



## Clinical trial results:

### An Open-Label, Randomized, Phase 2 Study of the Safety and Tolerability of Pirfenidone When Administered to Patients With Systemic SclerosisRelated Interstitial Lung Disease

#### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2013-001353-28    |
| Trial protocol           | IT                |
| Global end of trial date | 16 September 2014 |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 22 July 2016 |
| First version publication date | 22 July 2016 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | PSSc-001 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01933334 |
| 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               | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com |
| Scientific contact           | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, 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                                       | Final           |
| Date of interim/final analysis                       | 09 October 2014 |
| Is this the analysis of the primary completion data? | No              |

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|                                  |                   |
|----------------------------------|-------------------|
| Global end of trial reached?     | Yes               |
| Global end of trial date         | 16 September 2014 |
| Was the trial ended prematurely? | No                |

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Notes:

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**General information about the trial**

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Main objective of the trial:

This was a Phase 2, multinational, open-label, randomized, parallel-group study to evaluate safety and tolerability of pirfenidone in participants with systemic sclerosis-related interstitial lung disease (SSc-ILD).

Protection of trial subjects:

This study was conducted according to the principles of Good Clinical Practices (GCP) as described in the International Conference on Harmonisation (ICH) document, Guidance for Industry-E6, Good Clinical Practice: Consolidated Guidance, and in keeping with local legal and regulatory requirements and the Declaration of Helsinki as currently endorsed by regional regulatory health authorities.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 31 October 2013 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | No              |

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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 | Canada: 3         |
| Country: Number of subjects enrolled | Italy: 6          |
| Country: Number of subjects enrolled | United States: 54 |
| Worldwide total number of subjects   | 63                |
| EEA total number of subjects         | 6                 |

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Notes:

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**Subjects enrolled per age group**

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|   |    |
|---|----|
| 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)                      | 54 |

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|                     |   |
|---------------------|---|
| From 65 to 84 years | 9 |
| 85 years and over   | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Participants were screened based on the the diagnosis of SSc which was based on the American College of Rheumatology, with SSc disease duration less than (<) 7 years. The diagnosis of SSc-ILD was to be confirmed by a high-resolution computed tomography scan (obtained 2 years before written informed consent).

### Period 1

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

### Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                  |                                     |
|------------------|-------------------------------------|
| <b>Arm title</b> | Pirfenidone: 4-Week Titration Group |
|------------------|-------------------------------------|

Arm description:

Participants received one 267 milligrams (mg) oral pirfenidone capsule three times daily (TID) (801 mg per day [mg/day]) for 2 weeks followed by two 267 mg oral pirfenidone capsules TID (1602 mg/day) for 2 weeks (titration period) and then three 267 mg oral pirfenidone capsules TID (2403 mg/day) for 12 weeks (maintenance period).

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Pirfenidone  |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

Participants received one 267 mg oral pirfenidone capsule TID (801 mg/day) for 2 weeks followed by two 267 mg oral pirfenidone capsules TID (1602 mg/day) for 2 weeks (titration period) and then three 267 mg oral pirfenidone capsules TID (2403 mg/day) for 12 weeks (maintenance period).

|                  |                                     |
|------------------|-------------------------------------|
| <b>Arm title</b> | Pirfenidone: 2-Week Titration Group |
|------------------|-------------------------------------|

Arm description:

Participants received one 267 mg oral pirfenidone capsule TID (801 mg/day) for 1 week followed by two 267 mg oral pirfenidone capsules TID (1602 mg/day) for 1 week (titration period) and then three 267 mg oral pirfenidone capsules TID (2403 mg/day) for 14 weeks (maintenance period).

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Pirfenidone  |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

Participants received one 267 mg oral pirfenidone capsule TID (801 mg/day) for 1 week followed by two 267 mg oral pirfenidone capsules TID (1602 mg/day) for 1 week (titration period) and then three 267 mg oral pirfenidone capsules TID (2403 mg/day) for 14 weeks (maintenance period).

| <b>Number of subjects in period 1</b> | Pirfenidone: 4-Week<br>Titration Group | Pirfenidone: 2-Week<br>Titration Group |
|---------------------------------------|--|--|
| Started                               | 31                                     | 32                                     |
| Completed                             | 29                                     | 27                                     |
| Not completed                         | 2                                      | 5                                      |
| Consent withdrawn by subject          | 1                                      | -                                      |
| Adverse event                         | 1                                      | 5                                      |

## Baseline characteristics

### Reporting groups

|   |                                     |
|---|-------------------------------------|
| Reporting group title   | Pirfenidone: 4-Week Titration Group |
| Reporting group description:<br>Participants received one 267 milligrams (mg) oral pirfenidone capsule three times daily (TID) (801 mg per day [mg/day]) for 2 weeks followed by two 267 mg oral pirfenidone capsules TID (1602 mg/day) for 2 weeks (titration period) and then three 267 mg oral pirfenidone capsules TID (2403 mg/day) for 12 weeks (maintenance period). |                                     |
| Reporting group title   | Pirfenidone: 2-Week Titration Group |
| Reporting group description:<br>Participants received one 267 mg oral pirfenidone capsule TID (801 mg/day) for 1 week followed by two 267 mg oral pirfenidone capsules TID (1602 mg/day) for 1 week (titration period) and then three 267 mg oral pirfenidone capsules TID (2403 mg/day) for 14 weeks (maintenance period).   |                                     |

| Reporting group values  | Pirfenidone: 4-Week Titration Group | Pirfenidone: 2-Week Titration Group | Total |
|---|-------------------------------------|-------------------------------------|-------|
| Number of subjects  | 31                                  | 32                                  | 63    |
| Age categorical<br>Units: Subjects                                      |                                     |                                     |       |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 51.9<br>± 12.52                     | 49.3<br>± 12.08                     | -     |
| Gender categorical<br>Units: Subjects                                   |                                     |                                     |       |
| Female  | 26                                  | 26                                  | 52    |
| Male  | 5                                   | 6                                   | 11    |

## End points

### End points reporting groups

|   |                                     |
|---|-------------------------------------|
| Reporting group title   | Pirfenidone: 4-Week Titration Group |
| Reporting group description:<br>Participants received one 267 milligrams (mg) oral pirfenidone capsule three times daily (TID) (801 mg per day [mg/day]) for 2 weeks followed by two 267 mg oral pirfenidone capsules TID (1602 mg/day) for 2 weeks (titration period) and then three 267 mg oral pirfenidone capsules TID (2403 mg/day) for 12 weeks (maintenance period). |                                     |
| Reporting group title   | Pirfenidone: 2-Week Titration Group |
| Reporting group description:<br>Participants received one 267 mg oral pirfenidone capsule TID (801 mg/day) for 1 week followed by two 267 mg oral pirfenidone capsules TID (1602 mg/day) for 1 week (titration period) and then three 267 mg oral pirfenidone capsules TID (2403 mg/day) for 14 weeks (maintenance period).   |                                     |

### Primary: Percentage of Participants With Treatment-Emergent Adverse Events (AEs)

|   |  |
|---|--|
| End point title   | Percentage of Participants With Treatment-Emergent Adverse Events (AEs) <sup>[1]</sup> |
| End point description:<br>Percentage of participants who had treatment-emergent AEs, defined as newly occurring or worsening after first dose. Participants with multiple occurrences of an AE within a category were counted once within the category. Safety population included all randomized participants who provided written informed consent and received at least one dose of study treatment. |  |
| End point type  | Primary  |
| End point timeframe:<br>From baseline up to 28 days after the last dose of study drug (last dose = Week 16)   |  |
| Notes:<br>[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.<br>Justification: No statistical analysis was planned for the safety endpoint.  |  |

| End point values                  | Pirfenidone: 4-Week Titration Group | Pirfenidone: 2-Week Titration Group |  |  |
|-----------------------------------|-------------------------------------|-------------------------------------|--|--|
| Subject group type                | Reporting group                     | Reporting group                     |  |  |
| Number of subjects analysed       | 31                                  | 32                                  |  |  |
| Units: percentage of participants |                                     |                                     |  |  |
| number (not applicable)           | 96.8                                | 96.9                                |  |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Participants With Treatment-Emergent Serious Adverse Events (SAEs)

|   |   |
|---|---|
| End point title   | Percentage of Participants With Treatment-Emergent Serious Adverse Events (SAEs) <sup>[2]</sup> |
| End point description:<br>An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of |   |

dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent are events between first dose of study drug and up to 28 days after last dose that were absent before treatment or that worsened relative to pretreatment state. Safety Population.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From baseline up to 28 days after the last dose of study drug (last dose = Week 16)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned for the safety endpoint.

| End point values                  | Pirfenidone: 4-Week Titration Group | Pirfenidone: 2-Week Titration Group |  |  |
|-----------------------------------|-------------------------------------|-------------------------------------|--|--|
| Subject group type                | Reporting group                     | Reporting group                     |  |  |
| Number of subjects analysed       | 31                                  | 32                                  |  |  |
| Units: percentage of participants |                                     |                                     |  |  |
| number (not applicable)           | 0                                   | 9.4                                 |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: University of California at Los Angeles (UCLA) Scleroderma Clinical Trial Consortium (SCTC) Gastrointestinal Trial (GIT) Questionnaire Scale Scores

|                 |   |
|-----------------|---|
| End point title | University of California at Los Angeles (UCLA) Scleroderma Clinical Trial Consortium (SCTC) Gastrointestinal Trial (GIT) Questionnaire Scale Scores |
|-----------------|---|

End point description:

UCLA SCTC GIT Scale 2.0 is a 34-item self-administered questionnaire to obtain participant's assessment of frequency of GI symptoms in preceding 7 days and how symptoms affected his/her life. All but 2 items were scored on a 0-3 scale (0=better health, 3=worse health); remaining 2 items were scored as 0 (better health), 1 (worse health). The 34 items are divided into 7 scales (reflux, distention/bloating, fecal soilage, diarrhea, social functioning, emotional well-being, and constipation). Individual scale score was calculated as the average of items in scale. Individual scale score ranged from 0-3 for reflux, distention/bloating, fecal soilage, social functioning, and emotional well-being; 0-2 for diarrhea; and 0-2.5 for constipation. A total score was also calculated as average of 6 of 7 scales (omitting constipation) and ranged from 0-2.83. For individual and total scores 0 indicated better health and higher score indicates worse health. Safety Population. CFB=change from baseline.

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

End point timeframe:

Baseline, Weeks 4, 8, 12, and 16

| End point values                     | Pirfenidone: 4-Week Titration Group | Pirfenidone: 2-Week Titration Group |  |  |
|--------------------------------------|-------------------------------------|-------------------------------------|--|--|
| Subject group type                   | Reporting group                     | Reporting group                     |  |  |
| Number of subjects analysed          | 31 <sup>[3]</sup>                   | 32 <sup>[4]</sup>                   |  |  |
| Units: units on a scale              |                                     |                                     |  |  |
| arithmetic mean (standard deviation) |                                     |                                     |  |  |
| Reflux: Baseline (n=31, 32)          | 0.3347 (± 0.29117)                  | 0.3398 (± 0.34083)                  |  |  |



|   |                     |                     |  |  |
|---|---------------------|---------------------|--|--|
| Reflux: Week 4 (n=31, 32)                   | 0.3548 (± 0.36529)  | 0.4727 (± 0.4327)   |  |  |
| Reflux: CFB Week 4 (n=31, 32)               | 0.0202 (± 0.26437)  | 0.1328 (± 0.36469)  |  |  |
| Reflux: Week 8 (n=31, 32)                   | 0.4389 (± 0.46573)  | 0.466 (± 0.39881)   |  |  |
| Reflux: CFB Week 8 (n=31, 32)               | 0.1043 (± 0.41664)  | 0.1261 (± 0.36875)  |  |  |
| Reflux: Week 12 (n=30, 27)                  | 0.3417 (± 0.33142)  | 0.4306 (± 0.41069)  |  |  |
| Reflux: CFB Week 12 (n=30, 27)              | 0.0042 (± 0.26155)  | 0.088 (± 0.35494)   |  |  |
| Reflux: Week 16 (n=28, 25)                  | 0.3348 (± 0.39682)  | 0.395 (± 0.3727)    |  |  |
| Reflux: CFB Week 16 (n=28, 25)              | -0.0045 (± 0.3182)  | 0.075 (± 0.25259)   |  |  |
| Distention/Bloating: Baseline (n=31, 32)    | 0.5968 (± 0.58693)  | 0.3984 (± 0.571)    |  |  |
| Distention/Bloating: Week 4 (n=31, 32)      | 0.4919 (± 0.65346)  | 0.6406 (± 0.65049)  |  |  |
| Distention/Bloating: CFB Week 4 (n=31, 32)  | -0.1048 (± 0.50734) | 0.2422 (± 0.41874)  |  |  |
| Distention/Bloating: Week 8 (n=31, 32)      | 0.4247 (± 0.57188)  | 0.5703 (± 0.60985)  |  |  |
| Distention/Bloating: CFB Week 8 (n=31, 32)  | -0.172 (± 0.43245)  | 0.1719 (± 0.4728)   |  |  |
| Distention/Bloating: Week 12 (n=30, 27)     | 0.425 (± 0.56152)   | 0.537 (± 0.7061)    |  |  |
| Distention/Bloating: CFB Week 12 (n=30, 27) | -0.1833 (± 0.47766) | 0.213 (± 0.59929)   |  |  |
| Distention/Bloating: Week 16 (n=28, 25)     | 0.4286 (± 0.48523)  | 0.48 (± 0.61627)    |  |  |
| Distention/Bloating: CFB Week 16 (n=28, 25) | -0.1518 (± 0.45307) | 0.12 (± 0.45139)    |  |  |
| Diarrhea: Baseline (n=31, 32)               | 0.2742 (± 0.48026)  | 0.3281 (± 0.48542)  |  |  |
| Diarrhea: Week 4 (n=31, 32)                 | 0.2258 (± 0.48026)  | 0.3125 (± 0.48775)  |  |  |
| Diarrhea: CFB Week 4 (n=31, 32)             | -0.0484 (± 0.43503) | -0.0156 (± 0.5748)  |  |  |
| Diarrhea: Week 8 (n=31, 32)                 | 0.3226 (± 0.556)    | 0.2813 (± 0.37968)  |  |  |
| Diarrhea: CFB Week 8 (n=31, 32)             | 0.0484 (± 0.58245)  | -0.0469 (± 0.46419) |  |  |
| Diarrhea: Week 12 (n=30, 27)                | 0.2 (± 0.48423)     | 0.2778 (± 0.46685)  |  |  |
| Diarrhea: CFB Week 12 (n=30, 27)            | -0.0667 (± 0.58329) | -0.0556 (± 0.56045) |  |  |
| Diarrhea: Week 16 (n=28, 25)                | 0.25 (± 0.51819)    | 0.34 (± 0.51478)    |  |  |
| Diarrhea: CFB Week 16 (n=28, 25)            | -0.0179 (± 0.61587) | 0.04 (± 0.57591)    |  |  |
| Social Functioning: Baseline (n=31, 32)     | 0.1893 (± 0.43585)  | 0.125 (± 0.28078)   |  |  |
| Social Functioning: Week 4 (n=31, 32)       | 0.1775 (± 0.27199)  | 0.1563 (± 0.26072)  |  |  |
| Social Functioning: CFB Week 4 (n=31, 32)   | -0.0118 (± 0.28143) | 0.0313 (± 0.25893)  |  |  |
| Social Functioning: Week 8 (n=31, 32)       | 0.1936 (± 0.33647)  | 0.1886 (± 0.31322)  |  |  |
| Social Functioning: CFB Week 8 (n=31, 32)   | 0.0044 (± 0.37997)  | 0.0635 (± 0.29233)  |  |  |

|   |                     |                    |  |  |
|---|---------------------|--------------------|--|--|
| Social Functioning: Week 12 (n=30, 27)      | 0.1944 (± 0.30028)  | 0.1173 (± 0.23488) |  |  |
| Social Functioning: CFB Week 12 (n=30, 27)  | -0.0011 (± 0.3573)  | 0.0432 (± 0.25154) |  |  |
| Social Functioning: Week 16 (n=28, 25)      | 0.01667 (± 0.27596) | 0.06 (± 0.13502)   |  |  |
| Social Functioning: CFB Week 16 (n=28, 25)  | -0.0131 (± 0.40515) | 0.0133 (± 0.16607) |  |  |
| Emotional Wellbeing: Baseline (n=31, 32)    | 0.1326 (± 0.4191)   | 0.0937 (± 0.26033) |  |  |
| Emotional Wellbeing: Week 4 (n=30, 32)      | 0.0778 (± 0.32516)  | 0.0937 (± 0.21697) |  |  |
| Emotional Wellbeing: CFB Week 4 (n=30, 32)  | -0.0593 (± 0.14808) | 0 (± 0.17831)      |  |  |
| Emotional Wellbeing: Week 8 (n=31, 32)      | 0.0825 (± 0.2968)   | 0.1181 (± 0.33273) |  |  |
| Emotional Wellbeing: CFB Week 8 (n=31, 32)  | -0.0502 (± 0.19846) | 0.0243 (± 0.11887) |  |  |
| Emotional Wellbeing: Week 12 (n=30, 27)     | 0.0852 (± 0.30979)  | 0.0493 (± 0.13182) |  |  |
| Emotional Wellbeing: CFB Week 12 (n=30, 27) | -0.0482 (± 0.14786) | 0.0123 (± 0.12055) |  |  |
| Emotional Wellbeing: Week 16 (n=28, 25)     | 0.0833 (± 0.39959)  | 0.0266 (± 0.0803)  |  |  |
| Emotional Wellbeing: CFB Week 16 (n=28, 25) | -0.0357 (± 0.12851) | 0 (± 0.10627)      |  |  |
| Fecal Soilage: Baseline (n=31, 32)          | 0.129 (± 0.42755)   | 0.0313 (± 0.17678) |  |  |
| Fecal Soilage: Week 4 (n=31, 32)            | 0.129 (± 0.42755)   | 0.0313 (± 0.17678) |  |  |
| Fecal Soilage: CFB Week 4 (n=31, 32)        | 0 (± 0)             | 0 (± 0)            |  |  |
| Fecal Soilage: Week 8 (n=31, 32)            | 0.1613 (± 0.45437)  | 0.0313 (± 0.17678) |  |  |
| Fecal Soilage: CFB Week 8 (n=31, 32)        | 0.0323 (± 0.17961)  | 0 (± 0)            |  |  |
| Fecal Soilage: Week 12 (n=30, 27)           | 0.1333 (± 0.43417)  | 0.037 (± 0.19245)  |  |  |
| Fecal Soilage: CFB Week 12 (n=30, 27)       | 0 (± 0)             | 0.037 (± 0.19245)  |  |  |
| Fecal Soilage: Week 16 (n=28, 25)           | 0.1071 (± 0.41627)  | 0.04 (± 0.2)       |  |  |
| Fecal Soilage: CFB Week 16 (n=28, 25)       | 0 (± 0)             | 0.04 (± 0.2)       |  |  |
| Constipation: Baseline (n=31, 32)           | 0.1694 (± 0.2613)   | 0.2422 (± 0.40899) |  |  |
| Constipation: Week 4 (n=30, 32)             | 0.15 (± 0.29066)    | 0.2656 (± 0.34159) |  |  |
| Constipation: CFB Week 4 (n=30, 32)         | -0.025 (± 0.30336)  | 0.0234 (± 0.42293) |  |  |
| Constipation: Week 8 (n=31, 32)             | 0.1613 (± 0.46345)  | 0.2578 (± 0.39901) |  |  |
| Constipation: CFB Week 8 (n=31, 32)         | -0.0081 (± 0.38989) | 0.0156 (± 0.2535)  |  |  |
| Constipation: Week 12 (n=30, 27)            | 0.2111 (± 0.36075)  | 0.2407 (± 0.38904) |  |  |
| Constipation: CFB Week 12 (n=30, 27)        | 0.0528 (± 0.49008)  | 0.037 (± 0.37148)  |  |  |
| Constipation: Week 16 (n=28, 25)            | 0.1518 (± 0.27504)  | 0.18 (± 0.29333)   |  |  |
| Constipation: CFB Week 16 (n=28, 25)        | -0.0179 (± 0.42453) | 0.02 (± 0.37444)   |  |  |
| Total Score: Baseline (n=32, 31)            | 0.2761 (± 0.32679)  | 0.2194 (± 0.24262) |  |  |

|                                     |                        |                       |  |  |
|-------------------------------------|------------------------|-----------------------|--|--|
| Total Score: Week 4 (n=32, 31)      | 0.2432 (±<br>0.31264)  | 0.2845 (±<br>0.28528) |  |  |
| Total Score: CFB Week 4 (n=32, 31)  | -0.033 (±<br>0.13591)  | 0.0651 (±<br>0.20058) |  |  |
| Total Score: Week 8 (n=32, 31)      | 0.2706 (±<br>0.29132)  | 0.2759 (±<br>0.26133) |  |  |
| Total Score: CFB Week 8 (n=32, 31)  | -0.0055 (±<br>0.20053) | 0.0564 (±<br>0.15749) |  |  |
| Total Score: Week 12 (n=27, 30)     | 0.2299 (±<br>0.27136)  | 0.2416 (±<br>0.25329) |  |  |
| Total Score: CFB Week 12 (n=27, 30) | -0.0492 (±<br>0.17709) | 0.0564 (±<br>0.1679)  |  |  |
| Total Score: Week 16 (n=25, 28)     | 0.2284 (±<br>0.26906)  | 0.2237 (±<br>0.19767) |  |  |
| Total Score: CFB Week 16 (n=25, 28) | -0.0372 (±<br>0.20737) | 0.0481 (±<br>0.14444) |  |  |

Notes:

[3] - n = number of participants analyzed at specified time

[4] - n = number of participants analyzed at specified time

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From baseline up to 28 days after the last dose of study drug (last dose = Week 16)

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 11.0 |
|--------------------|------|

### Reporting groups

|                       |                                     |
|-----------------------|-------------------------------------|
| Reporting group title | Pirfenidone: 2-Week Titration Group |
|-----------------------|-------------------------------------|

Reporting group description:

Participants received one 267 mg oral pirfenidone capsule (801 mg/day) TID for 1 week followed by two 267 mg oral pirfenidone capsules (1602 mg/day) TID for 1 week (titration period) and then three 267 mg oral pirfenidone capsules TID (2403 mg/day) for 14 weeks (maintenance period).

|                       |                                     |
|-----------------------|-------------------------------------|
| Reporting group title | Pirfenidone: 4-Week Titration Group |
|-----------------------|-------------------------------------|

Reporting group description:

Participants received one 267 mg oral pirfenidone capsule (801 mg/day) TID for 2 weeks followed by two 267 mg oral pirfenidone capsules (1602 mg/day) TID for 2 weeks (titration period) and then three 267 mg oral pirfenidone capsules TID (2403 mg/day) for 12 weeks (maintenance period).

| Serious adverse events                            | Pirfenidone: 2-Week Titration Group | Pirfenidone: 4-Week Titration Group |  |
|---|-------------------------------------|-------------------------------------|--|
| Total subjects affected by serious adverse events |                                     |                                     |  |
| subjects affected / exposed                       | 3 / 32 (9.38%)                      | 0 / 31 (0.00%)                      |  |
| number of deaths (all causes)                     | 0                                   | 0                                   |  |
| number of deaths resulting from adverse events    |                                     |                                     |  |
| Gastrointestinal disorders                        |                                     |                                     |  |
| Small intestinal obstruction                      |                                     |                                     |  |
| subjects affected / exposed                       | 1 / 32 (3.13%)                      | 0 / 31 (0.00%)                      |  |
| occurrences causally related to treatment / all   | 0 / 1                               | 0 / 0                               |  |
| deaths causally related to treatment / all        | 0 / 0                               | 0 / 0                               |  |
| Respiratory, thoracic and mediastinal disorders   |                                     |                                     |  |
| Interstitial lung disease                         |                                     |                                     |  |
| subjects affected / exposed                       | 1 / 32 (3.13%)                      | 0 / 31 (0.00%)                      |  |
| occurrences causally related to treatment / all   | 0 / 1                               | 0 / 0                               |  |
| deaths causally related to treatment / all        | 0 / 0                               | 0 / 0                               |  |
| Pulmonary hypertension                            |                                     |                                     |  |
| subjects affected / exposed                       | 1 / 32 (3.13%)                      | 0 / 31 (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                     |                |                |  |
| Bronchitis                                      |                |                |  |
| subjects affected / exposed                     | 1 / 32 (3.13%) | 0 / 31 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

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

| <b>Non-serious adverse events</b>                     | Pirfenidone: 2-Week Titration Group | Pirfenidone: 4-Week Titration Group |  |
|---|-------------------------------------|-------------------------------------|--|
| Total subjects affected by non-serious adverse events |                                     |                                     |  |
| subjects affected / exposed                           | 31 / 32 (96.88%)                    | 30 / 31 (96.77%)                    |  |
| Vascular disorders                                    |                                     |                                     |  |
| Hot flush   |                                     |                                     |  |
| subjects affected / exposed                           | 1 / 32 (3.13%)                      | 2 / 31 (6.45%)                      |  |
| occurrences (all)                                     | 1                                   | 2                                   |  |
| Hypotension   |                                     |                                     |  |
| subjects affected / exposed                           | 3 / 32 (9.38%)                      | 0 / 31 (0.00%)                      |  |
| occurrences (all)                                     | 3                                   | 0                                   |  |
| General disorders and administration site conditions  |                                     |                                     |  |
| Asthenia  |                                     |                                     |  |
| subjects affected / exposed                           | 2 / 32 (6.25%)                      | 5 / 31 (16.13%)                     |  |
| occurrences (all)                                     | 3                                   | 6                                   |  |
| Chest discomfort                                      |                                     |                                     |  |
| subjects affected / exposed                           | 2 / 32 (6.25%)                      | 0 / 31 (0.00%)                      |  |
| occurrences (all)                                     | 2                                   | 0                                   |  |
| Chills  |                                     |                                     |  |
| subjects affected / exposed                           | 2 / 32 (6.25%)                      | 0 / 31 (0.00%)                      |  |
| occurrences (all)                                     | 2                                   | 0                                   |  |
| Fatigue   |                                     |                                     |  |
| subjects affected / exposed                           | 13 / 32 (40.63%)                    | 10 / 31 (32.26%)                    |  |
| occurrences (all)                                     | 18                                  | 12                                  |  |
| Oedema peripheral                                     |                                     |                                     |  |
| subjects affected / exposed                           | 3 / 32 (9.38%)                      | 1 / 31 (3.23%)                      |  |
| occurrences (all)                                     | 4                                   | 2                                   |  |
| Pyrexia   |                                     |                                     |  |

|  |                        |                        |  |
|--|------------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 2 / 32 (6.25%)<br>3    | 0 / 31 (0.00%)<br>0    |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all) | 10 / 32 (31.25%)<br>11 | 4 / 31 (12.90%)<br>4   |  |
| Dysphonia<br>subjects affected / exposed<br>occurrences (all)  | 1 / 32 (3.13%)<br>1    | 2 / 31 (6.45%)<br>2    |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)   | 3 / 32 (9.38%)<br>3    | 4 / 31 (12.90%)<br>4   |  |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all)                        | 2 / 32 (6.25%)<br>3    | 5 / 31 (16.13%)<br>7   |  |
| Investigations<br>Weight decreased<br>subjects affected / exposed<br>occurrences (all)                       | 3 / 32 (9.38%)<br>3    | 1 / 31 (3.23%)<br>1    |  |
| Injury, poisoning and procedural complications<br>Fall<br>subjects affected / exposed<br>occurrences (all)   | 0 / 32 (0.00%)<br>0    | 3 / 31 (9.68%)<br>3    |  |
| Cardiac disorders<br>Palpitations<br>subjects affected / exposed<br>occurrences (all)                        | 3 / 32 (9.38%)<br>4    | 2 / 31 (6.45%)<br>2    |  |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)                    | 5 / 32 (15.63%)<br>6   | 5 / 31 (16.13%)<br>5   |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)   | 14 / 32 (43.75%)<br>18 | 14 / 31 (45.16%)<br>19 |  |
| Hypoaesthesia  |                        |                        |  |

|  |                     |                     |  |
|--|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all) | 2 / 32 (6.25%)<br>2 | 1 / 31 (3.23%)<br>1 |  |
| Gastrointestinal disorders                       |                     |                     |  |
| Abdominal distension                             |                     |                     |  |
| subjects affected / exposed                      | 4 / 32 (12.50%)     | 2 / 31 (6.45%)      |  |
| occurrences (all)                                | 4                   | 2                   |  |
| Abdominal pain                                   |                     |                     |  |
| subjects affected / exposed                      | 1 / 32 (3.13%)      | 2 / 31 (6.45%)      |  |
| occurrences (all)                                | 1                   | 3                   |  |
| Abdominal pain upper                             |                     |                     |  |
| subjects affected / exposed                      | 1 / 32 (3.13%)      | 2 / 31 (6.45%)      |  |
| occurrences (all)                                | 2                   | 2                   |  |
| Constipation                                     |                     |                     |  |
| subjects affected / exposed                      | 5 / 32 (15.63%)     | 2 / 31 (6.45%)      |  |
| occurrences (all)                                | 6                   | 3                   |  |
| Diarrhoea  |                     |                     |  |
| subjects affected / exposed                      | 9 / 32 (28.13%)     | 10 / 31 (32.26%)    |  |
| occurrences (all)                                | 14                  | 11                  |  |
| Dry mouth  |                     |                     |  |
| subjects affected / exposed                      | 2 / 32 (6.25%)      | 0 / 31 (0.00%)      |  |
| occurrences (all)                                | 2                   | 0                   |  |
| Dyspepsia  |                     |                     |  |
| subjects affected / exposed                      | 4 / 32 (12.50%)     | 4 / 31 (12.90%)     |  |
| occurrences (all)                                | 6                   | 5                   |  |
| Flatulence                                       |                     |                     |  |
| subjects affected / exposed                      | 2 / 32 (6.25%)      | 1 / 31 (3.23%)      |  |
| occurrences (all)                                | 2                   | 1                   |  |
| Gastrooesophageal reflux disease                 |                     |                     |  |
| subjects affected / exposed                      | 6 / 32 (18.75%)     | 7 / 31 (22.58%)     |  |
| occurrences (all)                                | 7                   | 10                  |  |
| Nausea   |                     |                     |  |
| subjects affected / exposed                      | 16 / 32 (50.00%)    | 15 / 31 (48.39%)    |  |
| occurrences (all)                                | 18                  | 19                  |  |
| Stomach discomfort                               |                     |                     |  |
| subjects affected / exposed                      | 3 / 32 (9.38%)      | 4 / 31 (12.90%)     |  |
| occurrences (all)                                | 3                   | 5                   |  |

|   |                       |                       |  |
|---|-----------------------|-----------------------|--|
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                  | 9 / 32 (28.13%)<br>9  | 9 / 31 (29.03%)<br>11 |  |
| Skin and subcutaneous tissue disorders  |                       |                       |  |
| Erythema<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 32 (3.13%)<br>1   | 2 / 31 (6.45%)<br>3   |  |
| Photosensitivity reaction<br>subjects affected / exposed<br>occurrences (all) | 2 / 32 (6.25%)<br>3   | 2 / 31 (6.45%)<br>2   |  |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)                  | 4 / 32 (12.50%)<br>5  | 4 / 31 (12.90%)<br>5  |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)                      | 8 / 32 (25.00%)<br>10 | 5 / 31 (16.13%)<br>5  |  |
| Musculoskeletal and connective tissue disorders                               |                       |                       |  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)                | 5 / 32 (15.63%)<br>5  | 4 / 31 (12.90%)<br>6  |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)                 | 5 / 32 (15.63%)<br>6  | 3 / 31 (9.68%)<br>4   |  |
| Joint swelling<br>subjects affected / exposed<br>occurrences (all)            | 2 / 32 (6.25%)<br>2   | 0 / 31 (0.00%)<br>0   |  |
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all)             | 1 / 32 (3.13%)<br>1   | 2 / 31 (6.45%)<br>2   |  |
| Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all)      | 0 / 32 (0.00%)<br>0   | 2 / 31 (6.45%)<br>2   |  |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 32 (0.00%)<br>0   | 2 / 31 (6.45%)<br>2   |  |
| Pain in extremity   |                       |                       |  |



|  |                     |                     |  |
|--|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all) | 1 / 32 (3.13%)<br>1 | 2 / 31 (6.45%)<br>2 |  |
| Infections and infestations                      |                     |                     |  |
| Influenza  |                     |                     |  |
| subjects affected / exposed                      | 1 / 32 (3.13%)      | 3 / 31 (9.68%)      |  |
| occurrences (all)                                | 1                   | 3                   |  |
| Nasopharyngitis                                  |                     |                     |  |
| subjects affected / exposed                      | 3 / 32 (9.38%)      | 2 / 31 (6.45%)      |  |
| occurrences (all)                                | 3                   | 2                   |  |
| Pneumonia  |                     |                     |  |
| subjects affected / exposed                      | 2 / 32 (6.25%)      | 0 / 31 (0.00%)      |  |
| occurrences (all)                                | 2                   | 0                   |  |
| Sinusitis  |                     |                     |  |
| subjects affected / exposed                      | 0 / 32 (0.00%)      | 2 / 31 (6.45%)      |  |
| occurrences (all)                                | 0                   | 2                   |  |
| Upper respiratory tract infection                |                     |                     |  |
| subjects affected / exposed                      | 1 / 32 (3.13%)      | 3 / 31 (9.68%)      |  |
| occurrences (all)                                | 1                   | 3                   |  |
| Urinary tract infection                          |                     |                     |  |
| subjects affected / exposed                      | 0 / 32 (0.00%)      | 2 / 31 (6.45%)      |  |
| occurrences (all)                                | 0                   | 2                   |  |
| Gastroenteritis viral                            |                     |                     |  |
| subjects affected / exposed                      | 2 / 32 (6.25%)      | 0 / 31 (0.00%)      |  |
| occurrences (all)                                | 2                   | 0                   |  |
| Metabolism and nutrition disorders               |                     |                     |  |
| Anorexia   |                     |                     |  |
| subjects affected / exposed                      | 5 / 32 (15.63%)     | 2 / 31 (6.45%)      |  |
| occurrences (all)                                | 5                   | 3                   |  |
| Decreased appetite                               |                     |                     |  |
| subjects affected / exposed                      | 1 / 32 (3.13%)      | 2 / 31 (6.45%)      |  |
| occurrences (all)                                | 1                   | 2                   |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment  |
|-----------------|--|
| 21 January 2014 | This amendment was done to include a change of mycophenolate mofetil to mycophenolate which is inclusive of mycophenolate mofetil or mycophenolate acid. Additional global changes included an administrative change to clarify the Mahler Dyspnea Index includes the Baseline Dyspnea Index (BDI) in addition to the Translational Dyspnea Index (TDI) as part of it standard assessment. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported