



## Clinical trial results:

**A 24-week, double-blind, randomised, parallel-group study evaluating the efficacy and safety of oral nintedanib co-administered with oral sildenafil, compared to treatment with nintedanib alone, in patients with idiopathic pulmonary fibrosis (IPF) and advanced lung function impairment.**

### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2015-002619-14    |
| Trial protocol           | DE ES BE GB FR IT |
| Global end of trial date | 13 April 2018     |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v2 (current)     |
| This version publication date  | 01 December 2021 |
| First version publication date | 20 April 2019    |
| Version creation reason        |                  |

### Trial information

#### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | 1199.36 |
|-----------------------|---------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02802345 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |                                                                                                                                                                                  |
|------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Boehringer Ingelheim                                                                                                                                                             |
| Sponsor organisation address | Binger Strasse 173, Ingelheim am Rhein, Germany, 55216                                                                                                                           |
| Public contact               | Scientific contact QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com |
| Scientific contact           | Scientific contact QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, 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:

## Results analysis stage

|                                                      |                  |
|------------------------------------------------------|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 04 June 2018     |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 19 December 2017 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 13 April 2018    |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective was to assess the efficacy and safety of concomitant treatment with nintedanib and sildenafil in patients with idiopathic pulmonary fibrosis (IPF) with advanced lung function impairment.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

|                                                           |              |
|-----------------------------------------------------------|--------------|
| Actual start date of recruitment                          | 08 July 2016 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | Yes          |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Australia: 9           |
| Country: Number of subjects enrolled | Belgium: 17            |
| Country: Number of subjects enrolled | Canada: 23             |
| Country: Number of subjects enrolled | France: 42             |
| Country: Number of subjects enrolled | Germany: 39            |
| Country: Number of subjects enrolled | India: 28              |
| Country: Number of subjects enrolled | Italy: 44              |
| Country: Number of subjects enrolled | Japan: 29              |
| Country: Number of subjects enrolled | Korea, Republic of: 42 |
| Country: Number of subjects enrolled | Mexico: 34             |
| Country: Number of subjects enrolled | Spain: 25              |
| Country: Number of subjects enrolled | United Kingdom: 22     |
| Country: Number of subjects enrolled | United States: 52      |
| Worldwide total number of subjects   | 406                    |
| EEA total number of subjects         | 167                    |

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)                      | 88  |
| From 65 to 84 years                       | 306 |
| 85 years and over                         | 12  |

## Subject disposition

### Recruitment

Recruitment details:

Randomised, double-blind, parallel design comparison of nintedanib 150 milligram (mg) twice daily (bid) and sildenafil 20 mg three times a day (tid) to nintedanib 150 mg bid and placebo matching sildenafil tid administered orally over 24 weeks.

### Pre-assignment

Screening details:

All patients were screened for eligibility to participate in the trial. Patients attended specialist sites to ensure that all patients met all inclusion/exclusion criteria. Patients were not to be randomized to trial if any one of the specific entry criteria were not met.

### Period 1

|                              |                                                        |
|------------------------------|--------------------------------------------------------|
| Period 1 title               | Overall Study (overall period)                         |
| Is this the baseline period? | Yes                                                    |
| Allocation method            | Randomised - controlled                                |
| Blinding used                | Double blind                                           |
| Roles blinded                | Subject, Investigator, Monitor, Assessor, Data analyst |

Blinding implementation details:

It was a double-blind trial.

### Arms

|                              |                    |
|------------------------------|--------------------|
| Are arms mutually exclusive? | Yes                |
| <b>Arm title</b>             | Nintedanib+placebo |

Arm description:

Patients administered 150 milligram (mg) Nintedanib soft gelatine capsule orally twice daily (bid), with a possibility of dose reduction to 100 mg capsule bid along with placebo matching to Sildenafil for 24 weeks.

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

Dosage and administration details:

Patients administered 150 milligram (mg) Nintedanib soft gelatine capsule orally twice daily (bid), with a possibility of dose reduction to 100 mg capsule bid along with placebo matching to Sildenafil for 24 weeks.

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

Dosage and administration details:

Patients administered 150 milligram (mg) Nintedanib soft gelatine capsule orally twice daily (bid), with a possibility of dose reduction to 100 mg capsule bid along with placebo matching to Sildenafil for 24 weeks.

|                  |                       |
|------------------|-----------------------|
| <b>Arm title</b> | Nintedanib+sildenafil |
|------------------|-----------------------|

Arm description:

Patients administered 150 milligram (mg) Nintedanib soft gelatine capsule orally twice daily (bid), with a possibility of dose reduction to 100 mg capsule bid along with 20 mg thrice daily (tid) Sildenafil for 24 weeks.

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

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

Dosage and administration details:

Patients administered 150 milligram (mg) Nintedanib soft gelatine capsule orally twice daily (bid), with a possibility of dose reduction to 100 mg capsule bid along with 20 mg thrice daily (tid) Sildenafil for 24 weeks.

|                                        |            |
|----------------------------------------|------------|
| Investigational medicinal product name | Sildenafil |
| Investigational medicinal product code |            |
| Other name                             |            |
| Pharmaceutical forms                   | Capsule    |
| Routes of administration               | Oral use   |

Dosage and administration details:

Patients administered 150 milligram (mg) Nintedanib soft gelatine capsule orally twice daily (bid), with a possibility of dose reduction to 100 mg capsule bid along with 20 mg thrice daily (tid) Sildenafil for 24 weeks.

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Nintedanib+placebo | Nintedanib+sildenafil |
|-----------------------------------------------------|--------------------|-----------------------|
| Started                                             | 136                | 137                   |
| Completed                                           | 104                | 108                   |
| Not completed                                       | 32                 | 29                    |
| Adverse event, serious fatal                        | 8                  | 6                     |
| Consent withdrawn by subject                        | 3                  | 3                     |
| Adverse event, non-fatal                            | 20                 | 14                    |
| Other than listed                                   | 1                  | 5                     |
| Protocol deviation                                  | -                  | 1                     |

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: 406 were enrolled worldwide whereof 273 were included in this trial.

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                                                             |                       |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Reporting group title                                                                                                                                                                                                       | Nintedanib+placebo    |
| Reporting group description:                                                                                                                                                                                                |                       |
| Patients administered 150 milligram (mg) Nintedanib soft gelatine capsule orally twice daily (bid), with a possibility of dose reduction to 100 mg capsule bid along with placebo matching to Sildenafil for 24 weeks.      |                       |
| Reporting group title                                                                                                                                                                                                       | Nintedanib+sildenafil |
| Reporting group description:                                                                                                                                                                                                |                       |
| Patients administered 150 milligram (mg) Nintedanib soft gelatine capsule orally twice daily (bid), with a possibility of dose reduction to 100 mg capsule bid along with 20 mg thrice daily (tid) Sildenafil for 24 weeks. |                       |

| Reporting group values | Nintedanib+placebo | Nintedanib+sildenafil | Total |
|------------------------|--------------------|-----------------------|-------|
| Number of subjects     | 136                | 137                   | 273   |
| Age categorical        |                    |                       |       |
| Units: Subjects        |                    |                       |       |

|                                                                                                                                                    |       |       |     |
|----------------------------------------------------------------------------------------------------------------------------------------------------|-------|-------|-----|
| Age Continuous                                                                                                                                     |       |       |     |
| Treated Set (TS): TS included all patients who were randomised to a treatment group and received at least one dose of randomised study medication. |       |       |     |
| Units: years                                                                                                                                       |       |       |     |
| arithmetic mean                                                                                                                                    | 70.0  | 70.3  |     |
| standard deviation                                                                                                                                 | ± 7.9 | ± 8.6 | -   |
| Sex: Female, Male                                                                                                                                  |       |       |     |
| TS                                                                                                                                                 |       |       |     |
| Units: Subjects                                                                                                                                    |       |       |     |
| Male                                                                                                                                               | 106   | 110   | 216 |
| Female                                                                                                                                             | 30    | 27    | 57  |
| Race (NIH/OMB)                                                                                                                                     |       |       |     |
| TS                                                                                                                                                 |       |       |     |
| Units: Subjects                                                                                                                                    |       |       |     |
| American Indian or Alaska Native                                                                                                                   | 2     | 3     | 5   |
| Asian                                                                                                                                              | 39    | 30    | 69  |
| Native Hawaiian or Other Pacific Islander                                                                                                          | 0     | 0     | 0   |
| Black or African American                                                                                                                          | 0     | 0     | 0   |
| White                                                                                                                                              | 95    | 103   | 198 |
| More than one race                                                                                                                                 | 0     | 1     | 1   |
| Unknown or Not Reported                                                                                                                            | 0     | 0     | 0   |
| Ethnicity (NIH/OMB)                                                                                                                                |       |       |     |
| TS                                                                                                                                                 |       |       |     |
| Units: Subjects                                                                                                                                    |       |       |     |
| Hispanic or Latino                                                                                                                                 | 15    | 23    | 38  |
| Not Hispanic or Latino                                                                                                                             | 121   | 114   | 235 |
| Unknown or Not Reported                                                                                                                            | 0     | 0     | 0   |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                             |                       |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Reporting group title                                                                                                                                                                                                                                       | Nintedanib+placebo    |
| Reporting group description:<br>Patients administered 150 milligram (mg) Nintedanib soft gelatine capsule orally twice daily (bid), with a possibility of dose reduction to 100 mg capsule bid along with placebo matching to Sildenafil for 24 weeks.      |                       |
| Reporting group title                                                                                                                                                                                                                                       | Nintedanib+sildenafil |
| Reporting group description:<br>Patients administered 150 milligram (mg) Nintedanib soft gelatine capsule orally twice daily (bid), with a possibility of dose reduction to 100 mg capsule bid along with 20 mg thrice daily (tid) Sildenafil for 24 weeks. |                       |

### Primary: Change from baseline in St George's Respiratory Questionnaire (SGRQ) total score at Week 12

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                             |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Change from baseline in St George's Respiratory Questionnaire (SGRQ) total score at Week 12 |
| End point description:<br>The SGRQ is a 50-item questionnaire developed to measure health status (quality of life). Scores are calculated for three domains: Symptoms, Activity and Impacts (Psycho-social) as well as a total score. A minimum change in score of 4 units was established as clinically relevant after patient and clinician testing. Scores range from 0 to 100, with higher scores indicating more limitations. The mean and standard error presented are actually adjusted mean for change from baseline and its standard error. Treated Set (TS): TS included all patients who were randomised to a treatment group and received at least one dose of randomised study medication. |                                                                                             |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Primary                                                                                     |
| End point timeframe:<br>Baseline and week 12                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                             |

| End point values                 | Nintedanib+placebo | Nintedanib+sildenafil |  |  |
|----------------------------------|--------------------|-----------------------|--|--|
| Subject group type               | Reporting group    | Reporting group       |  |  |
| Number of subjects analysed      | 133 <sup>[1]</sup> | 132 <sup>[2]</sup>    |  |  |
| Units: Unit on scale             |                    |                       |  |  |
| arithmetic mean (standard error) | -0.77 (± 1.009)    | -1.28 (± 1.013)       |  |  |

Notes:

[1] - TS

[2] - TS

### Statistical analyses

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                            |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| Statistical analysis title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Statistical Analysis 1                     |
| Statistical analysis description:<br>Mixed Model for Repeated Measures (MMRM) included fixed effects for treatment, visit, presence of any echocardiographic signs, baseline SGRQ total score as covariate, treatment-by-visit and baseline SGRQ total score-by-visit interaction terms using an unstructured covariance matrix. No imputation was planned. Data collected after Visit 5 (planned 12 weeks after start of study treatment) were not used for analysis. Roger- Kenward approximation was used to estimate denominator degrees of freedom. |                                            |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Nintedanib+sildenafil v Nintedanib+placebo |

|                                         |                                          |
|-----------------------------------------|------------------------------------------|
| Number of subjects included in analysis | 265                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority <sup>[3]</sup>               |
| P-value                                 | = 0.7191                                 |
| Method                                  | Mixed Model for Repeated Measures (MMRM) |
| Parameter estimate                      | Adjusted mean difference                 |
| Point estimate                          | -0.52                                    |
| Confidence interval                     |                                          |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -3.33                                    |
| upper limit                             | 2.3                                      |
| Variability estimate                    | Standard error of the mean               |
| Dispersion value                        | 1.431                                    |

Notes:

[3] - Adjusted mean is based on all analyzed patients in model (not only patients with a measurement at baseline and 12 weeks). H0: There is no difference in mean change from baseline in SGRQ total score at Week 12 between treatment with nintedanib co-administered with sildenafil and treatment with nintedanib alone. Ha: There is a difference in mean change from baseline in SGRQ total score at Week 12 between treatment with nintedanib coadministered with sildenafil and treatment with nintedanib alone.

## Secondary: Change from baseline in dyspnoea using the University of California San Diego Shortness of Breath Questionnaire (UCSD SOBQ) at Week 12

|                 |                                                                                                                                        |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Change from baseline in dyspnoea using the University of California San Diego Shortness of Breath Questionnaire (UCSD SOBQ) at Week 12 |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The UCSD SOBQ is a 24-item questionnaire developed to measure breathlessness on a scale between zero and five where 0 is not at all breathless and 5 is maximally breathless or too breathless to do the activity. The mean and standard error presented for descriptive statistics are actually adjusted mean for change from baseline and its standard error. TS.

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

End point timeframe:

Baseline and week 12

| End point values                 | Nintedanib+placebo | Nintedanib+sildenafil |  |  |
|----------------------------------|--------------------|-----------------------|--|--|
| Subject group type               | Reporting group    | Reporting group       |  |  |
| Number of subjects analysed      | 122 <sup>[4]</sup> | 120 <sup>[5]</sup>    |  |  |
| Units: Unit on scale             |                    |                       |  |  |
| arithmetic mean (standard error) | 4.40 (± 1.529)     | 1.46 (± 1.575)        |  |  |

Notes:

[4] - TS

[5] - TS

## Statistical analyses

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

Statistical analysis description:

MMRM included fixed effects for treatment, visit, presence of any echocardiographic signs, baseline UCSD SOBQ total score as covariate, treatment-by-visit and baseline UCSD SOBQ total score-by-visit interaction terms using an unstructured covariance matrix. No imputation was planned. Data collected after Visit 5 (planned 12 weeks after start of study treatment) were not used for analysis. Roger-



Kenward approximation was used to estimate denominator degrees of freedom.

|                                         |                                            |
|-----------------------------------------|--------------------------------------------|
| Comparison groups                       | Nintedanib+placebo v Nintedanib+sildenafil |
| Number of subjects included in analysis | 242                                        |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | superiority <sup>[6]</sup>                 |
| P-value                                 | = 0.1823                                   |
| Method                                  | Mixed Model for Repeated Measures (MMRM)   |
| Parameter estimate                      | Adjusted mean difference                   |
| Point estimate                          | -2.94                                      |
| Confidence interval                     |                                            |
| level                                   | 95 %                                       |
| sides                                   | 2-sided                                    |
| lower limit                             | -7.27                                      |
| upper limit                             | 1.39                                       |
| Variability estimate                    | Standard error of the mean                 |
| Dispersion value                        | 2.198                                      |

Notes:

[6] - Adjusted mean is based on all analyzed patients in the model (not only patients with a measurement at baseline and at 12 weeks).

## Secondary: Change from baseline in SGRQ total score at Week 24

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                     |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Change from baseline in SGRQ total score at Week 24 |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                     |
| The SGRQ is a 50-item questionnaire developed to measure health status (quality of life). Scores are calculated for three domains: Symptoms, Activity and Impacts (Psycho-social) as well as a total score. A minimum change in score of 4 units was established as clinically relevant after patient and clinician testing. The mean and standard error presented for descriptive statistics are actually adjusted mean for change from baseline and its standard error. TS |                                                     |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Secondary                                           |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                     |
| Baseline and week 24                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                     |

| End point values                 | Nintedanib+placebo | Nintedanib+sildenafil |  |  |
|----------------------------------|--------------------|-----------------------|--|--|
| Subject group type               | Reporting group    | Reporting group       |  |  |
| Number of subjects analysed      | 133 <sup>[7]</sup> | 132 <sup>[8]</sup>    |  |  |
| Units: Unit on scale             |                    |                       |  |  |
| arithmetic mean (standard error) | 2.42 (± 1.158)     | 0.23 (± 1.148)        |  |  |

Notes:

[7] - TS

[8] - TS

## Statistical analyses

|                                                                                                                                                                                                                                                                                                                                                                                                          |                                            |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| Statistical analysis title                                                                                                                                                                                                                                                                                                                                                                               | Statistical Analysis 1                     |
| Statistical analysis description:                                                                                                                                                                                                                                                                                                                                                                        |                                            |
| Mixed Model for Repeated Measures (MMRM) included fixed effects for treatment, visit, presence of any echocardiographic signs, baseline SGRQ total score as covariate, treatment-by-visit and baseline SGRQ total score-by-visit interaction terms using an unstructured covariance matrix. No imputation was planned. Roger- Kenward approximation was used to estimate denominator degrees of freedom. |                                            |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                                                        | Nintedanib+placebo v Nintedanib+sildenafil |

|                                         |                                          |
|-----------------------------------------|------------------------------------------|
| Number of subjects included in analysis | 265                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority <sup>[9]</sup>               |
| P-value                                 | = 0.1809                                 |
| Method                                  | Mixed Model for Repeated Measures (MMRM) |
| Parameter estimate                      | Adjusted mean difference                 |
| Point estimate                          | -2.19                                    |
| Confidence interval                     |                                          |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -5.4                                     |
| upper limit                             | 1.02                                     |
| Variability estimate                    | Standard error of the mean               |
| Dispersion value                        | 1.631                                    |

Notes:

[9] - Adjusted mean is based on all analyzed patients in the model (not only patients with a measurement at baseline and at 12 weeks).

### Secondary: Change from baseline in dyspnoea using UCSD SOBQ at Week 24

|                 |                                                             |
|-----------------|-------------------------------------------------------------|
| End point title | Change from baseline in dyspnoea using UCSD SOBQ at Week 24 |
|-----------------|-------------------------------------------------------------|

End point description:

The UCSD SOBQ is a 24-item questionnaire developed to measure breathlessness on a scale between zero and five where 0 is not at all breathless and 5 is maximally breathless or too breathless to do the activity. The mean and standard error presented for descriptive statistics are actually adjusted mean for change from baseline and its standard error. TS

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

End point timeframe:

Baseline and week 24

| End point values                 | Nintedanib+placebo  | Nintedanib+sildenafil |  |  |
|----------------------------------|---------------------|-----------------------|--|--|
| Subject group type               | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed      | 124 <sup>[10]</sup> | 123 <sup>[11]</sup>   |  |  |
| Units: Unit on scale             |                     |                       |  |  |
| arithmetic mean (standard error) | 6.85 (± 1.791)      | 4.44 (± 1.779)        |  |  |

Notes:

[10] - TS

[11] - TS

### Statistical analyses

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

Statistical analysis description:

Mixed Model for Repeated Measures (MMRM) included fixed effects for treatment, visit, presence of any echocardiographic signs, baseline UCSD SOBQ total score as covariate, treatment-by-visit and baseline UCSD SOBQ total score-by-visit interaction terms using an unstructured covariance matrix. No imputation was planned. The Roger- Kenward approximation was used to estimate denominator degrees of freedom.

|                   |                                            |
|-------------------|--------------------------------------------|
| Comparison groups | Nintedanib+placebo v Nintedanib+sildenafil |
|-------------------|--------------------------------------------|

|                                         |                                          |
|-----------------------------------------|------------------------------------------|
| Number of subjects included in analysis | 247                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority <sup>[12]</sup>              |
| P-value                                 | = 0.3421                                 |
| Method                                  | Mixed Model for Repeated Measures (MMRM) |
| Parameter estimate                      | Adjusted mean difference                 |
| Point estimate                          | -2.41                                    |
| Confidence interval                     |                                          |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -7.39                                    |
| upper limit                             | 2.58                                     |
| Variability estimate                    | Standard error of the mean               |
| Dispersion value                        | 2.529                                    |

Notes:

[12] - Adjusted mean is based on all analyzed patients in the model (not only patients with a measurement at baseline and at 12 weeks).

### Secondary: Percentage of patients with on-treatment serious adverse events (SAE) from baseline to Week 24

|                        |                                                                                                                 |
|------------------------|-----------------------------------------------------------------------------------------------------------------|
| End point title        | Percentage of patients with on-treatment serious adverse events (SAE) from baseline to Week 24                  |
| End point description: | Percentage of patients with on-treatment serious adverse events (SAE) from baseline to Week 24 is presented. TS |
| End point type         | Secondary                                                                                                       |
| End point timeframe:   | Baseline and week 24                                                                                            |

| End point values                      | Nintedanib+placebo  | Nintedanib+sildenafil |  |  |
|---------------------------------------|---------------------|-----------------------|--|--|
| Subject group type                    | Reporting group     | Reporting group       |  |  |
| Number of subjects analysed           | 136 <sup>[13]</sup> | 137 <sup>[14]</sup>   |  |  |
| Units: Percentage of participants (%) |                     |                       |  |  |
| number (not applicable)               | 32.4                | 27.0                  |  |  |

Notes:

[13] - TS

[14] - TS

### Statistical analyses

|                                   |                                                                                                                                                                                                                                                                                                                               |
|-----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Statistical analysis title        | Statistical Analysis 1                                                                                                                                                                                                                                                                                                        |
| Statistical analysis description: | Relative risk, Comparison of treatment groups is calculated by Cochran–Mantel–Haenszel test adjusting for the categorical covariate presence of any echocardiographic signs indicative of right heart dysfunction (yes/no), adjusted Mantel–Haenszel type risk ratios and risk differences with 95% confidence are presented. |
| Comparison groups                 | Nintedanib+placebo v Nintedanib+sildenafil                                                                                                                                                                                                                                                                                    |

|                                         |                             |
|-----------------------------------------|-----------------------------|
| Number of subjects included in analysis | 273                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[15]</sup> |
| Parameter estimate                      | Percentage ratio (%)        |
| Point estimate                          | 0.83                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 0.58                        |
| upper limit                             | 1.2                         |

Notes:

[15] - Within strata confidence limits are calculated according to Wald. Percentage ratio = (% of Nintedanib+sildenafil) / (% of Nintedanib+placebo).

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical Analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

Risk difference, Comparison of treatment groups is calculated by Cochran–Mantel–Haenszel test adjusting for the categorical covariate presence of any echocardiographic signs indicative of right heart dysfunction (yes/no), adjusted Mantel–Haenszel type risk ratios and risk differences with 95% confidence are presented.

|                                         |                                            |
|-----------------------------------------|--------------------------------------------|
| Comparison groups                       | Nintedanib+placebo v Nintedanib+sildenafil |
| Number of subjects included in analysis | 273                                        |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | superiority <sup>[16]</sup>                |
| P-value                                 | = 0.334                                    |
| Method                                  | Cochran-Mantel-Haenszel                    |
| Parameter estimate                      | Percentage difference (%)                  |
| Point estimate                          | -5.37                                      |
| Confidence interval                     |                                            |
| level                                   | 95 %                                       |
| sides                                   | 2-sided                                    |
| lower limit                             | -16.25                                     |
| upper limit                             | 5.52                                       |

Notes:

[16] - Within strata confidence limits are calculated according to Wald. Percentage difference = (% of Nintedanib+sildenafil) - (% of Nintedanib+placebo).

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the first drug administration until 28 days after the last drug administration.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 21.0 |
|--------------------|------|

### Reporting groups

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | Nintedanib+sildenafil |
|-----------------------|-----------------------|

Reporting group description:

Patients administered 150 milligram (mg) Nintedanib soft gelatine capsule orally twice daily (bid), with a possibility of dose reduction to 100 mg capsule bid along with 20 mg thrice daily (tid) Sildenafil for 24 weeks.

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Nintedanib+placebo |
|-----------------------|--------------------|

Reporting group description:

Patients administered 150 milligram (mg) Nintedanib soft gelatine capsule orally twice daily (bid), with a possibility of dose reduction to 100 mg capsule bid along with placebo matching to Sildenafil for 24 weeks.

| Serious adverse events                                              | Nintedanib+sildenafil | Nintedanib+placebo |  |
|---------------------------------------------------------------------|-----------------------|--------------------|--|
| Total subjects affected by serious adverse events                   |                       |                    |  |
| subjects affected / exposed                                         | 37 / 137 (27.01%)     | 44 / 136 (32.35%)  |  |
| number of deaths (all causes)                                       | 12                    | 12                 |  |
| number of deaths resulting from adverse events                      | 12                    | 12                 |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                       |                    |  |
| Neuroendocrine carcinoma of the skin                                |                       |                    |  |
| subjects affected / exposed                                         | 1 / 137 (0.73%)       | 0 / 136 (0.00%)    |  |
| occurrences causally related to treatment / all                     | 0 / 1                 | 0 / 0              |  |
| deaths causally related to treatment / all                          | 0 / 0                 | 0 / 0              |  |
| Lung adenocarcinoma                                                 |                       |                    |  |
| subjects affected / exposed                                         | 0 / 137 (0.00%)       | 1 / 136 (0.74%)    |  |
| occurrences causally related to treatment / all                     | 0 / 0                 | 0 / 1              |  |
| deaths causally related to treatment / all                          | 0 / 0                 | 0 / 0              |  |
| Neoplasm malignant                                                  |                       |                    |  |
| subjects affected / exposed                                         | 0 / 137 (0.00%)       | 1 / 136 (0.74%)    |  |
| occurrences causally related to treatment / all                     | 0 / 0                 | 0 / 1              |  |
| deaths causally related to treatment / all                          | 0 / 0                 | 0 / 0              |  |

|                                                      |                 |                 |  |
|------------------------------------------------------|-----------------|-----------------|--|
| Skin cancer                                          |                 |                 |  |
| subjects affected / exposed                          | 1 / 137 (0.73%) | 0 / 136 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Small cell lung cancer                               |                 |                 |  |
| subjects affected / exposed                          | 1 / 137 (0.73%) | 0 / 136 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 0           |  |
| Squamous cell carcinoma                              |                 |                 |  |
| subjects affected / exposed                          | 1 / 137 (0.73%) | 0 / 136 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Vascular disorders                                   |                 |                 |  |
| Circulatory collapse                                 |                 |                 |  |
| subjects affected / exposed                          | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Deep vein thrombosis                                 |                 |                 |  |
| subjects affected / exposed                          | 1 / 137 (0.73%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Phlebitis                                            |                 |                 |  |
| subjects affected / exposed                          | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Pyrexia                                              |                 |                 |  |
| subjects affected / exposed                          | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Oedema                                               |                 |                 |  |
| subjects affected / exposed                          | 1 / 137 (0.73%) | 0 / 136 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Sudden death                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 137 (0.73%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 1 / 1           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Asthma                                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute respiratory failure                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 137 (0.73%) | 2 / 136 (1.47%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Dyspnoea                                        |                 |                 |  |
| subjects affected / exposed                     | 5 / 137 (3.65%) | 2 / 136 (1.47%) |  |
| occurrences causally related to treatment / all | 1 / 5           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemothorax                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoxia                                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Idiopathic pulmonary fibrosis                   |                 |                 |  |
| subjects affected / exposed                     | 8 / 137 (5.84%) | 9 / 136 (6.62%) |  |
| occurrences causally related to treatment / all | 2 / 9           | 0 / 10          |  |
| deaths causally related to treatment / all      | 1 / 3           | 0 / 3           |  |
| Lung disorder                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Pneumothorax                                    |                 |                 |  |
| subjects affected / exposed                     | 2 / 137 (1.46%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumothorax spontaneous                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 137 (0.73%) | 0 / 136 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Pulmonary congestion                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary embolism                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 2 / 136 (1.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary hypertension                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 137 (0.73%) | 4 / 136 (2.94%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory failure                             |                 |                 |  |
| subjects affected / exposed                     | 2 / 137 (1.46%) | 3 / 136 (2.21%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 2           |  |
| Investigations                                  |                 |                 |  |
| Alanine aminotransferase increased              |                 |                 |  |
| subjects affected / exposed                     | 1 / 137 (0.73%) | 0 / 136 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Eosinophil percentage increased                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 137 (0.73%) | 0 / 136 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Aspartate aminotransferase                      |                 |                 |  |



|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| increased                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 137 (0.73%) | 0 / 136 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Eosinophil count increased                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 137 (0.73%) | 0 / 136 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic enzyme increased                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                 |                 |  |
| Thoracic vertebral fracture                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 137 (0.73%) | 0 / 136 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pelvic fracture                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 137 (0.73%) | 0 / 136 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Rib fracture                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 137 (0.73%) | 0 / 136 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Traumatic intracranial haemorrhage              |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Atrial fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 137 (0.73%) | 0 / 136 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Cardiac arrest                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Cardiac failure congestive                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coronary artery occlusion                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 137 (0.73%) | 0 / 136 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Left ventricular failure                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myocarditis                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| 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 / 137 (0.73%) | 0 / 136 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Right ventricular failure                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 3 / 136 (2.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 2           |  |
| Nervous system disorders                        |                 |                 |  |
| Cerebrovascular accident                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hemianopia homonymous                           |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 137 (0.73%) | 0 / 136 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Syncope                                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Transient ischaemic attack                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 137 (0.73%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders            |                 |                 |  |
| Anaemia                                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 137 (0.73%) | 0 / 136 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Disseminated intravascular coagulation          |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lymphadenopathy                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 137 (0.73%) | 0 / 136 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thrombocytopenia                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 137 (0.73%) | 0 / 136 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Gastritis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Diarrhoea                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ileus                                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| 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                     | 1 / 137 (0.73%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intestinal ischaemia                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| Pancreatitis acute                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| 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 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| 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                     | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Liver injury                                    |                 |                 |  |
| subjects affected / exposed                     | 2 / 137 (1.46%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Drug-induced liver injury                       |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 137 (0.73%) | 0 / 136 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatitis                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 137 (0.73%) | 0 / 136 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Portal vein thrombosis                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Acute kidney injury                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematuria                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary retention                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Osteoarthritis                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 137 (0.73%) | 0 / 136 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Bronchitis                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 137 (0.73%) | 0 / 136 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Influenza                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Liver abscess                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cellulitis                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lower respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 2 / 136 (1.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung infection                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sepsis                                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| 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                     | 0 / 137 (0.00%) | 2 / 136 (1.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 5 / 137 (3.65%) | 8 / 136 (5.88%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 1 / 8           |  |
| deaths causally related to treatment / all      | 0 / 1           | 1 / 3           |  |
| Septic shock                                    |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 137 (1.46%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 2           | 1 / 1           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Decreased appetite                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 137 (0.73%) | 0 / 136 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyponatraemia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoglycaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetes mellitus inadequate control            |                 |                 |  |
| subjects affected / exposed                     | 2 / 137 (1.46%) | 0 / 136 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypophagia                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 136 (0.74%) |  |
| 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>                     | Nintedanib+sildenafil | Nintedanib+placebo |  |
|-------------------------------------------------------|-----------------------|--------------------|--|
| Total subjects affected by non-serious adverse events |                       |                    |  |
| subjects affected / exposed                           | 118 / 137 (86.13%)    | 113 / 136 (83.09%) |  |
| Investigations                                        |                       |                    |  |
| Alanine aminotransferase increased                    |                       |                    |  |
| subjects affected / exposed                           | 8 / 137 (5.84%)       | 8 / 136 (5.88%)    |  |
| occurrences (all)                                     | 9                     | 9                  |  |
| Aspartate aminotransferase increased                  |                       |                    |  |
| subjects affected / exposed                           | 5 / 137 (3.65%)       | 7 / 136 (5.15%)    |  |
| occurrences (all)                                     | 6                     | 10                 |  |
| C-reactive protein increased                          |                       |                    |  |
| subjects affected / exposed                           | 6 / 137 (4.38%)       | 7 / 136 (5.15%)    |  |
| occurrences (all)                                     | 6                     | 9                  |  |
| Weight decreased                                      |                       |                    |  |
| subjects affected / exposed                           | 7 / 137 (5.11%)       | 12 / 136 (8.82%)   |  |
| occurrences (all)                                     | 7                     | 13                 |  |
| Gamma-glutamyltransferase increased                   |                       |                    |  |
| subjects affected / exposed                           | 7 / 137 (5.11%)       | 7 / 136 (5.15%)    |  |
| occurrences (all)                                     | 7                     | 9                  |  |
| Nervous system disorders                              |                       |                    |  |
| Dizziness                                             |                       |                    |  |
| subjects affected / exposed                           | 6 / 137 (4.38%)       | 8 / 136 (5.88%)    |  |
| occurrences (all)                                     | 6                     | 8                  |  |
| Headache                                              |                       |                    |  |
| subjects affected / exposed                           | 21 / 137 (15.33%)     | 10 / 136 (7.35%)   |  |
| occurrences (all)                                     | 24                    | 12                 |  |
| General disorders and administration site conditions  |                       |                    |  |
| Asthenia                                              |                       |                    |  |
| subjects affected / exposed                           | 6 / 137 (4.38%)       | 7 / 136 (5.15%)    |  |
| occurrences (all)                                     | 6                     | 8                  |  |
| Fatigue                                               |                       |                    |  |
| subjects affected / exposed                           | 7 / 137 (5.11%)       | 6 / 136 (4.41%)    |  |
| occurrences (all)                                     | 7                     | 6                  |  |
| Oedema peripheral                                     |                       |                    |  |



|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 7 / 137 (5.11%)   | 6 / 136 (4.41%)   |  |
| occurrences (all)                               | 8                 | 6                 |  |
| Pyrexia                                         |                   |                   |  |
| subjects affected / exposed                     | 6 / 137 (4.38%)   | 9 / 136 (6.62%)   |  |
| occurrences (all)                               | 9                 | 10                |  |
| Gastrointestinal disorders                      |                   |                   |  |
| Abdominal pain                                  |                   |                   |  |
| subjects affected / exposed                     | 4 / 137 (2.92%)   | 9 / 136 (6.62%)   |  |
| occurrences (all)                               | 4                 | 10                |  |
| Abdominal pain upper                            |                   |                   |  |
| subjects affected / exposed                     | 6 / 137 (4.38%)   | 7 / 136 (5.15%)   |  |
| occurrences (all)                               | 8                 | 8                 |  |
| Constipation                                    |                   |                   |  |
| subjects affected / exposed                     | 3 / 137 (2.19%)   | 8 / 136 (5.88%)   |  |
| occurrences (all)                               | 3                 | 10                |  |
| Diarrhoea                                       |                   |                   |  |
| subjects affected / exposed                     | 79 / 137 (57.66%) | 66 / 136 (48.53%) |  |
| occurrences (all)                               | 152               | 110               |  |
| Dyspepsia                                       |                   |                   |  |
| subjects affected / exposed                     | 9 / 137 (6.57%)   | 4 / 136 (2.94%)   |  |
| occurrences (all)                               | 9                 | 4                 |  |
| Gastrooesophageal reflux disease                |                   |                   |  |
| subjects affected / exposed                     | 7 / 137 (5.11%)   | 5 / 136 (3.68%)   |  |
| occurrences (all)                               | 7                 | 9                 |  |
| Nausea                                          |                   |                   |  |
| subjects affected / exposed                     | 22 / 137 (16.06%) | 14 / 136 (10.29%) |  |
| occurrences (all)                               | 30                | 15                |  |
| Vomiting                                        |                   |                   |  |
| subjects affected / exposed                     | 19 / 137 (13.87%) | 9 / 136 (6.62%)   |  |
| occurrences (all)                               | 32                | 12                |  |
| Respiratory, thoracic and mediastinal disorders |                   |                   |  |
| Cough                                           |                   |                   |  |
| subjects affected / exposed                     | 20 / 137 (14.60%) | 13 / 136 (9.56%)  |  |
| occurrences (all)                               | 24                | 13                |  |
| Dyspnoea                                        |                   |                   |  |

|                                                                                 |                         |                         |  |
|---------------------------------------------------------------------------------|-------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                | 13 / 137 (9.49%)<br>14  | 11 / 136 (8.09%)<br>11  |  |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)                   | 11 / 137 (8.03%)<br>15  | 6 / 136 (4.41%)<br>6    |  |
| Musculoskeletal and connective tissue disorders                                 |                         |                         |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)                   | 7 / 137 (5.11%)<br>8    | 2 / 136 (1.47%)<br>2    |  |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)                     | 7 / 137 (5.11%)<br>8    | 3 / 136 (2.21%)<br>3    |  |
| Infections and infestations                                                     |                         |                         |  |
| Influenza<br>subjects affected / exposed<br>occurrences (all)                   | 4 / 137 (2.92%)<br>4    | 7 / 136 (5.15%)<br>7    |  |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)                  | 12 / 137 (8.76%)<br>13  | 4 / 136 (2.94%)<br>5    |  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)             | 9 / 137 (6.57%)<br>9    | 8 / 136 (5.88%)<br>8    |  |
| Respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 8 / 137 (5.84%)<br>9    | 4 / 136 (2.94%)<br>4    |  |
| Metabolism and nutrition disorders                                              |                         |                         |  |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)          | 19 / 137 (13.87%)<br>20 | 23 / 136 (16.91%)<br>24 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date           | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 04 March 2016  | The text describing potential risks of sildenafil treatment was updated. The number of participating sites and the number of patients per site were modified based on a site feasibility assessment. In the exclusion criteria 6, 'partial thromboplastin time' was replaced by 'activated thromboplastin time'. Exclusion criteria 34, concerning patients with chronic liver disease, was added. Measurements of nintedanib metabolites were removed from the planned pharmacokinetic (PK) assessments. The amount of blood needed for biomarker assessments was increased.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 18 August 2016 | A trade name (INSTAGETM) was assigned to the trial. Pancreatitis and thrombocytopenia were added as risks of nintedanib treatment. major cardiovascular events (MACE) was added to the list of events to be adjudicated. The inclusion and exclusion criteria were modified to allow retesting, within a defined time frame, for the parameters mentioned in the inclusion criterion 5 and the exclusion criteria 4, 9 and 15, in case values at Visit 1 were abnormal. Footnote 1 of the inclusion and exclusion criteria was modified to also allow retesting of blood pressure and lung function tests, in addition to the laboratory parameters. In the exclusion criterion 15, 'systolic blood pressure (SBP) >180 millimeter of mercury (mmHg); diastolic blood pressure (DBP) >100 mmHg' was changed to (SBP >180 mmHg or DBP >100 mmHg). In the exclusion criterion 23 'treatment for pulmonary hypertension' was changed to 'treatment'. Clarifications were added regarding restrictions in concomitant medication use. The method of measuring oxygen saturation was corrected. The definition of acute IPF exacerbation was modified according to the new definition by an international working group. It was clarified that biobanking is an optional procedure, requiring local approval. Details of analyses of further endpoints were added in the statistical methods. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported