the time to the first occurrence of a >10% absolute decline in percent predicted FVC, non-elective respiratory hospitalization, or death. The intent-to-treat (ITT) population was defined as all randomized subjects. The ITT population was the primary analysis population for all efficacy analyses. 9999=not estimable |                                 |
| End point type                                                                                                                                                                                                                                                                                                                                | Secondary                       |
| End point timeframe:                                                                                                                                                                                                                                                                                                                          |                                 |
| Baseline (Day 1) to Week 24                                                                                                                                                                                                                                                                                                                   |                                 |

| End point values                 | Pirfenidone          | Placebo              |  |  |
|----------------------------------|----------------------|----------------------|--|--|
| Subject group type               | Reporting group      | Reporting group      |  |  |
| Number of subjects analysed      | 127                  | 126                  |  |  |
| Units: Week                      |                      |                      |  |  |
| median (confidence interval 95%) | 9999 (24.86 to 9999) | 9999 (24.00 to 9999) |  |  |

## Statistical analyses

| Statistical analysis title              | Superiority             |
|-----------------------------------------|-------------------------|
| Comparison groups                       | Pirfenidone v Placebo   |
| Number of subjects included in analysis | 253                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           |                         |
| P-value                                 | = 0.2726                |
| Method                                  | Logrank                 |
| Parameter estimate                      | Cox proportional hazard |
| Point estimate                          | 0.79                    |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 0.52                    |
| upper limit                             | 1.2                     |

## Secondary: Time to Death From any Cause

|                                                                                                                                                                                                                                                       |                              |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|
| End point title                                                                                                                                                                                                                                       | Time to Death From any Cause |
| End point description:                                                                                                                                                                                                                                |                              |
| Time to first documented death from start of treatment is reported. The intent-to-treat (ITT) population was defined as all randomized subjects. The ITT population was the primary analysis population for all efficacy analyses. 9999=not estimable |                              |
| End point type                                                                                                                                                                                                                                        | Secondary                    |
| End point timeframe:                                                                                                                                                                                                                                  |                              |
| Baseline (Day 1) to Week 24                                                                                                                                                                                                                           |                              |

| End point values                 | Pirfenidone         | Placebo             |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 127 <sup>[24]</sup> | 126 <sup>[25]</sup> |  |  |
| Units: Week                      |                     |                     |  |  |
| median (confidence interval 95%) | 9999 (9999 to 9999) | 9999 (9999 to 9999) |  |  |

Notes:

[24] - The end point could not be analysed due to the limited number of events.

[25] - The end point could not be analysed due to the limited number of events

## Statistical analyses

|                                         |                         |
|-----------------------------------------|-------------------------|
| <b>Statistical analysis title</b>       | Superiority             |
| Comparison groups                       | Pirfenidone v Placebo   |
| Number of subjects included in analysis | 253                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           |                         |
| P-value                                 | = 0.9969                |
| Method                                  | Logrank                 |
| Parameter estimate                      | Cox proportional hazard |
| Point estimate                          | 1.01                    |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 0.06                    |
| upper limit                             | 16.08                   |

## Secondary: Time to Death from Respiratory Diseases

|                                                                                                                                                                                                                                                                                                                  |                                         |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                  | Time to Death from Respiratory Diseases |
| End point description:<br>Time to first documented death due to respiratory diseases from start of treatment will be reported. The intent-to-treat (ITT) population was defined as all randomized subjects. The ITT population was the primary analysis population for all efficacy analyses. 9999=not estimable |                                         |
| End point type                                                                                                                                                                                                                                                                                                   | Secondary                               |
| End point timeframe:<br>Baseline (Day 1) to Week 24                                                                                                                                                                                                                                                              |                                         |

|                                  |                     |                     |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| <b>End point values</b>          | Pirfenidone         | Placebo             |  |  |
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 127 <sup>[26]</sup> | 126 <sup>[27]</sup> |  |  |
| Units: Week                      |                     |                     |  |  |
| median (confidence interval 95%) | 9999 (9999 to 9999) | 9999 (9999 to 9999) |  |  |

Notes:

[26] - The end point could not be analysed due to the limited number of events

[27] - The end point could not be analysed due to the limited number of events

## Statistical analyses

|                                   |                       |
|-----------------------------------|-----------------------|
| <b>Statistical analysis title</b> | Superiority           |
| Comparison groups                 | Pirfenidone v Placebo |

|                                         |                         |
|-----------------------------------------|-------------------------|
| Number of subjects included in analysis | 253                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           |                         |
| P-value                                 | = 0.3231                |
| Method                                  | Logrank                 |
| Parameter estimate                      | Cox proportional hazard |
| Point estimate                          | 0                       |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 0                       |
| upper limit                             | 0                       |

## Secondary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs)

|                 |                                                                   |
|-----------------|-------------------------------------------------------------------|
| End point title | Number of Subjects With Treatment-emergent Adverse Events (TEAEs) |
|-----------------|-------------------------------------------------------------------|

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. The safety population was defined as all subjects with at least one intake of pirfenidone or placebo, i.e., at least one record in the drug-log of the double-blind period with a non-zero dose. Subjects in the safety population were assigned to a treatment arm according to the actual treatment they received.

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

End point timeframe:

Baseline (Day 1) to Week 28

| End point values            | Pirfenidone     | Placebo             |  |  |
|-----------------------------|-----------------|---------------------|--|--|
| Subject group type          | Reporting group | Reporting group     |  |  |
| Number of subjects analysed | 127             | 124 <sup>[28]</sup> |  |  |
| Units: Subjects             | 120             | 101                 |  |  |

Notes:

[28] - Two subjects did not receive treatment.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With Dose Reductions and Treatment Interruptions

|                 |                                                                     |
|-----------------|---------------------------------------------------------------------|
| End point title | Number of Subjects With Dose Reductions and Treatment Interruptions |
|-----------------|---------------------------------------------------------------------|

End point description:

Number of subjects with dose reduction and treatment interruptions are reported. The safety population was defined as all subjects with at least one intake of pirfenidone or placebo, i.e., at least one record in the drug-log of the double-blind period with a non-zero dose. Subjects in the safety population were assigned to a treatment arm according to the actual treatment they received.

|                                                                |           |
|----------------------------------------------------------------|-----------|
| End point type                                                 | Secondary |
| End point timeframe:                                           |           |
| From administration of the first dose of study drug to Week 24 |           |

| End point values                             | Pirfenidone     | Placebo         |  |  |
|----------------------------------------------|-----------------|-----------------|--|--|
| Subject group type                           | Reporting group | Reporting group |  |  |
| Number of subjects analysed                  | 127             | 124             |  |  |
| Units: Subjects                              |                 |                 |  |  |
| Subjects with at least one dose modification | 51              | 34              |  |  |
| Subjects with at least one dose interruption | 38              | 10              |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects Withdrawn from Trial Treatment or Trial Discontinuations

|                 |                                                                             |
|-----------------|-----------------------------------------------------------------------------|
| End point title | Number of Subjects Withdrawn from Trial Treatment or Trial Discontinuations |
|-----------------|-----------------------------------------------------------------------------|

End point description:

Number of subjects withdrawn from trial treatment or trial discontinuations are reported. The safety population was defined as all subjects with at least one intake of pirfenidone or placebo, i.e., at least one record in the drug-log of the double-blind period with a non-zero dose. Subjects in the safety population were assigned to a treatment arm according to the actual treatment they received.

|                             |           |
|-----------------------------|-----------|
| End point type              | Secondary |
| End point timeframe:        |           |
| Baseline (Day 1) to Week 24 |           |

| End point values            | Pirfenidone     | Placebo             |  |  |
|-----------------------------|-----------------|---------------------|--|--|
| Subject group type          | Reporting group | Reporting group     |  |  |
| Number of subjects analysed | 127             | 124 <sup>[29]</sup> |  |  |
| Units: Subjects             | 25              | 12                  |  |  |

Notes:

[29] - Two subjects did not receive treatment.

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline (Day 1) to Week 28

Adverse event reporting additional description:

The safety population was defined as all subjects with at least one intake of pirfenidone or placebo, i.e., at least one record in the drug-log of the double-blind period with a non-zero dose. Subjects in the safety population were assigned to a treatment arm according to the actual treatment they received.

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

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 21.1 |
|--------------------|------|

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Pirfenidone |
|-----------------------|-------------|

Reporting group description:

Participants received pirfenidone 267 mg capsule three times a day from Day 1 to 7 followed by 2 capsules three times a day from Day 8 to 14 then 3 capsules three times a day from Day 15 up to Week 24.

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Participants received matching placebo capsule three times a day from Day 1 to 7 followed by 2 capsules three times a day from Day 8 to 14 then 3 capsules three times a day from Day 15 up to Week 24.

| Serious adverse events                                              | Pirfenidone       | Placebo           |  |
|---------------------------------------------------------------------|-------------------|-------------------|--|
| Total subjects affected by serious adverse events                   |                   |                   |  |
| subjects affected / exposed                                         | 18 / 127 (14.17%) | 20 / 124 (16.13%) |  |
| number of deaths (all causes)                                       | 4                 | 7                 |  |
| number of deaths resulting from adverse events                      |                   |                   |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                   |  |
| Prostate cancer                                                     |                   |                   |  |
| subjects affected / exposed                                         | 1 / 127 (0.79%)   | 0 / 124 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             |  |
| General disorders and administration site conditions                |                   |                   |  |
| General physical health deterioration                               |                   |                   |  |
| subjects affected / exposed                                         | 0 / 127 (0.00%)   | 1 / 124 (0.81%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             |  |
| Immune system disorders                                             |                   |                   |  |

|                                                          |                 |                 |  |
|----------------------------------------------------------|-----------------|-----------------|--|
| Lung transplant rejection<br>subjects affected / exposed | 0 / 127 (0.00%) | 1 / 124 (0.81%) |  |
| occurrences causally related to<br>treatment / all       | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all            | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal<br>disorders       |                 |                 |  |
| Chronic obstructive pulmonary<br>disease                 |                 |                 |  |
| subjects affected / exposed                              | 1 / 127 (0.79%) | 0 / 124 (0.00%) |  |
| occurrences causally related to<br>treatment / all       | 0 / 2           | 0 / 0           |  |
| deaths causally related to<br>treatment / all            | 0 / 0           | 0 / 0           |  |
| Cough                                                    |                 |                 |  |
| subjects affected / exposed                              | 1 / 127 (0.79%) | 0 / 124 (0.00%) |  |
| occurrences causally related to<br>treatment / all       | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all            | 0 / 0           | 0 / 0           |  |
| Dyspnoea                                                 |                 |                 |  |
| subjects affected / exposed                              | 1 / 127 (0.79%) | 2 / 124 (1.61%) |  |
| occurrences causally related to<br>treatment / all       | 0 / 1           | 0 / 2           |  |
| deaths causally related to<br>treatment / all            | 0 / 0           | 0 / 0           |  |
| Interstitial lung disease                                |                 |                 |  |
| subjects affected / exposed                              | 2 / 127 (1.57%) | 4 / 124 (3.23%) |  |
| occurrences causally related to<br>treatment / all       | 0 / 2           | 0 / 4           |  |
| deaths causally related to<br>treatment / all            | 0 / 0           | 0 / 0           |  |
| Pulmonary embolism                                       |                 |                 |  |
| subjects affected / exposed                              | 1 / 127 (0.79%) | 0 / 124 (0.00%) |  |
| occurrences causally related to<br>treatment / all       | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all            | 0 / 0           | 0 / 0           |  |
| Pulmonary fibrosis                                       |                 |                 |  |
| subjects affected / exposed                              | 1 / 127 (0.79%) | 1 / 124 (0.81%) |  |
| occurrences causally related to<br>treatment / all       | 0 / 1           | 0 / 1           |  |
| deaths causally related to<br>treatment / all            | 0 / 1           | 0 / 0           |  |
| Respiratory disorder                                     |                 |                 |  |
| subjects affected / exposed                              | 1 / 127 (0.79%) | 0 / 124 (0.00%) |  |
| occurrences causally related to<br>treatment / all       | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all            | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Investigations                                  |                 |                 |  |
| Alanine aminotransferase increased              |                 |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%) | 1 / 124 (0.81%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                 |                 |  |
| Procedural pain                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%) | 0 / 124 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal compression fracture                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%) | 1 / 124 (0.81%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal fracture                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%) | 0 / 124 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wrist fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%) | 0 / 124 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Acute myocardial infarction                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%) | 1 / 124 (0.81%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Atrial fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%) | 1 / 124 (0.81%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure                                 |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 127 (0.79%) | 0 / 124 (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 / 127 (0.79%) | 0 / 124 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardio-respiratory arrest                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%) | 1 / 124 (0.81%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Pericarditis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%) | 1 / 124 (0.81%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Cerebrovascular accident                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%) | 1 / 124 (0.81%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Loss of consciousness                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%) | 0 / 124 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Eye disorders                                   |                 |                 |  |
| Retinal detachment                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%) | 0 / 124 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Renal failure                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%) | 1 / 124 (0.81%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Musculoskeletal pain                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%) | 0 / 124 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Campylobacter gastroenteritis                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%) | 0 / 124 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%) | 0 / 124 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Influenza                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%) | 0 / 124 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lower respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%) | 1 / 124 (0.81%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Parainfluenzae virus infection                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%) | 1 / 124 (0.81%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%) | 3 / 124 (2.42%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory tract infection                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%) | 0 / 124 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                                                         |                 |                 |  |
|-----------------------------------------------------------------------------------------|-----------------|-----------------|--|
| Respiratory tract infection bacterial<br>subjects affected / exposed                    | 1 / 127 (0.79%) | 0 / 124 (0.00%) |  |
| occurrences causally related to<br>treatment / all                                      | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                                           | 0 / 0           | 0 / 0           |  |
| Urinary tract infection<br>subjects affected / exposed                                  | 1 / 127 (0.79%) | 0 / 124 (0.00%) |  |
| occurrences causally related to<br>treatment / all                                      | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                                           | 0 / 0           | 0 / 0           |  |
| Urosepsis<br>subjects affected / exposed                                                | 1 / 127 (0.79%) | 0 / 124 (0.00%) |  |
| occurrences causally related to<br>treatment / all                                      | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                                           | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed | 1 / 127 (0.79%) | 0 / 124 (0.00%) |  |
| occurrences causally related to<br>treatment / all                                      | 1 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                                           | 0 / 0           | 0 / 0           |  |
| Gout<br>subjects affected / exposed                                                     | 1 / 127 (0.79%) | 0 / 124 (0.00%) |  |
| occurrences causally related to<br>treatment / all                                      | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                                           | 0 / 0           | 0 / 0           |  |
| Hyponatraemia<br>subjects affected / exposed                                            | 1 / 127 (0.79%) | 0 / 124 (0.00%) |  |
| occurrences causally related to<br>treatment / all                                      | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                                           | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                                 | Pirfenidone        | Placebo           |  |
|-------------------------------------------------------------------|--------------------|-------------------|--|
| Total subjects affected by non-serious<br>adverse events          |                    |                   |  |
| subjects affected / exposed                                       | 107 / 127 (84.25%) | 81 / 124 (65.32%) |  |
| Investigations<br>Weight decreased<br>subjects affected / exposed | 11 / 127 (8.66%)   | 6 / 124 (4.84%)   |  |
| occurrences (all)                                                 | 11                 | 6                 |  |

|                                                      |                   |                   |  |
|------------------------------------------------------|-------------------|-------------------|--|
| Nervous system disorders                             |                   |                   |  |
| Dizziness                                            |                   |                   |  |
| subjects affected / exposed                          | 11 / 127 (8.66%)  | 13 / 124 (10.48%) |  |
| occurrences (all)                                    | 13                | 14                |  |
| Headache                                             |                   |                   |  |
| subjects affected / exposed                          | 13 / 127 (10.24%) | 4 / 124 (3.23%)   |  |
| occurrences (all)                                    | 19                | 5                 |  |
| General disorders and administration site conditions |                   |                   |  |
| Fatigue                                              |                   |                   |  |
| subjects affected / exposed                          | 21 / 127 (16.54%) | 19 / 124 (15.32%) |  |
| occurrences (all)                                    | 22                | 20                |  |
| Gastrointestinal disorders                           |                   |                   |  |
| Constipation                                         |                   |                   |  |
| subjects affected / exposed                          | 7 / 127 (5.51%)   | 4 / 124 (3.23%)   |  |
| occurrences (all)                                    | 7                 | 4                 |  |
| Diarrhoea                                            |                   |                   |  |
| subjects affected / exposed                          | 23 / 127 (18.11%) | 23 / 124 (18.55%) |  |
| occurrences (all)                                    | 27                | 24                |  |
| Dyspepsia                                            |                   |                   |  |
| subjects affected / exposed                          | 17 / 127 (13.39%) | 7 / 124 (5.65%)   |  |
| occurrences (all)                                    | 21                | 7                 |  |
| Gastrooesophageal reflux disease                     |                   |                   |  |
| subjects affected / exposed                          | 10 / 127 (7.87%)  | 6 / 124 (4.84%)   |  |
| occurrences (all)                                    | 10                | 7                 |  |
| Nausea                                               |                   |                   |  |
| subjects affected / exposed                          | 40 / 127 (31.50%) | 9 / 124 (7.26%)   |  |
| occurrences (all)                                    | 49                | 10                |  |
| Vomiting                                             |                   |                   |  |
| subjects affected / exposed                          | 14 / 127 (11.02%) | 6 / 124 (4.84%)   |  |
| occurrences (all)                                    | 17                | 7                 |  |
| Respiratory, thoracic and mediastinal disorders      |                   |                   |  |
| Cough                                                |                   |                   |  |
| subjects affected / exposed                          | 19 / 127 (14.96%) | 16 / 124 (12.90%) |  |
| occurrences (all)                                    | 21                | 17                |  |
| Dyspnoea                                             |                   |                   |  |

|                                                  |                         |                         |  |
|--------------------------------------------------|-------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all) | 14 / 127 (11.02%)<br>16 | 22 / 124 (17.74%)<br>25 |  |
| Skin and subcutaneous tissue disorders           |                         |                         |  |
| Photosensitivity reaction                        |                         |                         |  |
| subjects affected / exposed                      | 8 / 127 (6.30%)         | 0 / 124 (0.00%)         |  |
| occurrences (all)                                | 9                       | 0                       |  |
| Rash                                             |                         |                         |  |
| subjects affected / exposed                      | 9 / 127 (7.09%)         | 7 / 124 (5.65%)         |  |
| occurrences (all)                                | 12                      | 8                       |  |
| Psychiatric disorders                            |                         |                         |  |
| Depression                                       |                         |                         |  |
| subjects affected / exposed                      | 7 / 127 (5.51%)         | 0 / 124 (0.00%)         |  |
| occurrences (all)                                | 7                       | 0                       |  |
| Musculoskeletal and connective tissue disorders  |                         |                         |  |
| Back pain                                        |                         |                         |  |
| subjects affected / exposed                      | 8 / 127 (6.30%)         | 3 / 124 (2.42%)         |  |
| occurrences (all)                                | 8                       | 3                       |  |
| Infections and infestations                      |                         |                         |  |
| Bronchitis                                       |                         |                         |  |
| subjects affected / exposed                      | 10 / 127 (7.87%)        | 3 / 124 (2.42%)         |  |
| occurrences (all)                                | 11                      | 3                       |  |
| Lower respiratory tract infection                |                         |                         |  |
| subjects affected / exposed                      | 8 / 127 (6.30%)         | 13 / 124 (10.48%)       |  |
| occurrences (all)                                | 10                      | 16                      |  |
| Nasopharyngitis                                  |                         |                         |  |
| subjects affected / exposed                      | 7 / 127 (5.51%)         | 6 / 124 (4.84%)         |  |
| occurrences (all)                                | 8                       | 9                       |  |
| Respiratory tract infection                      |                         |                         |  |
| subjects affected / exposed                      | 11 / 127 (8.66%)        | 5 / 124 (4.03%)         |  |
| occurrences (all)                                | 11                      | 7                       |  |
| Upper respiratory tract infection                |                         |                         |  |
| subjects affected / exposed                      | 12 / 127 (9.45%)        | 9 / 124 (7.26%)         |  |
| occurrences (all)                                | 15                      | 10                      |  |
| Metabolism and nutrition disorders               |                         |                         |  |
| Decreased appetite                               |                         |                         |  |

|                             |                   |                  |  |
|-----------------------------|-------------------|------------------|--|
| subjects affected / exposed | 18 / 127 (14.17%) | 11 / 124 (8.87%) |  |
| occurrences (all)           | 22                | 11               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|---------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 03 March 2017 | 1) Version included additional safety monitoring during the 12-month safety follow-up period, in accordance with the pirfenidone Investigator's Brochure (RO0220912) and the Summary of Product Characteristics (Esbriet). Increased safety monitoring included additional liver function and pregnancy tests initially at monthly visits during the first 6 months and approximately every 3 months, thereafter. Urine pregnancy tests would continue to be performed on a monthly basis. Relevant sections of the protocol including the Schedule of Assessments have been amended. 2) Guidance text for sections on inclusion and exclusion criteria was amended in order to provide more clear guidance as to when subjects must fulfil the eligibility criteria in order to participate in the trial since results for screening assessments may not all be available at the time of screening. 3) Inclusion criterion no. 11 was amended in order to correct the error in the classification of the acceptable methods of contraception. 4) Section on 'Trial Rationale and Benefit-Risk Assessment' was amended to provide further clarification that trial subjects are allowed to be treated with mycophenolate (MMF) regardless of which treatment arm they were randomized onto during the 24-week double-blind period and throughout the study. |
| 03 March 2017 | 5) Section on 'Pirfenidone and Placebo' was amended in order to correct that no markings were made on the capsules. The list of printing ink ingredients was deleted. 6) Section on 'Method of Treatment Assignment and Unblinding' was amended in order to delete the sentence providing Investigators with the option of unblinding subjects for any other reason but safety. Unblinding could only occur for safety reasons. 6) Section on 'Electrocardiograms' was amended in order to revise the template text requiring for ECGs to be obtained prior to other trial procedures and not prior to treatment administration. This template text did not apply to this trial as there were no cardiac safety concerns with pirfenidone treatment or any justification for requiring ECGs to be obtained prior to any other study procedures. 7) The 'Cough Visual Analogue Scale' was amended in order to replace the previous scale with the actual scale and guidance text that would be provided to the subjects.                                                                                                                                                                                                                                                                                                                                     |
| 28 June 2018  | Protocol was amended mainly in order to provide additional guidance on trial specific procedures. Changes to the protocol including the rationale for each change: 1) Synopsis (Target Population) and Protocol Section 4.1 (Patients) of the protocol were amended in order to provide guidance on conditions for allowing the rescreening of subjects. 2) Section 4.5.5 (FVC) was amended to provide guidance on when to use a short-acting bronchodilator prior to on-site spirometry for subjects who are routinely treated with such medication. 3) Sections 4.5.9 (Electrocardiograms) and 5.1.1.8 (Management of Increases in QT Interval) were amended to provide more clear guidance for ECGs and the management of increases in QT interval. 4) Section 4.5.10 (Patient-Reported Outcomes) was amended as the timing for the completion of the Patient-Reported Outcomes was independent of the administration time of the trial treatment. 5) Section 4.6.1 (Patient Discontinuation) was amended to include lung transplantation during the trial as a reason for subject discontinuation. 6) Schedule of Assessments was amended to reflect the changes made to the body of the protocol and also to provide further trial-specific guidance.                                                                                                  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported