



## Clinical trial results:

**A 52 weeks, double blind, randomized, placebo-controlled trial evaluating the effect of oral BIBF 1120, 150 mg twice daily, on annual Forced Vital Capacity decline, in patients with Idiopathic Pulmonary Fibrosis (IPF)**

### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2010-024251-87    |
| Trial protocol           | DE GB BE IE CZ IT |
| Global end of trial date | 09 October 2013   |

### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 20 June 2016   |
| First version publication date | 01 August 2015 |

### Trial information

#### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | 1199.32 |
|-----------------------|---------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01335464 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |                                                                                                                                                                                             |
|------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Boehringer Ingelheim                                                                                                                                                                        |
| Sponsor organisation address | Binger Strasse 173 , Ingelheim am Rhein , Germany,                                                                                                                                          |
| Public contact               | QRPE Processes and Systems Coordination<br>Clinical Trial Information Disclosure , Boehringer Ingelheim<br>Pharma GmbH & Co. KG, +1 800243 0127,<br>clintriage.rdg@boehringer-ingelheim.com |
| Scientific contact           | QRPE Processes and Systems Coordination<br>Clinical Trial Information Disclosure , Boehringer Ingelheim<br>Pharma GmbH & Co. KG, +1 800243 0127,<br>clintriage.rdg@boehringer-ingelheim.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**

|                                                      |                   |
|------------------------------------------------------|-------------------|
| Analysis stage                                       | Final             |
| Date of interim/final analysis                       | 21 November 2013  |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 09 September 2013 |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 09 October 2013   |
| Was the trial ended prematurely?                     | No                |

Notes:

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**General information about the trial**

Main objective of the trial:

To demonstrate a reduction of lung function decline, as measured by a change of the yearly rate of decline of forced vital capacity (FVC).

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Rescue medication was allowed for all patients as required.

Background therapy: -

Evidence for comparator: -

|                                                           |             |
|-----------------------------------------------------------|-------------|
| Actual start date of recruitment                          | 09 May 2011 |
| Long term follow-up planned                               | Yes         |
| Long term follow-up rationale                             | Safety      |
| Long term follow-up duration                              | 7 Years     |
| Independent data monitoring committee (IDMC) involvement? | Yes         |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Australia: 41      |
| Country: Number of subjects enrolled | Belgium: 34        |
| Country: Number of subjects enrolled | China: 68          |
| Country: Number of subjects enrolled | Czech Republic: 7  |
| Country: Number of subjects enrolled | France: 95         |
| Country: Number of subjects enrolled | Germany: 80        |
| Country: Number of subjects enrolled | India: 15          |
| Country: Number of subjects enrolled | Ireland: 3         |
| Country: Number of subjects enrolled | Israel: 25         |
| Country: Number of subjects enrolled | Italy: 105         |
| Country: Number of subjects enrolled | Japan: 72          |
| Country: Number of subjects enrolled | United Kingdom: 61 |
| Country: Number of subjects enrolled | United States: 112 |
| Worldwide total number of subjects   | 718                |
| EEA total number of subjects         | 385                |

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)                      | 260 |
| From 65 to 84 years                       | 452 |
| 85 years and over                         | 6   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended one specialist site which would then ensure that they (the subjects) met all inclusion/exclusion criteria. Subjects were not to be randomised to trial treatment if any one of the specific entry criteria were violated.

### Period 1

|                              |                                   |
|------------------------------|-----------------------------------|
| Period 1 title               | Treatment period (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>             | Placebo |

Arm description:

Oral administration of placebo matching nintedanib soft gelatine capsules

Two patients were randomised to the placebo arm, however those two patients were not treated. Consequently, number of subjects that started is 206 but only 204 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.

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

Dosage and administration details:

Oral administration of placebo matching nintedanib soft gelatine capsules twice daily (bid)

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | Nintedanib 150mg |
|------------------|------------------|

Arm description:

Oral administration of soft gelatine capsules of nintedanib 150mg twice daily (bid).

Dose interruption and reduction to 100 mg bid dose were allowed to manage adverse events.

|                                        |                  |
|----------------------------------------|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | Nintedanib 150mg |
| Investigational medicinal product code |                  |
| Other name                             |                  |
| Pharmaceutical forms                   | Capsule, soft    |
| Routes of administration               | Oral use         |

Dosage and administration details:

Oral administration of soft gelatine capsules of nintedanib 150mg twice daily (bid).

In case of lack of tolerability of Nintedanib 150mg bid, the dose could have been reduced to 100mg bid.

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Placebo | Nintedanib 150mg |
|-----------------------------------------------------|---------|------------------|
| Started                                             | 204     | 309              |
| Completed                                           | 174     | 260              |
| Not completed                                       | 30      | 49               |
| Adverse event, serious fatal                        | 10      | 9                |
| Consent withdrawn by subject                        | 12      | 23               |
| Reason other than those stated above                | 1       | 1                |
| Adverse event, non-fatal                            | 5       | 16               |
| Protocol deviation                                  | 2       | -                |

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Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one of the trial medication.

## Baseline characteristics

### Reporting groups

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

Reporting group description:

Oral administration of placebo matching nintedanib soft gelatine capsules

Two patients were randomised to the placebo arm, however those two patients were not treated. Consequently, number of subjects that started is 206 but only 204 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Nintedanib 150mg |
|-----------------------|------------------|

Reporting group description:

Oral administration of soft gelatine capsules of nintedanib 150mg twice daily (bid).

Dose interruption and reduction to 100 mg bid dose were allowed to manage adverse events.

| Reporting group values | Placebo | Nintedanib 150mg | Total |
|------------------------|---------|------------------|-------|
| Number of subjects     | 204     | 309              | 513   |
| Age categorical        |         |                  |       |
| Units: Subjects        |         |                  |       |

|                                                                                                                                                                                |       |       |     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|-------|-----|
| Age continuous                                                                                                                                                                 |       |       |     |
| Treated set (TS): The TS consisted of randomised patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment |       |       |     |
| Units: years                                                                                                                                                                   |       |       |     |
| arithmetic mean                                                                                                                                                                | 66.9  | 66.9  |     |
| standard deviation                                                                                                                                                             | ± 8.2 | ± 8.4 | -   |
| Gender categorical                                                                                                                                                             |       |       |     |
| Treated set (TS): The TS consisted of randomised patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment |       |       |     |
| Units: Subjects                                                                                                                                                                |       |       |     |
| Female                                                                                                                                                                         | 41    | 58    | 99  |
| Male                                                                                                                                                                           | 163   | 251   | 414 |

## End points

### End points reporting groups

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

Reporting group description:

Oral administration of placebo matching nintedanib soft gelatine capsules

Two patients were randomised to the placebo arm, however those two patients were not treated. Consequently, number of subjects that started is 206 but only 204 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Nintedanib 150mg |
|-----------------------|------------------|

Reporting group description:

Oral administration of soft gelatine capsules of nintedanib 150mg twice daily (bid).

Dose interruption and reduction to 100 mg bid dose were allowed to manage adverse events.

### Primary: Annual Rate of Decline in Forced Vital Capacity (FVC) Over 52 Weeks

|                 |                                                                     |
|-----------------|---------------------------------------------------------------------|
| End point title | Annual Rate of Decline in Forced Vital Capacity (FVC) Over 52 Weeks |
|-----------------|---------------------------------------------------------------------|

End point description:

Forced vital capacity (FVC) is the total amount of air exhaled during the lung function test. The reported mean represents the adjusted rate.

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

End point timeframe:

52 weeks

| End point values                 | Placebo            | Nintedanib 150mg   |  |  |
|----------------------------------|--------------------|--------------------|--|--|
| Subject group type               | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed      | 204 <sup>[1]</sup> | 309 <sup>[2]</sup> |  |  |
| Units: mL/year                   |                    |                    |  |  |
| arithmetic mean (standard error) | -239.91 (± 18.709) | -114.65 (± 15.327) |  |  |

Notes:

[1] - TS (Only patients with observed cases (OC) values were analysed)

[2] - TS (Only patients with observed cases (OC) values were analysed)

### Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Random coefficient regression with fixed effects for treatment, gender, age, height and random effect of patient specific intercept and time. A hierarchical procedure was used in order to demonstrate the superiority of nintedanib over placebo for the primary and two key secondary endpoints. The consecutive steps of the hierarchy were only considered if the previous step was significant at the one-sided 2.5% level and the results were in favour of nintedanib.

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Comparison groups                       | Placebo v Nintedanib 150mg     |
| Number of subjects included in analysis | 513                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[3]</sup>     |
| P-value                                 | < 0.0001                       |
| Method                                  | Random coefficient regression  |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 125.26                         |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 77.68                          |
| upper limit                             | 172.84                         |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 24.209                         |

Notes:

[3] - Nintedanib 150 mg bid versus Placebo

The Roger-Kenward approximation was used to estimate denominators degrees of freedom.

Within-patient errors are modeled by an Unstructured variance-covariance matrix.

Inter-individual variability is modelled by a Variance-components variance-covariance matrix.

### Secondary: Change From Baseline in Saint George's Respiratory Questionnaire (SGRQ) Total Score at 52 Weeks

|                 |                                                                                                 |
|-----------------|-------------------------------------------------------------------------------------------------|
| End point title | Change From Baseline in Saint George's Respiratory Questionnaire (SGRQ) Total Score at 52 Weeks |
|-----------------|-------------------------------------------------------------------------------------------------|

End point description:

This is a key secondary endpoint.

SGRQ is a health-related quality of life questionnaire divided into 3 components : symptoms, activity and impact.

The total score (summed weights) can range from 0 to 100 with a lower score denoting a better health status.

Means provided are the adjusted means based on all analyzed patients in the model (not only patients with a baseline and measurement at week 52).

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

End point timeframe:

baseline and 52 weeks

| End point values                 | Placebo            | Nintedanib 150mg   |  |  |
|----------------------------------|--------------------|--------------------|--|--|
| Subject group type               | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed      | 200 <sup>[4]</sup> | 289 <sup>[5]</sup> |  |  |
| Units: points on a scale         |                    |                    |  |  |
| arithmetic mean (standard error) | 4.39 (± 0.96)      | 4.34 (± 0.799)     |  |  |

Notes:

[4] - TS (Only patients with observed cases (OC) values were analysed)

[5] - TS (Only patients with observed cases (OC) values were analysed)

### Statistical analyses

|                                                                                                                                                                                                     |                                |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                   | Statistical Analysis 1         |
| Statistical analysis description:                                                                                                                                                                   |                                |
| Mixed Model for Repeated Measures (MMRM), with fixed effects for treatment, visit, treatment-by-visit, baseline SGRQ Total score, baseline SGRQ Total score by-visit and random effect for patient. |                                |
| Comparison groups                                                                                                                                                                                   | Placebo v Nintedanib 150mg     |
| Number of subjects included in analysis                                                                                                                                                             | 489                            |
| Analysis specification                                                                                                                                                                              | Pre-specified                  |
| Analysis type                                                                                                                                                                                       | superiority <sup>[6]</sup>     |
| P-value                                                                                                                                                                                             | = 0.9657                       |
| Method                                                                                                                                                                                              | Mixed models analysis          |
| Parameter estimate                                                                                                                                                                                  | Mean difference (final values) |
| Point estimate                                                                                                                                                                                      | -0.05                          |
| Confidence interval                                                                                                                                                                                 |                                |
| level                                                                                                                                                                                               | 95 %                           |
| sides                                                                                                                                                                                               | 2-sided                        |
| lower limit                                                                                                                                                                                         | -2.5                           |
| upper limit                                                                                                                                                                                         | 2.4                            |
| Variability estimate                                                                                                                                                                                | Standard error of the mean     |
| Dispersion value                                                                                                                                                                                    | 1.248                          |

Notes:

[6] - Nintedanib 150 mg bid versus Placebo.

Within-patient errors were modelled by compound symmetry covariance matrix.

## Secondary: Absolute Change From Baseline in FVC Over 52 weeks

|                                                                                                                                                                 |                                                    |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|
| End point title                                                                                                                                                 | Absolute Change From Baseline in FVC Over 52 weeks |
| End point description:                                                                                                                                          |                                                    |
| Absolute Change From Baseline in Forced Vital Capacity (FVC) Over 52 weeks.                                                                                     |                                                    |
| Means provided are the adjusted means. Adjusted mean is based on all analysed patients in the model (not only patients with a change from baseline to week 52). |                                                    |
| End point type                                                                                                                                                  | Secondary                                          |
| End point timeframe:                                                                                                                                            |                                                    |
| Baseline and 52 weeks                                                                                                                                           |                                                    |

| End point values                 | Placebo            | Nintedanib 150mg   |  |  |
|----------------------------------|--------------------|--------------------|--|--|
| Subject group type               | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed      | 204 <sup>[7]</sup> | 307 <sup>[8]</sup> |  |  |
| Units: mL                        |                    |                    |  |  |
| arithmetic mean (standard error) | -205 (± 16.544)    | -95.07 (± 14.375)  |  |  |

Notes:

[7] - TS (Only patients with observed cases (OC) values were analysed)

[8] - TS (Only patients with observed cases (OC) values were analysed)

## Statistical analyses

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical Analysis 1 |
|-----------------------------------|------------------------|

Statistical analysis description:

Based on Mixed Model for Repeated Measures (MMRM), with fixed effects for treatment, visit, gender, age, height, treatment-by-visit, baseline FVC, baseline FVC-by visit and random effect for patient.

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Comparison groups                       | Placebo v Nintedanib 150mg     |
| Number of subjects included in analysis | 511                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[9]</sup>     |
| P-value                                 | < 0.0001                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 109.93                         |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 71.27                          |
| upper limit                             | 148.59                         |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 19.708                         |

Notes:

[9] - Nintedanib 150 mg bid versus Placebo

Within-patient errors are modelled by compound symmetry covariance matrix

### Secondary: Absolute Change From Baseline in FVC (% predicted) over 52 weeks

|                                                                                                                                                                 |                                                                  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------|
| End point title                                                                                                                                                 | Absolute Change From Baseline in FVC (% predicted) over 52 weeks |
| End point description:                                                                                                                                          |                                                                  |
| Means provided are the adjusted means. Adjusted mean is based on all analysed patients in the model (not only patients with a change from baseline to week 52). |                                                                  |
| End point type                                                                                                                                                  | Secondary                                                        |
| End point timeframe:                                                                                                                                            |                                                                  |
| Baseline and 52 weeks                                                                                                                                           |                                                                  |

| End point values                 | Placebo             | Nintedanib 150mg    |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 204 <sup>[10]</sup> | 307 <sup>[11]</sup> |  |  |
| Units: %predicted                |                     |                     |  |  |
| arithmetic mean (standard error) | -5.98 (± 0.474)     | -2.76 (± 0.408)     |  |  |

Notes:

[10] - TS (Only patients with observed cases (OC) values were analysed)

[11] - TS (Only patients with observed cases (OC) values were analysed)

### Statistical analyses

|                                                                                                                                                                                                                                   |                            |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|
| Statistical analysis title                                                                                                                                                                                                        | Statistical Analysis 1     |
| Statistical analysis description:                                                                                                                                                                                                 |                            |
| Based on Mixed Model for Repeated Measures (MMRM), with fixed effects for treatment, visit, gender, age, height, treatment-by-visit, baseline FVC [%predicted], baseline FVC [%predicted]-by-visit and random effect for patient. |                            |
| Comparison groups                                                                                                                                                                                                                 | Placebo v Nintedanib 150mg |

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Number of subjects included in analysis | 511                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[12]</sup>    |
| P-value                                 | < 0.0001                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 3.22                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 2.11                           |
| upper limit                             | 4.33                           |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 0.564                          |

Notes:

[12] - Nintedanib 150 mg bid versus Placebo.

Within-patient errors are modelled by compound symmetry covariance matrix.

### Secondary: Absolute Categorical Change of FVC (% Predicted) - 5% Threshold

|                 |                                                                 |
|-----------------|-----------------------------------------------------------------|
| End point title | Absolute Categorical Change of FVC (% Predicted) - 5% Threshold |
|-----------------|-----------------------------------------------------------------|

End point description:

Absolute categorical change of FVC (% predicted) by categories at 52 weeks - 5% threshold (decrease by >5%, increase by >5%, and change within ≤5%).

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

End point timeframe:

Baseline and 52 weeks

| End point values                  | Placebo             | Nintedanib 150mg    |  |  |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type                | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed       | 165 <sup>[13]</sup> | 250 <sup>[14]</sup> |  |  |
| Units: percentage of participants |                     |                     |  |  |
| number (not applicable)           |                     |                     |  |  |
| Decrease > 5%                     | 52.7                | 34.8                |  |  |
| Change within ≤ 5%                | 41.2                | 54                  |  |  |
| Increase > 5%                     | 6.1                 | 11.2                |  |  |

Notes:

[13] - Treated Set (for patients with change from baseline in FVC (%predicted) at Week 52)

[14] - Treated Set (for patients with change from baseline in FVC (%predicted) at Week 52)

### Statistical analyses

No statistical analyses for this end point

### Secondary: Absolute Categorical Change of FVC (% Predicted) - 10% Threshold

|                 |                                                                  |
|-----------------|------------------------------------------------------------------|
| End point title | Absolute Categorical Change of FVC (% Predicted) - 10% Threshold |
|-----------------|------------------------------------------------------------------|

End point description:

Absolute categorical change of FVC (% predicted) by categories at 52 weeks - 10% threshold (decrease by > 10%, increase by >10%, and change

within  $\leq 10\%$ .

|                       |           |
|-----------------------|-----------|
| End point type        | Secondary |
| End point timeframe:  |           |
| Baseline and 52 weeks |           |

| End point values                  | Placebo             | Nintedanib<br>150mg |  |  |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type                | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed       | 165 <sup>[15]</sup> | 250 <sup>[16]</sup> |  |  |
| Units: percentage of participants |                     |                     |  |  |
| number (not applicable)           |                     |                     |  |  |
| Decrease > 10%                    | 29.7                | 12.8                |  |  |
| Change within $\leq 10\%$         | 69.1                | 84.4                |  |  |
| Increase > 10%                    | 1.2                 | 2.8                 |  |  |

Notes:

[15] - Treated Set (for patients with change from baseline in FVC (%predicted) at Week 52)

[16] - Treated Set (for patients with change from baseline in FVC (%predicted) at Week 52)

### Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of SGRQ Responders at 52 Weeks: Patient Reported Outcomes (PROs)

|                 |                                                                             |
|-----------------|-----------------------------------------------------------------------------|
| End point title | Proportion of SGRQ Responders at 52 Weeks: Patient Reported Outcomes (PROs) |
|-----------------|-----------------------------------------------------------------------------|

End point description:

Proportion of SGRQ Responders at 52 Weeks.

Responders defined as  $\leq -4$  points change in change from baseline in SGRQ total score at 52 weeks.

|                       |           |
|-----------------------|-----------|
| End point type        | Secondary |
| End point timeframe:  |           |
| Baseline and 52 weeks |           |

| End point values                  | Placebo                | Nintedanib<br>150mg    |  |  |
|-----------------------------------|------------------------|------------------------|--|--|
| Subject group type                | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed       | 204 <sup>[17]</sup>    | 309 <sup>[18]</sup>    |  |  |
| Units: percentage of participants |                        |                        |  |  |
| number (confidence interval 95%)  | 24.02 (18.67 to 30.33) | 20.39 (16.27 to 25.23) |  |  |

Notes:

[17] - Treated Set (Only patients with observed cases (OC) values were analysed)

[18] - Treated Set (Only patients with observed cases (OC) values were analysed)

### Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

|                                                                     |                             |
|---------------------------------------------------------------------|-----------------------------|
| Statistical analysis description:                                   |                             |
| Logistic regression with terms treatment, baseline SGRQ total score |                             |
| Comparison groups                                                   | Placebo v Nintedanib 150mg  |
| Number of subjects included in analysis                             | 513                         |
| Analysis specification                                              | Pre-specified               |
| Analysis type                                                       | superiority <sup>[19]</sup> |
| P-value                                                             | = 0.4298                    |
| Method                                                              | Regression, Logistic        |
| Parameter estimate                                                  | Odds ratio (OR)             |
| Point estimate                                                      | 0.84                        |
| Confidence interval                                                 |                             |
| level                                                               | 95 %                        |
| sides                                                               | 2-sided                     |
| lower limit                                                         | 0.55                        |
| upper limit                                                         | 1.29                        |

Notes:

[19] - Nintedanib 150 mg bid versus Placebo

## Secondary: Change From Baseline in SGRQ Symptom Score at 52 Weeks: Patient Reported Outcomes (PROs)

|                 |                                                                                          |
|-----------------|------------------------------------------------------------------------------------------|
| End point title | Change From Baseline in SGRQ Symptom Score at 52 Weeks: Patient Reported Outcomes (PROs) |
|-----------------|------------------------------------------------------------------------------------------|

End point description:

SGRQ Symptom score is a sub-component of SGRQ total score and is concerned with the effect of respiratory symptoms, their frequency and severity. This score calculated as summed weights ranges from 0 to 100 with lower score denoting a better symptom-related quality of life.

Means presented are the adjusted means and are based on all analyzed patients in the model (not only patients with a baseline and measurement at week 52).

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

End point timeframe:

Baseline and 52 weeks

| End point values                 | Placebo             | Nintedanib 150mg    |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 202 <sup>[20]</sup> | 300 <sup>[21]</sup> |  |  |
| Units: points on a scale         |                     |                     |  |  |
| arithmetic mean (standard error) | 3.89 (± 1.351)      | 1.56 (± 1.104)      |  |  |

Notes:

[20] - Treated Set (Only patients with observed cases (OC) values were analysed)

[21] - Treated Set (Only patients with observed cases (OC) values were analysed)

## Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Mixed Model for Repeated Measures (MMRM), with fixed effects for treatment, visit treatment-by-visit, baseline SGRQ Symptoms component, baseline SGRQ Symptoms component-by-visit and random effect for patient.

|                   |                            |
|-------------------|----------------------------|
| Comparison groups | Nintedanib 150mg v Placebo |
|-------------------|----------------------------|

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Number of subjects included in analysis | 502                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[22]</sup>    |
| P-value                                 | = 0.1832                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -2.32                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -5.74                          |
| upper limit                             | 1.1                            |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 1.744                          |

Notes:

[22] - Nintedanib 150 mg bid versus Placebo.

Within-patient errors are modelled by compound symmetry covariance matrix.

## Secondary: Change From Baseline in SGRQ Impact Score at 52 Weeks: Patient Reported Outcomes (PROs)

|                                                                                                                                                                                                                                                                                                                        |                                                                                         |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                        | Change From Baseline in SGRQ Impact Score at 52 Weeks: Patient Reported Outcomes (PROs) |
| End point description:                                                                                                                                                                                                                                                                                                 |                                                                                         |
| SGRQ Impact score is a sub-component of SGRQ total score and covers a range of aspects concerned with social functioning and psychological disturbances resulting from airway disease. This score calculated as summed weights ranges from 0 to 100 with lower score denoting a better impact-related quality of life. |                                                                                         |
| End point type                                                                                                                                                                                                                                                                                                         | Secondary                                                                               |
| End point timeframe:                                                                                                                                                                                                                                                                                                   |                                                                                         |
| baseline and 52 weeks                                                                                                                                                                                                                                                                                                  |                                                                                         |

| End point values                 | Placebo             | Nintedanib 150mg    |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 202 <sup>[23]</sup> | 291 <sup>[24]</sup> |  |  |
| Units: points on a scale         |                     |                     |  |  |
| arithmetic mean (standard error) | 4.01 (± 1.113)      | 4.87 (± 0.923)      |  |  |

Notes:

[23] - Treated Set (Only patients with observed cases (OC) values were analysed)

[24] - Treated Set (Only patients with observed cases (OC) values were analysed)

## Statistical analyses

|                                                                                                                                                                                                               |                            |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|
| Statistical analysis title                                                                                                                                                                                    | Statistical Analysis 1     |
| Statistical analysis description:                                                                                                                                                                             |                            |
| Mixed Model for Repeated Measures (MMRM), with fixed effects for treatment, visit, treatment-by-visit, baseline SGRQ impact component, baseline SGRQ Impact component-by-visit and random effect for patient. |                            |
| Comparison groups                                                                                                                                                                                             | Placebo v Nintedanib 150mg |

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Number of subjects included in analysis | 493                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[25]</sup>    |
| P-value                                 | = 0.551                        |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 0.86                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -1.97                          |
| upper limit                             | 3.7                            |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 1.446                          |

Notes:

[25] - Nintedanib 150 mg bid versus Placebo.

Within-patient errors are modelled by compound symmetry covariance matrix

## Secondary: Change From Baseline in SGRQ Activity Score at 52 Weeks: Patient Reported Outcomes (PROs)

|                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                           |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                    | Change From Baseline in SGRQ Activity Score at 52 Weeks: Patient Reported Outcomes (PROs) |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                           |
| SGRQ Activity score is a sub-component of SGRQ total score and concerned with activities that cause or are limited by breathlessness. This score calculated as summed weights ranges from 0 to 100 with lower score denoting a better activity-related quality of life. Means presented are the adjusted means and are based on all analyzed patients in the model (not only patients with a baseline and measurement at week 52). |                                                                                           |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                     | Secondary                                                                                 |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                           |
| baseline and 52 weeks                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                           |

| End point values                 | Placebo             | Nintedanib 150mg    |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 200 <sup>[26]</sup> | 295 <sup>[27]</sup> |  |  |
| Units: points on scale           |                     |                     |  |  |
| arithmetic mean (standard error) | 5.81 (± 1.103)      | 4.62 (± 0.906)      |  |  |

Notes:

[26] - Treated Set (Only patients with observed cases (OC) values were analysed)

[27] - Treated Set (Only patients with observed cases (OC) values were analysed)

## Statistical analyses

|                                                                                                                                                                                                                      |                            |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|
| Statistical analysis title                                                                                                                                                                                           | Statistical Analysis 1     |
| Statistical analysis description:                                                                                                                                                                                    |                            |
| Mixed Model for Repeated Measures (MMRM), with fixed effects for treatment, visit, treatment-by-visit, baseline SGRQ Activities component, baseline SGRQ Activities component-by-visit and random effect for patient |                            |
| Comparison groups                                                                                                                                                                                                    | Placebo v Nintedanib 150mg |

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Number of subjects included in analysis | 495                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[28]</sup>    |
| P-value                                 | = 0.4049                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -1.19                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -3.99                          |
| upper limit                             | 1.61                           |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 1.427                          |

Notes:

[28] - Nintedanib 150 mg bid versus Placebo.

Within-patient errors are modelled by compound symmetry covariance matrix.

### **Secondary: Change From Baseline in Idiopathic Pulmonary Fibrosis (IPF) Specific Version of SGRQ (SGRQ-I) Total Score at 52 Weeks: Patient Reported Outcomes (PROs)**

|                 |                                                                                                                                                         |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Change From Baseline in Idiopathic Pulmonary Fibrosis (IPF) Specific Version of SGRQ (SGRQ-I) Total Score at 52 Weeks: Patient Reported Outcomes (PROs) |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

SGRQ-I is the IPF specific version of SGRQ comprises of selected items from the SGRQ divided into three components, Symptoms, Activity and

Impact. Each component is scored separately. The weights for all items with a positive responses are summed and the weights from missed items are deducted from the maximum possible weight for the total score.

The total score is calculated by dividing the summed weights from positive items in the questionnaire by maximum possible weight for all items in the questionnaire. The total score can range from 0 to 100 with a lower score denoting a better health-related quality of life. Change from baseline is calculated as the difference between total score at week 52 and total score at baseline as measured by the scale.

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

End point timeframe:

Baseline and 52 weeks

| <b>End point values</b>          | Placebo             | Nintedanib 150mg    |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 200 <sup>[29]</sup> | 290 <sup>[30]</sup> |  |  |
| Units: points on a scale         |                     |                     |  |  |
| arithmetic mean (standard error) | 5.08 (± 0.992)      | 4.3 (± 0.824)       |  |  |

Notes:

[29] - Treated Set (Only patients with observed cases (OC) values were analysed)

[30] - Treated Set (Only patients with observed cases (OC) values were analysed)

### **Statistical analyses**

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical Analysis 1 |
|-----------------------------------|------------------------|

Statistical analysis description:

Mixed Model for Repeated Measures (MMRM), with fixed effects for treatment, visit,

treatment-by-visit, baseline SGRQ-I Total score, baseline SGRQ-I Total score-by-visit and random effect for patient.

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Comparison groups                       | Placebo v Nintedanib 150mg     |
| Number of subjects included in analysis | 490                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[31]</sup>    |
| P-value                                 | = 0.5446                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -0.78                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -3.31                          |
| upper limit                             | 1.75                           |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 1.289                          |

Notes:

[31] - Nintedanib 150mg versus placebo.

Within-patient errors are modelled by compound symmetry covariance matrix.

### Secondary: Change From Baseline in Shortness of Breath Questionnaire (SOBQ) at 52 Weeks: Patient Reported Outcomes (PROs)

|                 |                                                                                                                |
|-----------------|----------------------------------------------------------------------------------------------------------------|
| End point title | Change From Baseline in Shortness of Breath Questionnaire (SOBQ) at 52 Weeks: Patient Reported Outcomes (PROs) |
|-----------------|----------------------------------------------------------------------------------------------------------------|

End point description:

Shortness of Breath Questionnaire measures the shortness of breath. It comprises of 24 items. Each item is scored on a scale between 0-5 where 5 represents maximal breathlessness. The responses to all items are summed up to provide the overall score that can range from 0 (best outcome) to 120 (worst outcome).

Means presented are the adjusted means and are based on all analyzed patients in the model (not only patients with a baseline and measurement at week 52).

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

End point timeframe:

baseline and 52 weeks

| End point values                 | Placebo             | Nintedanib 150mg    |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 178 <sup>[32]</sup> | 267 <sup>[33]</sup> |  |  |
| Units: points on a scale         |                     |                     |  |  |
| arithmetic mean (standard error) | 7.61 (± 1.376)      | 6.73 (± 1.113)      |  |  |

Notes:

[32] - Treated Set (Only patients with observed cases (OC) values were analysed)

[33] - Treated Set (Only patients with observed cases (OC) values were analysed)

### Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Mixed Model for Repeated Measures (MMRM), with fixed effects for treatment, visit, treatment-by-visit, baseline SOBQ score, baseline SOBQ score-by-visit and random

effect for patient.

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Comparison groups                       | Placebo v Nintedanib 150mg     |
| Number of subjects included in analysis | 445                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[34]</sup>    |
| P-value                                 | = 0.6203                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -0.88                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -4.35                          |
| upper limit                             | 2.6                            |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 1.77                           |

Notes:

[34] - Nintedanib 150mg versus placebo.

Within-patient errors are modelled by compound symmetry covariance matrix.

---

### **Secondary: Change From Baseline in Cough Symptoms Score of the Cough and Sputum Assessment Questionnaire (CASA-Q) Score at 52 Weeks: Patient Reported Outcomes (PROs)**

|                 |                                                                                                                                                            |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Change From Baseline in Cough Symptoms Score of the Cough and Sputum Assessment Questionnaire (CASA-Q) Score at 52 Weeks: Patient Reported Outcomes (PROs) |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The cough domains of the Cough and Sputum Assessment Questionnaire (CASAQ(CD)) assess the frequency and severity of cough and sputum and their impact on everyday life. It contains 4 domains cough/sputum symptom and impact with each scale ranging from 0 to 100 with lower scores indicating higher symptoms/impact levels (worst outcome). Means presented are the adjusted means and are based on all analyzed patients in the model (not only patients with a baseline and measurement at week 52).

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

End point timeframe:

Baseline and 52 weeks

| <b>End point values</b>          | Placebo             | Nintedanib 150mg    |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 202 <sup>[35]</sup> | 302 <sup>[36]</sup> |  |  |
| Units: points on a scale         |                     |                     |  |  |
| arithmetic mean (standard error) | -0.52 (± 1.4)       | -0.76 (± 1.136)     |  |  |

Notes:

[35] - Treated Set (Only patients with observed cases (OC) values were analysed)

[36] - Treated Set (Only patients with observed cases (OC) values were analysed)

### **Statistical analyses**

|                                                                                                                                                                                                                                                                |                                |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                              | Statistical Analysis 1         |
| Statistical analysis description:<br>Mixed Model for Repeated Measures (MMRM), with fixed effects for treatment, visit, treatment-by-visit, baseline CASA-Q Cough symptoms score, baseline CASA-Q Cough symptoms score-by-visit and random effect for patient. |                                |
| Comparison groups                                                                                                                                                                                                                                              | Placebo v Nintedanib 150mg     |
| Number of subjects included in analysis                                                                                                                                                                                                                        | 504                            |
| Analysis specification                                                                                                                                                                                                                                         | Pre-specified                  |
| Analysis type                                                                                                                                                                                                                                                  | superiority <sup>[37]</sup>    |
| P-value                                                                                                                                                                                                                                                        | = 0.8942                       |
| Method                                                                                                                                                                                                                                                         | Mixed models analysis          |
| Parameter estimate                                                                                                                                                                                                                                             | Mean difference (final values) |
| Point estimate                                                                                                                                                                                                                                                 | -0.24                          |
| Confidence interval                                                                                                                                                                                                                                            |                                |
| level                                                                                                                                                                                                                                                          | 95 %                           |
| sides                                                                                                                                                                                                                                                          | 2-sided                        |
| lower limit                                                                                                                                                                                                                                                    | -3.78                          |
| upper limit                                                                                                                                                                                                                                                    | 3.3                            |
| Variability estimate                                                                                                                                                                                                                                           | Standard error of the mean     |
| Dispersion value                                                                                                                                                                                                                                               | 1.803                          |

Notes:

[37] - Nintedanib 150 mg versus Placebo.

Within- patient errors are modelled by compound symmetry covariance matrix.

### **Secondary: Change From Baseline in Cough Impact Score of the Cough and Sputum Assessment Questionnaire (CASA-Q) Score at 52 Weeks: Patient Reported Outcomes (PROs)**

|                 |                                                                                                                                                          |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Change From Baseline in Cough Impact Score of the Cough and Sputum Assessment Questionnaire (CASA-Q) Score at 52 Weeks: Patient Reported Outcomes (PROs) |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The cough domains of the Cough and Sputum Assessment Questionnaire (CASA-Q) assess the frequency and severity of cough and sputum and their impact on everyday life. It contains 4 domains cough/sputum symptom and impact with each scale ranging from 0 to 100 with lower scores indicating higher symptoms/impact levels (worst outcome).

Means presented are the adjusted means and are based on all analyzed patients in the model (not only patients with a baseline and measurement at week 52).

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

End point timeframe:

Baseline and 52 weeks

| <b>End point values</b>          | Placebo             | Nintedanib 150mg    |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 202 <sup>[38]</sup> | 302 <sup>[39]</sup> |  |  |
| Units: points on a scale         |                     |                     |  |  |
| arithmetic mean (standard error) | -4 (± 1.24)         | -2.36 (± 1.006)     |  |  |

Notes:

[38] - Treated Set (Only patients with observed cases (OC) values were analysed)

[39] - Treated Set (Only patients with observed cases (OC) values were analysed)

## Statistical analyses

|                                                                                                                                                                                                                                                            |                                |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                          | Statistical Analysis 1         |
| Statistical analysis description:<br>Mixed Model for Repeated Measures (MMRM), with fixed effects for treatment, visit, treatment-by-visit, baseline CASA-Q Cough impact score, baseline CASA-Q Cough impact score-by-visit and random effect for patient. |                                |
| Comparison groups                                                                                                                                                                                                                                          | Placebo v Nintedanib 150mg     |
| Number of subjects included in analysis                                                                                                                                                                                                                    | 504                            |
| Analysis specification                                                                                                                                                                                                                                     | Pre-specified                  |
| Analysis type                                                                                                                                                                                                                                              | superiority <sup>[40]</sup>    |
| P-value                                                                                                                                                                                                                                                    | = 0.3042                       |
| Method                                                                                                                                                                                                                                                     | Mixed models analysis          |
| Parameter estimate                                                                                                                                                                                                                                         | Mean difference (final values) |
| Point estimate                                                                                                                                                                                                                                             | 1.64                           |
| Confidence interval                                                                                                                                                                                                                                        |                                |
| level                                                                                                                                                                                                                                                      | 95 %                           |
| sides                                                                                                                                                                                                                                                      | 2-sided                        |
| lower limit                                                                                                                                                                                                                                                | -1.49                          |
| upper limit                                                                                                                                                                                                                                                | 4.77                           |
| Variability estimate                                                                                                                                                                                                                                       | Standard error of the mean     |
| Dispersion value                                                                                                                                                                                                                                           | 1.596                          |

Notes:

[40] - Nintedanib 150 mg versus Placebo.

Within-patient errors are modelled by compound symmetry covariance matrix.

## Secondary: Proportion of Patient's Global Impression of Change (PGI-C) Responders at 52 Weeks: Patient Reported Outcomes (PROs)

|                                                                                                                                                                                                            |                                                                                                                      |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                            | Proportion of Patient's Global Impression of Change (PGI-C) Responders at 52 Weeks: Patient Reported Outcomes (PROs) |
| End point description:<br>Proportion of Patient's Global Impression of Change (PGI-C) responders at 52 weeks. Responders are defined as 'Very much better'/ 'Much better'/ 'A little better'/ 'No change'. |                                                                                                                      |
| End point type                                                                                                                                                                                             | Secondary                                                                                                            |
| End point timeframe:<br>52 weeks                                                                                                                                                                           |                                                                                                                      |

|                                   |                       |                       |  |  |
|-----------------------------------|-----------------------|-----------------------|--|--|
| <b>End point values</b>           | Placebo               | Nintedanib 150mg      |  |  |
| Subject group type                | Reporting group       | Reporting group       |  |  |
| Number of subjects analysed       | 204 <sup>[41]</sup>   | 309 <sup>[42]</sup>   |  |  |
| Units: percentage of participants |                       |                       |  |  |
| number (confidence interval 95%)  | 54.9 (48.05 to 61.58) | 60.84 (55.3 to 66.12) |  |  |

Notes:

[41] - Treated Set (Only patients with observed cases (OC) values were analysed)

[42] - Treated Set (Only patients with observed cases (OC) values were analysed)

## Statistical analyses

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical Analysis 1 |
|-----------------------------------|------------------------|

|                                         |                             |
|-----------------------------------------|-----------------------------|
| Statistical analysis description:       |                             |
| Logistic regression with term treatment |                             |
| Comparison groups                       | Placebo v Nintedanib 150mg  |
| Number of subjects included in analysis | 513                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[43]</sup> |
| P-value                                 | = 0.1818                    |
| Method                                  | Regression, Logistic        |
| Parameter estimate                      | Odds ratio (OR)             |
| Point estimate                          | 1.276                       |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 0.89                        |
| upper limit                             | 1.83                        |

Notes:

[43] - Nintedanib 150mg versus placebo

## Secondary: Time to Death Over 52 Weeks

|                                                                                                                                                                                                                                                |                             |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| End point title                                                                                                                                                                                                                                | Time to Death Over 52 Weeks |
| End point description:                                                                                                                                                                                                                         |                             |
| Due to rare events, the median of time to event is not calculable, thus the percentages of patients who did or did not experienced death before or at 372 days after randomisation or last contact date (whichever occurs first) are reported. |                             |
| Failure is the proportion of patients who died over 52 weeks (up to 372 days after randomisation).                                                                                                                                             |                             |
| End point type                                                                                                                                                                                                                                 | Secondary                   |
| End point timeframe:                                                                                                                                                                                                                           |                             |
| 0-52 weeks                                                                                                                                                                                                                                     |                             |

| End point values                  | Placebo             | Nintedanib 150mg    |  |  |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type                | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed       | 204 <sup>[44]</sup> | 309 <sup>[45]</sup> |  |  |
| Units: percentage of participants |                     |                     |  |  |
| number (not applicable)           |                     |                     |  |  |
| Failure                           | 6.4                 | 4.2                 |  |  |
| Censored                          | 93.6                | 95.8                |  |  |

Notes:

[44] - Treated Set (Only patients with observed cases (OC) values were analysed)

[45] - Treated Set (Only patients with observed cases (OC) values were analysed)

## Statistical analyses

|                                                                                                    |                            |
|----------------------------------------------------------------------------------------------------|----------------------------|
| Statistical analysis title                                                                         | Statistical Analysis 1     |
| Statistical analysis description:                                                                  |                            |
| Hazard ratio is based on Cox 's regression model with terms for treatment, gender, age and height. |                            |
| Comparison groups                                                                                  | Placebo v Nintedanib 150mg |

|                                         |                             |
|-----------------------------------------|-----------------------------|
| Number of subjects included in analysis | 513                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[46]</sup> |
| P-value                                 | = 0.288                     |
| Method                                  | Logrank                     |
| Parameter estimate                      | Hazard ratio (HR)           |
| Point estimate                          | 0.63                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 0.29                        |
| upper limit                             | 1.36                        |

Notes:

[46] - Nintedanib 150mg versus Placebo.

## Secondary: Time to Death Due to Respiratory Cause Over 52 Weeks (Adjudicated)

|                 |                                                                    |
|-----------------|--------------------------------------------------------------------|
| End point title | Time to Death Due to Respiratory Cause Over 52 Weeks (Adjudicated) |
|-----------------|--------------------------------------------------------------------|

End point description:

Due to rare events, the median of time to event is not calculable, thus the percentages of participants who did or did not experienced death due to respiratory causes before or at 372 days after randomisation or last contact date (whichever occurs first) are reported.

Failure is the the proportion of patients who died due to respiratory causes over 52 weeks (up to 372 days after randomisation).

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

End point timeframe:

52 weeks

| End point values                  | Placebo             | Nintedanib 150mg    |  |  |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type                | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed       | 204 <sup>[47]</sup> | 309 <sup>[48]</sup> |  |  |
| Units: percentage of participants |                     |                     |  |  |
| number (not applicable)           |                     |                     |  |  |
| Failure                           | 4.9                 | 3.2                 |  |  |
| Censored                          | 95.1                | 96.8                |  |  |

Notes:

[47] - Treated Set (Only patients with observed cases (OC) values were analysed)

[48] - Treated Set (Only patients with observed cases (OC) values were analysed)

## Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Hazard ratio is based on Cox 's regression model with terms for treatment, gender, age and height

|                   |                            |
|-------------------|----------------------------|
| Comparison groups | Placebo v Nintedanib 150mg |
|-------------------|----------------------------|

|                                         |                             |
|-----------------------------------------|-----------------------------|
| Number of subjects included in analysis | 513                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[49]</sup> |
| P-value                                 | = 0.3515                    |
| Method                                  | Logrank                     |
| Parameter estimate                      | Hazard ratio (HR)           |
| Point estimate                          | 0.61                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 0.25                        |
| upper limit                             | 1.47                        |

Notes:

[49] - Nintedanib 150mg versus placebo

## Secondary: Time to On-treatment Death

|                                                                                                                                                                                                                                                                                                                                                                       |                            |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                       | Time to On-treatment Death |
| End point description:                                                                                                                                                                                                                                                                                                                                                |                            |
| Due to rare events, the median of time to event is not calculable, thus the percentages of participants who did or did not die before or at last trial medication intake + 28 days were censored at last trial medication intake + 28 days and reported. Failure is the the proportion of patients who died on-treatment (up to 28 days after last treatment intake). |                            |
| End point type                                                                                                                                                                                                                                                                                                                                                        | Secondary                  |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                  |                            |
| 52 weeks                                                                                                                                                                                                                                                                                                                                                              |                            |

| End point values                  | Placebo             | Nintedanib 150mg    |  |  |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type                | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed       | 204 <sup>[50]</sup> | 309 <sup>[51]</sup> |  |  |
| Units: percentage of participants |                     |                     |  |  |
| number (not applicable)           |                     |                     |  |  |
| Failure                           | 4.4                 | 2.6                 |  |  |
| Censored                          | 95.6                | 97.4                |  |  |

Notes:

[50] - Treated Set (Only patients with observed cases (OC) values were analysed)

[51] - Treated Set (Only patients with observed cases (OC) values were analysed)

## Statistical analyses

|                                                                                                     |                            |
|-----------------------------------------------------------------------------------------------------|----------------------------|
| Statistical analysis title                                                                          | Statistical Analysis 1     |
| Statistical analysis description:                                                                   |                            |
| Hazard ratio is based on a Cox 's regression model with terms for treatment, gender, age and height |                            |
| Comparison groups                                                                                   | Placebo v Nintedanib 150mg |

|                                         |                             |
|-----------------------------------------|-----------------------------|
| Number of subjects included in analysis | 513                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[52]</sup> |
| P-value                                 | = 0.4869                    |
| Method                                  | Logrank                     |
| Parameter estimate                      | Hazard ratio (HR)           |
| Point estimate                          | 0.68                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 0.26                        |
| upper limit                             | 1.82                        |

Notes:

[52] - Nintedanib 150mg versus placebo

## Secondary: Time to Death or Lung Transplant Over 52 Weeks

|                                                                                                                                                                                                                                                                                                                                                                                                           |                                                |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                           | Time to Death or Lung Transplant Over 52 Weeks |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                    |                                                |
| Due to rare events, the median of time to event is not calculable, thus the percentages of participants who did or did not experience event (death or lung transplant) before or at 372 days after randomisation or last contact date (whichever occurs first) are reported.<br>Failure is the proportion of patients who died or had lung transplant over 52 weeks (up to 372 days after randomisation). |                                                |
| End point type                                                                                                                                                                                                                                                                                                                                                                                            | Secondary                                      |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                      |                                                |
| 52 weeks                                                                                                                                                                                                                                                                                                                                                                                                  |                                                |

| End point values                  | Placebo             | Nintedanib 150mg    |  |  |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type                | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed       | 204 <sup>[53]</sup> | 309 <sup>[54]</sup> |  |  |
| Units: percentage of participants |                     |                     |  |  |
| number (not applicable)           |                     |                     |  |  |
| Failure                           | 6.9                 | 5.2                 |  |  |
| Censored                          | 93.1                | 94.8                |  |  |

Notes:

[53] - Treated Set (Only patients with observed cases (OC) values were analysed)

[54] - Treated Set (Only patients with observed cases (OC) values were analysed)

## Statistical analyses

|                                                                                                  |                            |
|--------------------------------------------------------------------------------------------------|----------------------------|
| Statistical analysis title                                                                       | Statistical Analysis 1     |
| Statistical analysis description:                                                                |                            |
| Hazard ratio is based on Cox's regression model with terms for treatment, gender, age and height |                            |
| Comparison groups                                                                                | Placebo v Nintedanib 150mg |

|                                         |                             |
|-----------------------------------------|-----------------------------|
| Number of subjects included in analysis | 513                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[55]</sup> |
| P-value                                 | = 0.443                     |
| Method                                  | Logrank                     |
| Parameter estimate                      | Hazard ratio (HR)           |
| Point estimate                          | 0.73                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 0.36                        |
| upper limit                             | 1.51                        |

Notes:

[55] - Nintedanib 150mg versus placebo

## Secondary: Time to Death or Lung Transplant or Qualifying for Lung Transplant Over 52 Weeks.

|                 |                                                                                   |
|-----------------|-----------------------------------------------------------------------------------|
| End point title | Time to Death or Lung Transplant or Qualifying for Lung Transplant Over 52 Weeks. |
|-----------------|-----------------------------------------------------------------------------------|

End point description:

Due to rare events, the median of time to event is not calculable, thus the percentages of participants who did or did not experienced death or lung transplant or qualifying for lung transplant over 52 weeks are reported. A patient was considered qualifying for lung transplant by the investigator if he or she fulfilled the following criteria:

FVC <45% predicted or Carbon monoxide diffusion capacity (DL(CO)) <30% pred or Oxygen saturation on pulse oximetry (SpO2) <88% at rest, at sea level (to be adapted for other heights).

These criteria were evaluated by investigators judgement.

Failure is the proportion of patients who died or had lung transplant or qualified for lung transplant over 52 weeks (373 days time-period).

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

End point timeframe:

52 weeks

| End point values                  | Placebo             | Nintedanib 150mg    |  |  |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type                | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed       | 204 <sup>[56]</sup> | 309 <sup>[57]</sup> |  |  |
| Units: percentage of participants |                     |                     |  |  |
| number (not applicable)           |                     |                     |  |  |
| Failure                           | 18.1                | 14.9                |  |  |
| Censored                          | 81.9                | 85.1                |  |  |

Notes:

[56] - Treated Set (Only patients with observed cases (OC) values were analysed)

[57] - Treated Set (Only patients with observed cases (OC) values were analysed)

## Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Hazard ratio is based on Cox's regression model with terms for treatment, gender, age and height

|                   |                            |
|-------------------|----------------------------|
| Comparison groups | Placebo v Nintedanib 150mg |
|-------------------|----------------------------|

|                                         |                             |
|-----------------------------------------|-----------------------------|
| Number of subjects included in analysis | 513                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[58]</sup> |
| P-value                                 | = 0.3558                    |
| Method                                  | Logrank                     |
| Parameter estimate                      | Hazard ratio (HR)           |
| Point estimate                          | 0.81                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 0.52                        |
| upper limit                             | 1.25                        |

Notes:

[58] - Nintedanib 150mg versus placebo

### Secondary: Change From Baseline in SpO2 (Oxygen Saturation, Expressed in Percent) at Rest up Over 52 Weeks

|                                                                                                                                                                 |                                                                                                 |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                 | Change From Baseline in SpO2 (Oxygen Saturation, Expressed in Percent) at Rest up Over 52 Weeks |
| End point description:                                                                                                                                          |                                                                                                 |
| Means presented are the adjusted means. Adjusted mean is based on all analyzed patients in the model (not only patients with a change from baseline to week 52) |                                                                                                 |
| End point type                                                                                                                                                  | Secondary                                                                                       |
| End point timeframe:                                                                                                                                            |                                                                                                 |
| Baseline and 52 weeks                                                                                                                                           |                                                                                                 |

| End point values                    | Placebo             | Nintedanib 150mg    |  |  |
|-------------------------------------|---------------------|---------------------|--|--|
| Subject group type                  | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed         | 199 <sup>[59]</sup> | 299 <sup>[60]</sup> |  |  |
| Units: percent of oxygen saturation |                     |                     |  |  |
| arithmetic mean (standard error)    | -0.53 (± 0.15)      | -0.24 (± 0.129)     |  |  |

Notes:

[59] - Treated Set (Only patients with observed cases (OC) values were analysed)

[60] - Treated Set (Only patients with observed cases (OC) values were analysed)

### Statistical analyses

|                                                                                                                                                                                                  |                            |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|
| Statistical analysis title                                                                                                                                                                       | Statistical Analysis 1     |
| Statistical analysis description:                                                                                                                                                                |                            |
| Mixed Model for Repeated Measures (MMRM), with fixed effects for treatment, visit, gender, age, height, treatment-by-visit, baseline SpO2, baseline SpO2-by-visit and random effect for patient. |                            |
| Comparison groups                                                                                                                                                                                | Placebo v Nintedanib 150mg |

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Number of subjects included in analysis | 498                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[61]</sup>    |
| P-value                                 | = 0.1138                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 0.29                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.07                          |
| upper limit                             | 0.64                           |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 0.181                          |

Notes:

[61] - Nintedanib 150mg versus placebo.

Within-patient errors are modelled by compound symmetry covariance matrix.

### Secondary: Proportion of FVC Responders Using 10% Threshold at 52 Weeks

|                                                                                                                                                                         |                                                              |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|
| End point title                                                                                                                                                         | Proportion of FVC Responders Using 10% Threshold at 52 Weeks |
| End point description:                                                                                                                                                  |                                                              |
| FVC responders using 10% threshold at 52 weeks, defined as patients with absolute decline in FVC% predicted no greater than 10% and with an FVC evaluation at 52 weeks. |                                                              |
| End point type                                                                                                                                                          | Secondary                                                    |
| End point timeframe:                                                                                                                                                    |                                                              |
| 52 weeks                                                                                                                                                                |                                                              |

| End point values                  | Placebo             | Nintedanib 150mg       |  |  |
|-----------------------------------|---------------------|------------------------|--|--|
| Subject group type                | Reporting group     | Reporting group        |  |  |
| Number of subjects analysed       | 204 <sup>[62]</sup> | 309 <sup>[63]</sup>    |  |  |
| Units: percentage of participants |                     |                        |  |  |
| number (confidence interval 95%)  | 56.86 (50 to 63.47) | 70.55 (65.24 to 75.36) |  |  |

Notes:

[62] - Treated Set (Only patients with observed cases (OC) values were analysed)

[63] - Treated Set (Only patients with observed cases (OC) values were analysed)

### Statistical analyses

|                                                                                            |                            |
|--------------------------------------------------------------------------------------------|----------------------------|
| Statistical analysis title                                                                 | Statistical Analysis 1     |
| Statistical analysis description:                                                          |                            |
| Logistic regression with terms treatment, age, gender, height and baseline FVC % predicted |                            |
| Comparison groups                                                                          | Placebo v Nintedanib 150mg |

|                                         |                             |
|-----------------------------------------|-----------------------------|
| Number of subjects included in analysis | 513                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[64]</sup> |
| P-value                                 | = 0.0007                    |
| Method                                  | Regression, Logistic        |
| Parameter estimate                      | Odds ratio (OR)             |
| Point estimate                          | 1.914                       |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 1.32                        |
| upper limit                             | 2.79                        |

Notes:

[64] - Nintedanib 150 mg bid versus Placebo

## Secondary: Proportion of FVC Responders Using 5% Threshold at 52 Weeks

|                        |                                                                                                                                                                                     |
|------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title        | Proportion of FVC Responders Using 5% Threshold at 52 Weeks                                                                                                                         |
| End point description: | Proportion of FVC responders using 5% threshold at 52 weeks, defined as patients with absolute decline in FVC% predicted no greater than 5% and with an FVC evaluation at 52 weeks. |
| End point type         | Secondary                                                                                                                                                                           |
| End point timeframe:   | 52 weeks                                                                                                                                                                            |

| End point values                  | Placebo                | Nintedanib 150mg       |  |  |
|-----------------------------------|------------------------|------------------------|--|--|
| Subject group type                | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed       | 204 <sup>[65]</sup>    | 309 <sup>[66]</sup>    |  |  |
| Units: percentage of participants |                        |                        |  |  |
| number (confidence interval 95%)  | 38.24 (31.84 to 45.06) | 52.75 (47.18 to 58.25) |  |  |

Notes:

[65] - Treated Set (Only patients with observed cases (OC) values were analysed)

[66] - Treated Set (Only patients with observed cases (OC) values were analysed)

## Statistical analyses

|                                         |                                                                                            |
|-----------------------------------------|--------------------------------------------------------------------------------------------|
| Statistical analysis title              | Statistical Analysis 1                                                                     |
| Statistical analysis description:       | Logistic regression with terms treatment, age, gender, height and baseline FVC % predicted |
| Comparison groups                       | Placebo v Nintedanib 150mg                                                                 |
| Number of subjects included in analysis | 513                                                                                        |
| Analysis specification                  | Pre-specified                                                                              |
| Analysis type                           | superiority <sup>[67]</sup>                                                                |
| P-value                                 | = 0.001                                                                                    |
| Method                                  | Regression, Logistic                                                                       |
| Parameter estimate                      | Odds ratio (OR)                                                                            |
| Point estimate                          | 1.847                                                                                      |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 1.28    |
| upper limit         | 2.66    |

Notes:

[67] - Nintedanib 150 mg bid versus Placebo

### Secondary: Change From Baseline in EuroQol 5-Dimensional Quality of Life Questionnaire (EQ-5D) Health State up to 52 Weeks: Patient Reported Outcomes (PROs)

|                 |                                                                                                                                                   |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Change From Baseline in EuroQol 5-Dimensional Quality of Life Questionnaire (EQ-5D) Health State up to 52 Weeks: Patient Reported Outcomes (PROs) |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The EuroQol 5-dimensional Health State is based on a visual analog scale (EQ-VAS) representing the general patient's health state labelled from 100 (best imaginable health state) to 0 (worst imaginable health state). A higher score indicating a better health state. Change from baseline is calculated as the difference between health state at week 12, 24 and 52 respectively and health state at baseline as measured by the scale.

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

End point timeframe:

baseline, 12 weeks, 24 weeks and 52 weeks

| End point values                     | Placebo             | Nintedanib 150mg    |  |  |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed          | 203 <sup>[68]</sup> | 306 <sup>[69]</sup> |  |  |
| Units: points on a scale             |                     |                     |  |  |
| arithmetic mean (standard deviation) |                     |                     |  |  |
| 12 weeks (N= 194, 287)               | 0.04 (± 15.46)      | -1.75 (± 16.42)     |  |  |
| 24 weeks (N= 190, 279)               | -0.84 (± 15.37)     | -0.74 (± 17.92)     |  |  |
| 52 weeks (N=160, 247)                | -5.88 (± 19.17)     | -2.46 (± 18.92)     |  |  |

Notes:

[68] - Treated Set (Only patients with observed cases (OC) values were analysed)

[69] - Treated Set (Only patients with observed cases (OC) values were analysed)

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Carbon Monoxide Diffusion Capacity (DLCO) at Rest Over 52 Weeks

|                 |                                                                                         |
|-----------------|-----------------------------------------------------------------------------------------|
| End point title | Change From Baseline in Carbon Monoxide Diffusion Capacity (DLCO) at Rest Over 52 Weeks |
|-----------------|-----------------------------------------------------------------------------------------|

End point description:

Means presented are the adjusted means. Adjusted mean is based on all analyzed patients in the model (not only patients with a change from baseline to week 52)

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

End point timeframe:  
Baseline and 52 weeks

| End point values                 | Placebo             | Nintedanib 150mg    |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 195 <sup>[70]</sup> | 286 <sup>[71]</sup> |  |  |
| Units: mmol/min/kPa              |                     |                     |  |  |
| arithmetic mean (standard error) | -0.365 (± 0.075)    | -0.38 (± 0.0644)    |  |  |

Notes:

[70] - Treated Set (Only patients with observed cases (OC) values were analysed)

[71] - Treated Set (Only patients with observed cases (OC) values were analysed)

## Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

Mixed Model for Repeated Measures with fixed effects for treatment, visit, gender, age, height treatment-by-visit, baseline DLCO (HGB Corrected) [mmol/min/kPa], baseline DLCO (HGB Corrected) [mmol/min/kPa]-by-visit and random effect for patient.

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Comparison groups                       | Placebo v Nintedanib 150mg     |
| Number of subjects included in analysis | 481                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[72]</sup>    |
| P-value                                 | = 0.865                        |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -0.015                         |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.191                         |
| upper limit                             | 0.161                          |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 0.0896                         |

Notes:

[72] - Nintedanib 150mg versus placebo.

Within-patient errors are modelled by compound symmetry covariance matrix.

## Secondary: Time to First Acute Idiopathic Pulmonary Fibrosis (IPF) Exacerbation

|                 |                                                                      |
|-----------------|----------------------------------------------------------------------|
| End point title | Time to First Acute Idiopathic Pulmonary Fibrosis (IPF) Exacerbation |
|-----------------|----------------------------------------------------------------------|

End point description:

Due to rare events, the median of time to event is not calculable, thus the percentages of patients with (IPF) exacerbation are reported and represented as a key secondary endpoint.

An acute exacerbation (reported as an AE by the investigator) was defined as follows:

Otherwise unexplained clinical features including all of the following:

- Unexplained worsening or development of dyspnoea within 30 days
- New diffuse pulmonary infiltrates on chest X-ray, and/or new HRCT parenchymal abnormalities with no pneumothorax or pleural effusion (new ground-glass opacities) since the last visit
- Exclusion of infection as per routine clinical practice and microbiological studies

- Exclusion of alternative causes as per routine clinical practice including left heart failure, pulmonary embolism and identifiable cause of acute lung injury.

Failure is the proportion of patients with at least one acute IPF exacerbation over 52 weeks (up to randomisation + 372 days), based on all investigato

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| 52 weeks             |           |

| End point values                  | Placebo             | Nintedanib 150mg    |  |  |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type                | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed       | 204 <sup>[73]</sup> | 309 <sup>[74]</sup> |  |  |
| Units: percentage of participants |                     |                     |  |  |
| number (not applicable)           |                     |                     |  |  |
| Failure                           | 5.4                 | 6.1                 |  |  |
| Censored                          | 94.6                | 93.9                |  |  |

Notes:

[73] - Treated Set (Only patients with observed cases (OC) values were analysed)

[74] - Treated Set (Only patients with observed cases (OC) values were analysed)

## Statistical analyses

|                                                                                                     |                             |
|-----------------------------------------------------------------------------------------------------|-----------------------------|
| Statistical analysis title                                                                          | Statistical Analysis 1      |
| Statistical analysis description:                                                                   |                             |
| Hazard Ratio is based on a Cox 's regression model with terms for treatment, gender, age and height |                             |
| Comparison groups                                                                                   | Placebo v Nintedanib 150mg  |
| Number of subjects included in analysis                                                             | 513                         |
| Analysis specification                                                                              | Pre-specified               |
| Analysis type                                                                                       | superiority <sup>[75]</sup> |
| P-value                                                                                             | = 0.6728                    |
| Method                                                                                              | Logrank                     |
| Parameter estimate                                                                                  | Hazard ratio (HR)           |
| Point estimate                                                                                      | 1.15                        |
| Confidence interval                                                                                 |                             |
| level                                                                                               | 95 %                        |
| sides                                                                                               | 2-sided                     |
| lower limit                                                                                         | 0.54                        |
| upper limit                                                                                         | 2.42                        |

Notes:

[75] - Nintedanib 150 mg bid versus Placebo

## Secondary: Relative Change From Baseline in FVC Over 52 weeks

|                                                                                                                                                                                                             |                                                    |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|
| End point title                                                                                                                                                                                             | Relative Change From Baseline in FVC Over 52 weeks |
| End point description:                                                                                                                                                                                      |                                                    |
| Percentage change from baseline in FVC over 52 weeks. Means provided are the adjusted means and are based on all analysed patients in the model (not only patients with a change from baseline to week 52). |                                                    |
| End point type                                                                                                                                                                                              | Secondary                                          |

End point timeframe:  
Baseline and 52 weeks

| End point values                 | Placebo             | Nintedanib 150mg    |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 204 <sup>[76]</sup> | 307 <sup>[77]</sup> |  |  |
| Units: percent change            |                     |                     |  |  |
| arithmetic mean (standard error) | -7.38 (± 0.633)     | -3.36 (± 0.55)      |  |  |

Notes:

[76] - TS (Only patients with observed cases (OC) values were analysed)

[77] - TS (Only patients with observed cases (OC) values were analysed)

## Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

Based on Mixed Model for Repeated Measures (MMRM), with fixed effects for treatment, visit, gender, age, height, treatment-by-visit, baseline FVC, baseline FVC-by visit and random effect for patient.

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Comparison groups                       | Nintedanib 150mg v Placebo     |
| Number of subjects included in analysis | 511                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[78]</sup>    |
| P-value                                 | < 0.0001                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 4.02                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 2.54                           |
| upper limit                             | 5.5                            |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 0.753                          |

Notes:

[78] - Nintedanib 150 mg bid versus Placebo.

Within-patient errors are modelled by compound symmetry covariance matrix.

## Secondary: Relative Change From Baseline in FVC (% predicted) over 52 weeks

|                 |                                                                  |
|-----------------|------------------------------------------------------------------|
| End point title | Relative Change From Baseline in FVC (% predicted) over 52 weeks |
|-----------------|------------------------------------------------------------------|

End point description:

Percentage change from baseline in FVC (% predicted) at 52 weeks. Means provided are the adjusted means and are based on all analysed patients in the model (not only patients with a change from baseline to week 52).

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

End point timeframe:

Baseline and 52 weeks

| End point values                 | Placebo             | Nintedanib 150mg    |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 204 <sup>[79]</sup> | 307 <sup>[80]</sup> |  |  |
| Units: percent change            |                     |                     |  |  |
| arithmetic mean (standard error) | -7.32 (± 0.634)     | -3.32 (± 0.547)     |  |  |

Notes:

[79] - TS (Only patients with observed cases (OC) values were analysed)

[80] - TS (Only patients with observed cases (OC) values were analysed)

## Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

Based on Mixed Model for Repeated Measures (MMRM), with fixed effects for treatment, visit, gender, age, height, treatment-by-visit, baseline FVC [%predicted], baseline FVC [%predicted]-by-visit and random effect for patient.

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Comparison groups                       | Placebo v Nintedanib 150mg     |
| Number of subjects included in analysis | 511                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority <sup>[81]</sup>    |
| P-value                                 | < 0.0001                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 4                              |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 2.52                           |
| upper limit                             | 5.48                           |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 0.753                          |

Notes:

[81] - Nintedanib 150 mg bid versus Placebo.

Within-patient errors are modelled by compound symmetry covariance matrix.

## Secondary: Risk of an Acute IPF Exacerbation Over 52 Weeks

|                 |                                                 |
|-----------------|-------------------------------------------------|
| End point title | Risk of an Acute IPF Exacerbation Over 52 Weeks |
|-----------------|-------------------------------------------------|

End point description:

Incidence rate of exacerbations (calculated as the number of patients with at least 1 acute IPF exacerbation divided by the total number of years at risk \*100)

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

End point timeframe:

52 weeks

| End point values             | Placebo             | Nintedanib 150mg    |  |  |
|------------------------------|---------------------|---------------------|--|--|
| Subject group type           | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed  | 204 <sup>[82]</sup> | 309 <sup>[83]</sup> |  |  |
| Units: participants/Year*100 |                     |                     |  |  |
| number (not applicable)      | 5.6                 | 6.6                 |  |  |

Notes:

[82] - Treated Set (Only patients with observed cases (OC) values were analysed)

[83] - Treated Set (Only patients with observed cases (OC) values were analysed)

## Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

Risk ratio was calculated as the ratio of risk of exacerbation in both treatment groups. The log of the risk ratio was assumed to follow a normal distribution with mean 0 and variance equal to the sum of the reciprocals of the number of patients with at least one exacerbation in each treatment arm.

|                                         |                             |
|-----------------------------------------|-----------------------------|
| Comparison groups                       | Nintedanib 150mg v Placebo  |
| Number of subjects included in analysis | 513                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[84]</sup> |
| P-value                                 | = 0.6793                    |
| Method                                  | Normal distribution         |
| Parameter estimate                      | Risk ratio (RR)             |
| Point estimate                          | 1.17                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 0.56                        |
| upper limit                             | 2.46                        |

Notes:

[84] - Nintedanib 150mg bid versus placebo

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the first drug administration until 28 days after the last drug administration, up to 425 days

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

### Reporting groups

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

Reporting group description:

Oral administration of placebo matching nintedanib soft gelatine capsules.

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Nintedanib 150mg bid |
|-----------------------|----------------------|

Reporting group description:

Oral administration of soft gelatine capsules of Nintedanib 150 mg twice daily (bid). Dose interruption and reduction to 100 mg bid dose were allowed to manage adverse events.

| Serious adverse events                                              | Placebo           | Nintedanib 150mg bid |  |
|---------------------------------------------------------------------|-------------------|----------------------|--|
| Total subjects affected by serious adverse events                   |                   |                      |  |
| subjects affected / exposed                                         | 55 / 204 (26.96%) | 96 / 309 (31.07%)    |  |
| number of deaths (all causes)                                       | 14                | 19                   |  |
| number of deaths resulting from adverse events                      | 1                 | 0                    |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                      |  |
| Adenocarcinoma pancreas                                             |                   |                      |  |
| subjects affected / exposed                                         | 0 / 204 (0.00%)   | 1 / 309 (0.32%)      |  |
| occurrences causally related to treatment / all                     | 0 / 0             | 0 / 1                |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0                |  |
| B-cell lymphoma                                                     |                   |                      |  |
| subjects affected / exposed                                         | 0 / 204 (0.00%)   | 1 / 309 (0.32%)      |  |
| occurrences causally related to treatment / all                     | 0 / 0             | 0 / 1                |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 1                |  |
| Basal cell carcinoma                                                |                   |                      |  |
| subjects affected / exposed                                         | 3 / 204 (1.47%)   | 2 / 309 (0.65%)      |  |
| occurrences causally related to treatment / all                     | 0 / 3             | 0 / 2                |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0                |  |
| Bladder neoplasm                                                    |                   |                      |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bladder transitional cell carcinoma             |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 0 / 309 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric cancer                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung adenocarcinoma                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung neoplasm malignant                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 4 / 309 (1.29%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 2           |  |
| Metastases to liver                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metastatic neoplasm                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Prostate cancer                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 0 / 309 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Squamous cell carcinoma                         |                 |                 |  |

|                                                             |                 |                 |  |
|-------------------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                                 | 4 / 204 (1.96%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all             | 0 / 4           | 0 / 1           |  |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           |  |
| <b>Vascular disorders</b>                                   |                 |                 |  |
| Aortic aneurysm                                             |                 |                 |  |
| subjects affected / exposed                                 | 1 / 204 (0.49%) | 0 / 309 (0.00%) |  |
| occurrences causally related to treatment / all             | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           |  |
| Deep vein thrombosis                                        |                 |                 |  |
| subjects affected / exposed                                 | 1 / 204 (0.49%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all             | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           |  |
| Hypertensive crisis                                         |                 |                 |  |
| subjects affected / exposed                                 | 1 / 204 (0.49%) | 2 / 309 (0.65%) |  |
| occurrences causally related to treatment / all             | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           |  |
| Hypotension                                                 |                 |                 |  |
| subjects affected / exposed                                 | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all             | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           |  |
| Microscopic polyangiitis                                    |                 |                 |  |
| subjects affected / exposed                                 | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all             | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           |  |
| Peripheral ischaemia                                        |                 |                 |  |
| subjects affected / exposed                                 | 1 / 204 (0.49%) | 0 / 309 (0.00%) |  |
| occurrences causally related to treatment / all             | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           |  |
| <b>General disorders and administration site conditions</b> |                 |                 |  |
| Asthenia                                                    |                 |                 |  |
| subjects affected / exposed                                 | 1 / 204 (0.49%) | 0 / 309 (0.00%) |  |
| occurrences causally related to treatment / all             | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Chest discomfort                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chest pain                                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 204 (0.98%) | 5 / 309 (1.62%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| General physical health deterioration           |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperthermia                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 0 / 309 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Impaired healing                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Multi-organ failure                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oedema peripheral                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 0 / 309 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Polyp                                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Systemic inflammatory response syndrome         |                 |                 |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 204 (0.00%)  | 1 / 309 (0.32%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Reproductive system and breast disorders        |                  |                  |  |
| Benign prostatic hyperplasia                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 204 (0.00%)  | 1 / 309 (0.32%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Respiratory, thoracic and mediastinal disorders |                  |                  |  |
| Acute respiratory failure                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 204 (0.98%)  | 5 / 309 (1.62%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Dyspnoea                                        |                  |                  |  |
| subjects affected / exposed                     | 3 / 204 (1.47%)  | 1 / 309 (0.32%)  |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Epistaxis                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 204 (0.49%)  | 1 / 309 (0.32%)  |  |
| occurrences causally related to treatment / all | 1 / 1            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemoptysis                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 204 (0.49%)  | 0 / 309 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypoxia                                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 204 (0.49%)  | 1 / 309 (0.32%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Idiopathic pulmonary fibrosis                   |                  |                  |  |
| subjects affected / exposed                     | 11 / 204 (5.39%) | 20 / 309 (6.47%) |  |
| occurrences causally related to treatment / all | 0 / 15           | 0 / 21           |  |
| deaths causally related to treatment / all      | 0 / 4            | 0 / 7            |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Pleurisy                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 0 / 309 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumomediastinum                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 2 / 309 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia aspiration                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumothorax                                    |                 |                 |  |
| subjects affected / exposed                     | 3 / 204 (1.47%) | 2 / 309 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Pulmonary arterial hypertension                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 2 / 309 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary embolism                              |                 |                 |  |
| subjects affected / exposed                     | 3 / 204 (1.47%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary hypertension                          |                 |                 |  |
| subjects affected / exposed                     | 6 / 204 (2.94%) | 5 / 309 (1.62%) |  |
| occurrences causally related to treatment / all | 0 / 7           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary mass                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary oedema                                |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 204 (0.00%) | 2 / 309 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory disorder                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory failure                             |                 |                 |  |
| subjects affected / exposed                     | 3 / 204 (1.47%) | 0 / 309 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Psychiatric disorders                           |                 |                 |  |
| Depression                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 0 / 309 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Substance-induced psychotic disorder            |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 0 / 309 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Hepatic enzyme increased                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 2 / 309 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary function test decreased               |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Weight decreased                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Injury, poisoning and procedural complications  |                 |                 |  |
| Fall                                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 0 / 309 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Foot fracture                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hip fracture                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 0 / 309 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lumbar vertebral fracture                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| 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 / 204 (0.49%) | 0 / 309 (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 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Angina pectoris                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 0 / 309 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| Atrial fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 3 / 309 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Atrial flutter                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Cardiac arrest                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| 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 / 204 (0.49%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure congestive                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiomegaly                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 0 / 309 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cor pulmonale                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 0 / 309 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coronary artery disease                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coronary artery occlusion                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coronary artery stenosis                        |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 3 / 204 (1.47%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diastolic dysfunction                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myocardial infarction                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 4 / 309 (1.29%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 4           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Myocardial ischaemia                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 0 / 309 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sinus tachycardia                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Balance disorder                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 0 / 309 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Carotid artery stenosis                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebrovascular accident                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 0 / 309 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Migraine                                        |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Motor dysfunction                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 0 / 309 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Polyneuropathy                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 0 / 309 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Syncope                                         |                 |                 |  |
| subjects affected / exposed                     | 2 / 204 (0.98%) | 3 / 309 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Transient ischaemic attack                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders            |                 |                 |  |
| Anaemia                                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Eye disorders                                   |                 |                 |  |
| Cataract                                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Optic ischaemic neuropathy                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Abdominal pain                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 0 / 309 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Constipation                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 0 / 309 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diarrhoea                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Duodenal ulcer                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Dysphagia                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal haemorrhage                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Haematemesis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Ileus                                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 2 / 309 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Inguinal hernia                                 |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 204 (0.49%) | 0 / 309 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Large intestinal obstruction                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 0 / 309 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Large intestine polyp                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oesophagitis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis acute                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vomiting                                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Cholecystitis                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholelithiasis                                  |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic cirrhosis                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatitis acute                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Cystitis haemorrhagic                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dysuria                                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 0 / 309 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Glomerulonephritis                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 0 / 309 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nephrolithiasis                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal failure                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 0 / 309 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal failure acute                             |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 204 (0.49%) | 3 / 309 (0.97%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal vasculitis                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 0 / 309 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Chondrocalcinosis                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intervertebral disc protrusion                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rhabdomyolysis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rheumatic disorder                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rheumatoid arthritis                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal disorder                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 0 / 309 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Synovitis                                       |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 204 (0.49%) | 0 / 309 (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                     |                 |                 |  |
| Appendicitis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 2 / 309 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchitis                                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 204 (0.98%) | 2 / 309 (0.65%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchopneumonia                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cellulitis                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis viral                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| H1N1 influenza                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lobar pneumonia                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 0 / 309 (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                     | 3 / 204 (1.47%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung infection                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 2 / 309 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mycobacterial infection                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peritoneal abscess                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 5 / 204 (2.45%) | 5 / 309 (1.62%) |  |
| occurrences causally related to treatment / all | 1 / 5           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Pyelonephritis acute                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory tract infection                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| Sepsis                                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Septic shock                                    |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 204 (0.49%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| Viral infection                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Decreased appetite                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dehydration                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 204 (0.49%) | 0 / 309 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoglycaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 204 (0.00%) | 1 / 309 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | Placebo            | Nintedanib 150mg bid |  |
|-------------------------------------------------------|--------------------|----------------------|--|
| Total subjects affected by non-serious adverse events |                    |                      |  |
| subjects affected / exposed                           | 140 / 204 (68.63%) | 262 / 309 (84.79%)   |  |
| Investigations                                        |                    |                      |  |
| Weight decreased                                      |                    |                      |  |
| subjects affected / exposed                           | 12 / 204 (5.88%)   | 24 / 309 (7.77%)     |  |
| occurrences (all)                                     | 12                 | 25                   |  |
| Nervous system disorders                              |                    |                      |  |
| Headache                                              |                    |                      |  |
| subjects affected / exposed                           | 12 / 204 (5.88%)   | 21 / 309 (6.80%)     |  |
| occurrences (all)                                     | 15                 | 23                   |  |
| General disorders and administration                  |                    |                      |  |

|                                                 |                   |                    |  |
|-------------------------------------------------|-------------------|--------------------|--|
| site conditions                                 |                   |                    |  |
| Fatigue                                         |                   |                    |  |
| subjects affected / exposed                     | 13 / 204 (6.37%)  | 14 / 309 (4.53%)   |  |
| occurrences (all)                               | 14                | 17                 |  |
| Gastrointestinal disorders                      |                   |                    |  |
| Abdominal pain                                  |                   |                    |  |
| subjects affected / exposed                     | 2 / 204 (0.98%)   | 26 / 309 (8.41%)   |  |
| occurrences (all)                               | 2                 | 31                 |  |
| Abdominal pain upper                            |                   |                    |  |
| subjects affected / exposed                     | 9 / 204 (4.41%)   | 23 / 309 (7.44%)   |  |
| occurrences (all)                               | 11                | 28                 |  |
| Constipation                                    |                   |                    |  |
| subjects affected / exposed                     | 6 / 204 (2.94%)   | 17 / 309 (5.50%)   |  |
| occurrences (all)                               | 6                 | 18                 |  |
| Diarrhoea                                       |                   |                    |  |
| subjects affected / exposed                     | 38 / 204 (18.63%) | 188 / 309 (60.84%) |  |
| occurrences (all)                               | 50                | 333                |  |
| Flatulence                                      |                   |                    |  |
| subjects affected / exposed                     | 1 / 204 (0.49%)   | 18 / 309 (5.83%)   |  |
| occurrences (all)                               | 1                 | 19                 |  |
| Nausea                                          |                   |                    |  |
| subjects affected / exposed                     | 12 / 204 (5.88%)  | 70 / 309 (22.65%)  |  |
| occurrences (all)                               | 13                | 94                 |  |
| Vomiting                                        |                   |                    |  |
| subjects affected / exposed                     | 4 / 204 (1.96%)   | 39 / 309 (12.62%)  |  |
| occurrences (all)                               | 4                 | 52                 |  |
| Respiratory, thoracic and mediastinal disorders |                   |                    |  |
| Cough                                           |                   |                    |  |
| subjects affected / exposed                     | 26 / 204 (12.75%) | 47 / 309 (15.21%)  |  |
| occurrences (all)                               | 30                | 51                 |  |
| Dyspnoea                                        |                   |                    |  |
| subjects affected / exposed                     | 21 / 204 (10.29%) | 22 / 309 (7.12%)   |  |
| occurrences (all)                               | 23                | 22                 |  |
| Idiopathic pulmonary fibrosis                   |                   |                    |  |
| subjects affected / exposed                     | 11 / 204 (5.39%)  | 10 / 309 (3.24%)   |  |
| occurrences (all)                               | 11                | 10                 |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| Skin and subcutaneous tissue disorders          |                   |                   |  |
| Rash                                            |                   |                   |  |
| subjects affected / exposed                     | 6 / 204 (2.94%)   | 16 / 309 (5.18%)  |  |
| occurrences (all)                               | 6                 | 16                |  |
| Musculoskeletal and connective tissue disorders |                   |                   |  |
| Back pain                                       |                   |                   |  |
| subjects affected / exposed                     | 16 / 204 (7.84%)  | 17 / 309 (5.50%)  |  |
| occurrences (all)                               | 17                | 19                |  |
| Infections and infestations                     |                   |                   |  |
| Bronchitis                                      |                   |                   |  |
| subjects affected / exposed                     | 27 / 204 (13.24%) | 35 / 309 (11.33%) |  |
| occurrences (all)                               | 35                | 47                |  |
| Lower respiratory tract infection               |                   |                   |  |
| subjects affected / exposed                     | 11 / 204 (5.39%)  | 16 / 309 (5.18%)  |  |
| occurrences (all)                               | 14                | 32                |  |
| Nasopharyngitis                                 |                   |                   |  |
| subjects affected / exposed                     | 34 / 204 (16.67%) | 39 / 309 (12.62%) |  |
| occurrences (all)                               | 47                | 54                |  |
| Upper respiratory tract infection               |                   |                   |  |
| subjects affected / exposed                     | 18 / 204 (8.82%)  | 28 / 309 (9.06%)  |  |
| occurrences (all)                               | 23                | 33                |  |
| Metabolism and nutrition disorders              |                   |                   |  |
| Decreased appetite                              |                   |                   |  |
| subjects affected / exposed                     | 14 / 204 (6.86%)  | 26 / 309 (8.41%)  |  |
| occurrences (all)                               | 15                | 26                |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 17 November 2011  | <ul style="list-style-type: none"><li>- 'Acute IPF exacerbation' was clarified each time 'exacerbation' was mentioned</li><li>- Procedures and appropriate measures in case of suspicion of a 'drug induced liver injury' event were implemented</li><li>- A re-test was allowed in case a laboratory parameter was found to be abnormal at Visit 1. This was to be conducted if laboratory tests were thought to be a measurement error and not related to the patient's condition</li><li>- Patients were to be excluded from the trial if they were not able to follow trial procedures including completion of self administered questionnaires without help</li><li>- Instructions were included for Investigators on the reporting of DLCO in the eCRF</li><li>- Addition of the 'always serious AEs' according to new BI standards to ensure proper reporting of these events</li><li>- Inclusion criterion 4 was changed to: 'Chest HRCT performed within 12 months of Visit 1', instead of 'Chest HRCT performed within 12 months of Visit 2'</li></ul> |
| 04 September 2012 | <ul style="list-style-type: none"><li>- Addition of exploratory biomarker analyses in order to explore the effect of nintedanib on biomarkers related to IPF pathology and prognostic markers of the disease. Exploratory analyses of samples from patients who gave specific informed consent were performed. Pharmacogenomic analysis was also added</li><li>- The criterion for poor compliance was defined as a protocol violation</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported