



Clinical trial results:

SENSCIS®: A double-blind, randomised, placebo-controlled trial evaluating efficacy and safety of oral nintedanib treatment for at least 52 weeks in patients with 'Systemic Sclerosis-associated Interstitial Lung Disease' (SSc-ILD)

Summary

| | |
|--------------------------|---|
| EudraCT number | 2015-000392-28 |
| Trial protocol | NL DE GB PT DK BE ES GR FR PL IE FI NO SE AT HU CZ IT |
| Global end of trial date | 28 November 2018 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v2 (current) |
| This version publication date | 14 November 2021 |
| First version publication date | 13 November 2019 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 1199.214 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02597933 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Boehringer Ingelheim |
| Sponsor organisation address | 173 Binger Strasse, Ingelheim am Rhein, Germany, 55216 |
| Public contact | QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 8002430127, clintriage.rdg@boehringer-ingelheim.com |
| Scientific contact | QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 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 | 19 December 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 31 October 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 November 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To investigate the efficacy and safety of nintedanib 150 mg twice daily (bid) in patients with SSc-ILD

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 30 November 2015 |
| 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 | Argentina: 7 |
| Country: Number of subjects enrolled | Australia: 13 |
| Country: Number of subjects enrolled | Austria: 2 |
| Country: Number of subjects enrolled | Belgium: 23 |
| Country: Number of subjects enrolled | Brazil: 7 |
| Country: Number of subjects enrolled | Canada: 6 |
| Country: Number of subjects enrolled | Chile: 8 |
| Country: Number of subjects enrolled | China: 39 |
| Country: Number of subjects enrolled | Czechia: 5 |
| Country: Number of subjects enrolled | Denmark: 15 |
| Country: Number of subjects enrolled | Finland: 5 |
| Country: Number of subjects enrolled | France: 73 |
| Country: Number of subjects enrolled | Germany: 63 |
| Country: Number of subjects enrolled | Greece: 18 |
| Country: Number of subjects enrolled | Hungary: 2 |
| Country: Number of subjects enrolled | India: 54 |
| Country: Number of subjects enrolled | Ireland: 2 |
| Country: Number of subjects enrolled | Israel: 15 |
| Country: Number of subjects enrolled | Italy: 41 |
| Country: Number of subjects enrolled | Japan: 92 |
| Country: Number of subjects enrolled | Malaysia: 8 |

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Mexico: 2 |
| Country: Number of subjects enrolled | Netherlands: 22 |
| Country: Number of subjects enrolled | Norway: 5 |
| Country: Number of subjects enrolled | Poland: 33 |
| Country: Number of subjects enrolled | Portugal: 17 |
| Country: Number of subjects enrolled | Spain: 27 |
| Country: Number of subjects enrolled | Sweden: 2 |
| Country: Number of subjects enrolled | Switzerland: 5 |
| Country: Number of subjects enrolled | Thailand: 9 |
| Country: Number of subjects enrolled | United Kingdom: 18 |
| Country: Number of subjects enrolled | United States: 181 |
| Worldwide total number of subjects | 819 |
| EEA total number of subjects | 355 |

Notes:

Subjects enrolled per age group

| | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 641 |
| From 65 to 84 years | 178 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This was a randomised, placebo-controlled, double-blind, parallel design trial.

Abbreviation used:

treatment (trt)

baseline (bl.)

categorical (cat.)

continuous (cont.)

number (no.)

patient (pt)

Placebo (pl.)

discontinued (disc.)

primary analysis (PA)

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in trial. Subjects attended specialist sites to ensure that they (the subjects) met all implemented inclusion/exclusion criteria. Subjects were not to be randomised to trial drug if any of the specific entry criteria was violated

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, Data analyst |

Blinding implementation details:

This was a randomised, placebo-controlled, double-blind, parallel design trial.

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description:

Patients were administered orally placebo matching nintedanib 150 milligram (mg) soft gelatine capsules, twice daily with a possibility to interrupt treatment or to reduce to 100mg to manage adverse events.

Two subjects randomised to matching placebo were not treated. Although the actual number of randomised patients is 290, as two subjects were not treated, the number of patients that provided data for analyses (shown in "Started" column) is 288. To be consistent with the baseline section the number of subjects treated is shown as started.

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

Dosage and administration details:

Patients were administered orally placebo matching nintedanib 150 milligram (mg) soft gelatine capsules, twice daily with a possibility to interrupt treatment or to reduce to 100mg to manage adverse events.

| | |
|------------------|------------|
| Arm title | Nintedanib |
|------------------|------------|

Arm description:

Patients were administered orally 150 milligram (mg) soft gelatin capsules, twice daily with a possibility to interrupt treatment or to reduce to 100mg to manage adverse events.

Two subjects randomised to Nintedanib were not treated. Although the actual number of randomised patients is 290, as two subjects were not treated, the number of patients that provided data for analyses (shown in "Started" column) is 288. To be consistent with the baseline section the number of subjects treated is shown as started.

| | |
|--|---------------|
| 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 were administered orally 150 milligram (mg) soft gelatin capsules, twice daily with a possibility to interrupt treatment or to reduce to 100mg to manage adverse events.

| Number of subjects in period 1^[1] | Placebo | Nintedanib |
|---|---------|------------|
| Started | 288 | 288 |
| Completed | 252 | 239 |
| Not completed | 36 | 49 |
| Consent withdrawn by subject | 7 | 5 |
| Adverse event, non-fatal | 20 | 28 |
| Protocol deviation | 2 | 2 |
| Other than stated above | 7 | 14 |

Notes:

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

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

Baseline characteristics

Reporting groups

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

Reporting group description:

Patients were administered orally placebo matching nintedanib 150 milligram (mg) soft gelatine capsules, twice daily with a possibility to interrupt treatment or to reduce to 100mg to manage adverse events.

Two subjects randomised to matching placebo were not treated. Although the actual number of randomised patients is 290, as two subjects were not treated, the number of patients that provided data for analyses (shown in "Started" column) is 288. To be consistent with the baseline section the number of subjects treated is shown as started.

| | |
|-----------------------|------------|
| Reporting group title | Nintedanib |
|-----------------------|------------|

Reporting group description:

Patients were administered orally 150 milligram (mg) soft gelatin capsules, twice daily with a possibility to interrupt treatment or to reduce to 100mg to manage adverse events.

Two subjects randomised to Nintedanib were not treated. Although the actual number of randomised patients is 290, as two subjects were not treated, the number of patients that provided data for analyses (shown in "Started" column) is 288. To be consistent with the baseline section the number of subjects treated is shown as started.

| Reporting group values | Placebo | Nintedanib | Total |
|------------------------|---------|------------|-------|
| Number of subjects | 288 | 288 | 576 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|--|--------|--------|-----|
| Age Continuous | | | |
| Treated set (TS): The treated set consisted of patients who were randomised to a treatment group and received at least 1 dose of trial medication. | | | |
| Units: years | | | |
| arithmetic mean | 53.4 | 54.6 | |
| standard deviation | ± 12.6 | ± 11.8 | - |
| Sex: Female, Male | | | |
| TS | | | |
| Units: Subjects | | | |
| Female | 212 | 221 | 433 |
| Male | 76 | 67 | 143 |
| Race (NIH/OMB) | | | |
| TS | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 3 | 2 | 5 |
| Asian | 81 | 62 | 143 |
| Native Hawaiian or Other Pacific Islander | 0 | 1 | 1 |
| Black or African American | 16 | 20 | 36 |
| White | 186 | 201 | 387 |
| More than one race | 2 | 2 | 4 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Ethnicity (NIH/OMB) | | | |
| TS | | | |
| Units: Subjects | | | |

| | | | |
|--|---------|---------|-----|
| Hispanic or Latino | 18 | 22 | 40 |
| Not Hispanic or Latino | 270 | 266 | 536 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Baseline pulmonary efficacy variables - Forced Vital Capacity (FVC) | | | |
| TS | | | |
| Units: mL | | | |
| arithmetic mean | 2541.0 | 2458.5 | |
| standard deviation | ± 815.5 | ± 735.9 | - |

End points

End points reporting groups

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

Reporting group description:

Patients were administered orally placebo matching nintedanib 150 milligram (mg) soft gelatine capsules, twice daily with a possibility to interrupt treatment or to reduce to 100mg to manage adverse events.

Two subjects randomised to matching placebo were not treated. Although the actual number of randomised patients is 290, as two subjects were not treated, the number of patients that provided data for analyses (shown in "Started" column) is 288. To be consistent with the baseline section the number of subjects treated is shown as started.

| | |
|-----------------------|------------|
| Reporting group title | Nintedanib |
|-----------------------|------------|

Reporting group description:

Patients were administered orally 150 milligram (mg) soft gelatin capsules, twice daily with a possibility to interrupt treatment or to reduce to 100mg to manage adverse events.

Two subjects randomised to Nintedanib were not treated. Although the actual number of randomised patients is 290, as two subjects were not treated, the number of patients that provided data for analyses (shown in "Started" column) is 288. To be consistent with the baseline section the number of subjects treated is shown as started.

Primary: Annual rate of decline in Forced Vital Capacity (FVC) over 52 weeks

| | |
|-----------------|---|
| End point title | Annual rate of decline in Forced Vital Capacity (FVC) over 52 weeks |
|-----------------|---|

End point description:

Forced vital capacity (FVC) is the total amount of air exhaled during the lung function test. For this endpoint reported means represent the adjusted rate.

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

End point timeframe:

up to week (wk) 52 after the start of administration

| End point values | Placebo | Nintedanib | | |
|----------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 288 ^[1] | 288 ^[2] | | |
| Units: millilitre (mL)/year (yr) | | | | |
| arithmetic mean (standard error) | -93.3 (± 13.5) | -52.4 (± 13.8) | | |

Notes:

[1] - Treated Set

[2] - Treated Set

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis I |
|----------------------------|------------------------|

Statistical analysis description:

The primary analysis is a restricted maximum likelihood (REML) based approach using a random slope & intercept model. The analysis included the fixed, categorical effects of treatment, ATA status & gender, fixed continuous effects of time & baseline FVC (mL), age and height as well as the treatment-by time & baseline-by-time interactions. Random effects was included for patient response for both time & intercept. Within-patient errors are modelled by an unstructured variance-covariance matrix

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Nintedanib |
| Number of subjects included in analysis | 576 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[3] |
| P-value | = 0.035 |
| Method | random coefficient regression |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 40.95 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.88 |
| upper limit | 79.01 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 19.38 |

Notes:

[3] - The model assumed that data were missing at random & that patients who dropped out would have behaved similarly to those who remained in trial.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis II |
|-----------------------------------|-------------------------|

Statistical analysis description:

This is a sensitivity analysis (SA) on primary endpoint including only on-trt measurements of FVC [mL]. The random coefficient model was used. The analysis included fixed, categorical effects of trt, ATA status & gender, fixed continuous effects of time & bl. FVC (mL), age, height, trt -by time & bl.-by-time interactions. Random effects included for patient response for both time & intercept. Within-patient errors were modelled by an Unstructured variance-covariance matrix.

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Nintedanib |
| Number of subjects included in analysis | 576 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[4] |
| P-value | = 0.0378 |
| Method | random coefficient regression |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 43.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.44 |
| upper limit | 83.83 |

Notes:

[4] - The model assumed that data were missing at random & that patients who dropped out would have behaved similarly to those who remained in trial.

| | |
|-----------------------------------|--------------------------|
| Statistical analysis title | Statistical Analysis III |
|-----------------------------------|--------------------------|

Statistical analysis description:

In multiple imputation SA 1, missing FVC values at wk 52 in pts who were alive at wk 52 were imputed assuming similar rate of FVC decline as in pts from corresponding trt group who prematurely disc. trial drug but had wk 52 FVC value. Missing FVC values at wk 52 in pts who died before wk 52 were imputed assuming similar rate of FVC decline as in pl. pts with wk 52 FVC value who prematurely disc. trial drug with most severe declines. The imputation model was similar to statistical model of PA.

| | |
|-------------------|----------------------|
| Comparison groups | Placebo v Nintedanib |
|-------------------|----------------------|

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 576 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.1046 |
| Method | random coefficient regression |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 30 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.22 |
| upper limit | 66.22 |

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis IV |
|-----------------------------------|-------------------------|

Statistical analysis description:

In multiple imputation SA 2, missing FVC values at wk 52 in pts who were alive at wk 52 were imputed assuming similar rate of FVC decline as in pts from pl. group who prematurely disc. trial drug but had a wk 52 FVC value. Missing FVC values at wk 52 in pts who died before wk 52 were imputed assuming similar rate of FVC decline as in pl. pts with a wk 52 FVC value who prematurely disc. trial drug with most severe declines. The imputation model was similar to the statistical model of the PA

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Nintedanib |
| Number of subjects included in analysis | 576 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.074 |
| Method | random coefficient regression |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 32.93 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.19 |
| upper limit | 69.06 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis V |
|-----------------------------------|------------------------|

Statistical analysis description:

In multiple imputation SA 3, missing FVC values at wk 52 in pts who were alive at wk 52 were imputed assuming a similar rate of FVC decline as in all pts in the pl. group who were included in the PA. Missing FVC values at wk 52 in pts who died before wk 52 were imputed assuming a similar rate of FVC decline as in all placebo patients included in the primary analysis with the most severe declines. The imputation model was similar to the statistical model of the PA.

| | |
|-------------------|----------------------|
| Comparison groups | Placebo v Nintedanib |
|-------------------|----------------------|

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 576 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0644 |
| Method | random coefficient regression |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 33.86 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.03 |
| upper limit | 69.75 |

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis VI |
|-----------------------------------|-------------------------|

Statistical analysis description:

This is sensitivity analysis using the model similar to the primary analysis but including a different set of covariates: the fixed, categorical effects of treatment, ATA status, the fixed continuous effects of time, baseline FVC (mL), and the treatment-by-time and baseline-by-time interactions. Random effects was included for patient response for both time and intercept.

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Nintedanib |
| Number of subjects included in analysis | 576 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0351 |
| Method | random coefficient regression |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 40.95 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.88 |
| upper limit | 79.01 |

| | |
|-----------------------------------|--------------------------|
| Statistical analysis title | Statistical Analysis VII |
|-----------------------------------|--------------------------|

Statistical analysis description:

This is sensitivity analysis using the model similar to the primary analysis but including a different set of covariates: the fixed, categorical effects of treatment, ATA status (Positive / Negative), gender and mycophenolate mofetil /sodium background therapy use (Yes / No), fixed continuous effects of time, age , height and baseline FVC (mL), the treatment-by-time and baseline-by-time interactions. Random effects was included for patient response for both time and intercept

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Nintedanib |
| Number of subjects included in analysis | 576 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0349 |
| Method | random coefficient regression |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 40.98 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.92 |
| upper limit | 79.04 |

Secondary: Absolute change from baseline in the Modified Rodnan Skin Score (mRSS) at Week 52

| | |
|-----------------|---|
| End point title | Absolute change from baseline in the Modified Rodnan Skin Score (mRSS) at Week 52 |
|-----------------|---|

End point description:

This is the first key secondary endpoint. The modified Rodnan Skin Score (mRSS) is an evaluation of the patient's skin thickness rated by clinical palpation using a 0 to 3 scale. The scale differentiates between 0 = normal skin, 1 = mild thickness, 2 = moderate thickness, and 3 = severe thickness with inability to pinch the skin into a fold. The palpation is done for each of the 17 surface anatomic areas of the body: face, anterior chest, abdomen, fingers (right and left separately), forearms, upper arms, thighs, lower legs, dorsum of hands and feet. The sum of these individual values is defined as the total skin score. The mRSS has a range from 0 (no thickening) to 51 (severe thickening in all 17 areas). A high score corresponds to worse skin thickness. Least square mean is actually the adjusted mean. Adjusted mean was based on all analysed patients in the model (not only patients with a baseline and measurement at Week 52).

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

End point timeframe:

Baseline and up to 52 weeks after the start of administration

| End point values | Placebo | Nintedanib | | |
|-------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 288 ^[5] | 288 ^[6] | | |
| Units: unit on scale | | | | |
| least squares mean (standard error) | -1.96 (± 0.26) | -2.17 (± 0.27) | | |

Notes:

[5] - Treated Set

[6] - Treated Set

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis I |
|----------------------------|------------------------|

Statistical analysis description:

The mixed model repeated measures (MMRM) approach was used. The model assumed that data were missing at random & that patients who dropped out would have behaved similarly to those who remained in trial.

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Nintedanib |
| Number of subjects included in analysis | 576 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.5785 |
| Method | MMRM |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.21 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.94 |
| upper limit | 0.53 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.37 |

Secondary: Absolute change from baseline in Saint George's Respiratory Questionnaire (SGRQ) total score at Week 52.

| | |
|-----------------|--|
| End point title | Absolute change from baseline in Saint George's Respiratory Questionnaire (SGRQ) total score at Week 52. |
|-----------------|--|

End point description:

This is the second key secondary endpoint. The Saint George's Respiratory Questionnaire measures the health status in patients with chronic airflow limitation. It consists of 2 parts that cover 3 domains: symptoms, activities, and impacts. The symptom domain relates to the effect, frequency and severity of respiratory symptoms. The activity domain relates to activities that cause or are limited by breathlessness. The impact domain evaluates a range of aspects concerned with social functioning and psychological disturbances resulting from airways disease. The scores of these domains range from 0 (no impairment) to 100 (worst possible). The calculated total score summarises the impact of the disease on overall health status. A high score corresponds to worse health. Least square mean is actually the adjusted mean. Adjusted mean was based on all analysed patients in the model (not only patients with a baseline and measurement at Week 52).

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

End point timeframe:

Baseline and up to 52 weeks after the start of administration

| End point values | Placebo | Nintedanib | | |
|-------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 288 ^[7] | 288 ^[8] | | |
| Units: unit on scale | | | | |
| least squares mean (standard error) | -0.88 (± 0.87) | 0.81 (± 0.88) | | |

Notes:

[7] - Treated Set

[8] - Treated Set

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis I |
|----------------------------|------------------------|

Statistical analysis description:

The mixed model repeated measures (MMRM) approach was used, with fixed categorical effects of ATA status, visit, treatment-by visit interaction and baseline-by-visit interaction. Visit was the repeated measure. Within-patient errors were modelled by unstructured variance-covariance structure.

| | |
|-------------------|----------------------|
| Comparison groups | Placebo v Nintedanib |
|-------------------|----------------------|

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 576 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[9] |
| P-value | = 0.1711 |
| Method | MMRM |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.69 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.73 |
| upper limit | 4.12 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.24 |

Notes:

[9] - The MMRM model assumed that data were missing at random & that patients who dropped out would have behaved similarly to those who remained in trial.

Secondary: Annual rate of decline in FVC in percentage (%) predicted over 52 weeks

| | |
|-----------------|---|
| End point title | Annual rate of decline in FVC in percentage (%) predicted over 52 weeks |
|-----------------|---|

End point description:

Annual rate of decline in FVC in percentage (%) predicted over 52 weeks. For this endpoint reported means represent the adjusted rate.

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

End point timeframe:

up to 52 weeks after the start of administration

| End point values | Placebo | Nintedanib | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 288 ^[10] | 288 ^[11] | | |
| Units: % predicted/yr | | | | |
| arithmetic mean (standard error) | -2.6 (± 0.4) | -1.4 (± 0.4) | | |

Notes:

[10] - Treated set

[11] - Treated set

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis I |
|----------------------------|------------------------|

Statistical analysis description:

Based on a random coefficient regression with fixed categorical effects of treatment, ATA status, fixed continuous effects of time, baseline FVC [% pred], & including treatment-by-time and baseline-by-time interactions. Random effect was included for patient specific intercept & time. Within-patient errors are modelled by an Unstructured variance-covariance matrix. Inter-individual variability is modelled by a Variance-Components variance-covariance matrix.

| | |
|-------------------|----------------------|
| Comparison groups | Placebo v Nintedanib |
|-------------------|----------------------|

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 576 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[12] |
| P-value | = 0.0331 |
| Method | MMRM |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.15 |
| Confidence interval | |
| level | Other: 1.15 % |
| sides | 2-sided |
| lower limit | 0.09 |
| upper limit | 2.21 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.54 |

Notes:

[12] - The model assumed that data were missing at random & that patients who dropped out would have behaved similarly to those who remained in trial.

Secondary: Absolute change from baseline in FVC in mL at Week 52

| | |
|---|---|
| End point title | Absolute change from baseline in FVC in mL at Week 52 |
| End point description: | |
| Absolute change from baseline in FVC in mL at Week 52. Least square mean is actually the adjusted mean. Adjusted mean was based on all analysed patients in the model (not only patients with a baseline and measurement at Week 52). | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and up to 52 weeks after the start of administration | |

| End point values | Placebo | Nintedanib | | |
|-------------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 288 ^[13] | 288 ^[14] | | |
| Units: mL | | | | |
| least squares mean (standard error) | -101.03 (± 13.62) | -54.63 (± 13.94) | | |

Notes:

[13] - Treated set

[14] - Treated set

Statistical analyses

| | |
|--|------------------------|
| Statistical analysis title | Statistical Analysis I |
| Statistical analysis description: | |
| The mixed model repeated measures (MMRM) approach was used, with fixed categorical effects of ATA status, visit, treatment-byvisit interaction and baseline-by-visit interaction. Visit was the repeated measure. Within-patient errors were modelled by unstructured variance-covariance structure. | |
| Comparison groups | Placebo v Nintedanib |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 576 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[15] |
| P-value | = 0.0177 |
| Method | MMRM |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 46.41 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 8.09 |
| upper limit | 84.73 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 19.51 |

Notes:

[15] - The model assumed that data were missing at random & that patients who dropped out would have behaved similarly to those who remained in trial.

Secondary: Relative change from baseline [%] of mRSS at Week 52

| | |
|------------------------|--|
| End point title | Relative change from baseline [%] of mRSS at Week 52 |
| End point description: | Relative change from baseline [%] of mRSS at Week 52. Least square mean is actually the adjusted mean. Adjusted mean was based on all analysed patients in the model (not only patients with a baseline and measurement at Week 52). |
| End point type | Secondary |
| End point timeframe: | Baseline and up to 52 weeks after the start of administration |

| End point values | Placebo | Nintedanib | | |
|-------------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 288 ^[16] | 288 ^[17] | | |
| Units: unit on scale | | | | |
| least squares mean (standard error) | -3.92 (± 5.89) | -10.20 (± 5.98) | | |

Notes:

[16] - Treated set

[17] - Treated set

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Statistical Analysis I |
| Statistical analysis description: | The mixed model repeated measures (MMRM) approach was used, with fixed categorical effects of ATA status, visit, treatment-by-visit interaction and baseline-by-visit interaction. Visit was the repeated measure. Within-patient errors were modelled by unstructured variance-covariance structure. |
| Comparison groups | Placebo v Nintedanib |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 576 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[18] |
| P-value | = 0.4547 |
| Method | MMRM |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -6.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -22.77 |
| upper limit | 10.21 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 8.39 |

Notes:

[18] - The model assumed that data were missing at random & that patients who dropped out would have behaved similarly to those who remained in trial.

Secondary: Time to death

| | |
|---|---------------|
| End point title | Time to death |
| End point description: | |
| Length of survival of patients treated with a placebo or Nintedanib 150 mg bid over the whole trial. The number of patients who observed an event are summarized below. | |
| End point type | Secondary |
| End point timeframe: | |
| From date of first trial drug intake up to date of death or last contact date (ie., up to 100 weeks) | |

| End point values | Placebo | Nintedanib | | |
|-----------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 288 ^[19] | 288 ^[20] | | |
| Units: Participants | | | | |
| number (not applicable) | 9 | 10 | | |

Notes:

[19] - Treated set

[20] - Treated set

Statistical analyses

| | |
|--|------------------------|
| Statistical analysis title | Statistical Analysis I |
| Statistical analysis description: | |
| Based on Cox's regression model (Wald test), stratified by ATA status. | |
| Comparison groups | Placebo v Nintedanib |
| Number of subjects included in analysis | 576 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.7535 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.16 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.47 |
| upper limit | 2.84 |

Secondary: The percentage (%) of responder based on Combined Response Index in Systemic Sclerosis (CRISS) at Week 52

| | |
|-----------------|---|
| End point title | The percentage (%) of responder based on Combined Response Index in Systemic Sclerosis (CRISS) at Week 52 |
|-----------------|---|

End point description:

The percentage (%) of responder based on Combined Response Index in Systemic Sclerosis (CRISS) at Week 52. This is a composite endpoint, based on the mRSS, FVC percent predicted, HAQ-DI, patient's global impression of overall health VAS and physician's global impression of patient's overall health VAS, as well as the absence of significant worsening of interstitial lung disease, a new scleroderma renal crisis, left ventricular failure or pulmonary arterial hypertension. The CRISS index score represents a probability of improvement and ranges between 0 and 1. This is a 2 stage process to predict probability of improvement: Step 1 – absence of major organ progression (SRC etc.) – score "0" Step 2 – predicted probability of improvement – (score "0 – 1").

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

End point timeframe:

Week 52

| End point values | Placebo | Nintedanib | | |
|--|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 288 ^[21] | 288 ^[22] | | |
| Units: (%) of responder based on CRISS | | | | |
| number (not applicable) | 11.8 | 12.2 | | |

Notes:

[21] - Treated set

[22] - Treated set

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis I |
|----------------------------|------------------------|

Statistical analysis description:

The comparison between both treatment groups was performed using a Cochran-Mantel-Haenszel test. CRISS score at Week 52 was transformed into 100 binary responder endpoints using multiple imputation. These were analyzed using a Cochran-Mantel-Haenszel test, stratified by ATA status. OR and the 95% CI as obtained from all 100 imputations were combined using Rubin's rule.

| | |
|---|-------------------------|
| Comparison groups | Placebo v Nintedanib |
| Number of subjects included in analysis | 576 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.9115 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.03 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.57 |
| upper limit | 1.88 |

Secondary: Absolute change from baseline in Carbon Monoxide Diffusion Capacity (DLco) in % predicted at Week 52

| | |
|---|--|
| End point title | Absolute change from baseline in Carbon Monoxide Diffusion Capacity (DLco) in % predicted at Week 52 |
| End point description: | |
| Absolute change from baseline in Carbon Monoxide Diffusion Capacity (DLco) in % predicted at Week 52. Least square mean is actually the adjusted mean. Adjusted mean is based on all analysed patients in the model (not only patients with a baseline and measurement at week 52). | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and up to 52 weeks after the start of administration | |

| End point values | Placebo | Nintedanib | | |
|-------------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 288 ^[23] | 288 ^[24] | | |
| Units: % predicted DLco | | | | |
| least squares mean (standard error) | -2.77 (± 0.54) | -3.21 (± 0.54) | | |

Notes:

[23] - Treated set

[24] - Treated set

Statistical analyses

| | |
|---|--------------------------------|
| Statistical analysis title | Statistical Analysis I |
| Statistical analysis description: | |
| The mixed model repeated measures (MMRM) approach was used, with fixed categorical effects of ATA status, visit, treatment-by-visit interaction and baseline-by-visit interaction. Visit was the repeated measure. Within-patient errors were modelled by unstructured variance-covariance structure. | |
| Comparison groups | Placebo v Nintedanib |
| Number of subjects included in analysis | 576 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.5668 |
| Method | MMRM |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.44 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.94 |
| upper limit | 1.06 |

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.76 |

Secondary: Absolute change from baseline in digital ulcer net burden at Week 52

| | |
|-----------------|--|
| End point title | Absolute change from baseline in digital ulcer net burden at Week 52 |
|-----------------|--|

End point description:

Absolute change from baseline in digital ulcer net burden (defined as the number of new digital ulcers (DUs) plus the number of DUs that have been verified at any earlier assessment during the trial) at Week 52. It is calculated at a visit by counting the total number of fingertips with ulcers (i.e. number of fingers with presence of digital ulcer ticked "Yes") at the corresponding visit Least square mean is actually the adjusted mean. Adjusted mean is based on all analysed patients in the model (not only patients with a baseline and measurement at week 52).

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

End point timeframe:

Baseline and up to 52 weeks after the start of administration

| End point values | Placebo | Nintedanib | | |
|-------------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 288 ^[25] | 288 ^[26] | | |
| Units: fingers | | | | |
| least squares mean (standard error) | 0.06 (± 0.04) | 0.03 (± 0.05) | | |

Notes:

[25] - Treated set

[26] - Treated set

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis I |
|----------------------------|------------------------|

Statistical analysis description:

The mixed model repeated measures (MMRM) approach was used, with fixed categorical effects of ATA status, visit, treatment-by-visit interaction and baseline-by-visit interaction. Visit was the repeated measure. Within-patient errors were modelled by unstructured variance-covariance structure.

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Nintedanib |
| Number of subjects included in analysis | 576 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.5914 |
| Method | MMRM |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.16 |
| upper limit | 0.09 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.06 |

Secondary: Absolute change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) score at Week 52

| | |
|-----------------|---|
| End point title | Absolute change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) score at Week 52 |
|-----------------|---|

End point description:

Absolute change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) score at Week 52. The HAQ-DI score is calculated as follows: Each question is scored 0–3 (where 0= “without difficulty” & 3= “unable to do”). There are 8 categories (Dressing & Grooming, Arising, Eating, Walking, Hygiene, Reach, Grip, Activities), each including 2 or 3 questions. The score for each category corresponds to maximum question score within each category. Finally, HAQ-DI score corresponds to sum of the sub-scores of all 8 categories divided by number of categories completed. Please note that if there are fewer than 6 categories with responses, then a score cannot be calculated. The HAQ-DI score scale has 25 possible values (i.e., 0, 0.125, 0.250, 0.375 ... 3). A high score corresponds to worse impairment. Least square mean is actually the adjusted mean. Adjusted mean is based on all analysed patients in the model (not only patients with a baseline and measurement at week 52).

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

End point timeframe:

Baseline and up to 52 weeks after the start of administration

| End point values | Placebo | Nintedanib | | |
|-------------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 288 ^[27] | 288 ^[28] | | |
| Units: unit on a scale | | | | |
| least squares mean (standard error) | 0.022 (± 0.024) | 0.054 (± 0.024) | | |

Notes:

[27] - Treated set

[28] - Treated set

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis I |
|----------------------------|------------------------|

Statistical analysis description:

Based on mixed model repeated measures (MMRM) approach was used, with fixed categorical effects of ATA status, visit, treatment-by-visit interaction and baseline-by-visit interaction. Visit was the repeated measure. Within-patient errors were modelled by unstructured variance-covariance structure.

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Nintedanib |
| Number of subjects included in analysis | 576 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.3447 |
| Method | MMRM |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.032 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.035 |
| upper limit | 0.099 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.034 |

Secondary: Absolute change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT) dyspnoea score at Week 52

| | |
|-----------------|---|
| End point title | Absolute change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT) dyspnoea score at Week 52 |
|-----------------|---|

End point description:

Absolute change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT) dyspnoea score at Week 52. FACIT-Dyspnoea (Dyspnoea) 10 Item Short Form include a 4-point rating scale (no shortness of breath=0; mildly short of breath=1; moderately short of breath = 2; severely short of breath =3; or I did not do this in the past 7 days =4). Next, using the same 10 items, respondents are asked to rate the amount of difficulty they experienced when doing these tasks on a 4-point Likert scale (no difficulty=0; a little difficulty=1; some difficulty =2; much difficulty = 3). The FACIT-Dyspnea short forms are scored such that a high score represents high levels of dyspnea. Least square mean is actually the adjusted mean. Adjusted mean is based on all analysed patients in the model (not only patients with a baseline and measurement at week 52).

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

End point timeframe:

Baseline and up to 52 weeks after the start of administration

| End point values | Placebo | Nintedanib | | |
|-------------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 288 ^[29] | 288 ^[30] | | |
| Units: Unit on a scale | | | | |
| least squares mean (standard error) | 0.34 (± 0.41) | 0.99 (± 0.42) | | |

Notes:

[29] - Treated set

[30] - Treated set

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis I |
|----------------------------|------------------------|

Statistical analysis description:

The mixed model repeated measures (MMRM) approach was used, with fixed categorical effects of ATA status, visit, treatment-by-visit interaction and baseline-by-visit interaction. Visit was the repeated measure. Within-patient errors were modelled by unstructured variance-covariance structure.

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Nintedanib |
| Number of subjects included in analysis | 576 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.2727 |
| Method | MMRM |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.64 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.51 |
| upper limit | 1.79 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.58 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From date of first trial drug intake up to date of death or last contact date (ie., up to 100 weeks).

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

Dictionary used

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

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

Reporting groups

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

Reporting group description:

Patients were administered orally placebo matching nintedanib 150 milligram (mg) soft gelatine capsules, twice daily with a possibility to interrupt treatment or to reduce to 100mg to manage adverse events. Two subjects randomised to matching placebo were not treated. Although the actual number of randomised patients is 290, as two subjects were not treated, the number of patients that provided data for analyses (shown in "Started" column) is 288. To be consistent with the baseline section the number of subjects treated is shown as started.

| | |
|-----------------------|------------|
| Reporting group title | Nintedanib |
|-----------------------|------------|

Reporting group description:

Patients were administered orally 150 milligram (mg) soft gelatin capsules, twice daily with a possibility to interrupt treatment or to reduce to 100mg to manage adverse events. Two subjects randomised to Nintedanib were not treated. Although the actual number of randomised patients is 290, as two subjects were not treated, the number of patients that provided data for analyses (shown in "Started" column) is 288. To be consistent with the baseline section the number of subjects treated is shown as started.

| Serious adverse events | Placebo | Nintedanib | |
|---|-------------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 79 / 288 (27.43%) | 88 / 288 (30.56%) | |
| number of deaths (all causes) | 9 | 10 | |
| number of deaths resulting from adverse events | 5 | 6 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Benign mesothelioma | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colon cancer | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric cancer | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (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 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Malignant melanoma | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mesothelioma malignant | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Nasopharyngeal cancer | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-small cell lung cancer | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal cancer | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma of skin | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 288 (0.35%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sweat gland tumour | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Extremity necrosis | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral artery occlusion | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Raynaud's phenomenon | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombophlebitis superficial | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vena cava thrombosis | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| 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 | | | |
| Brain death | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Polyp | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 288 (0.69%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systemic inflammatory response syndrome | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Anti-neutrophil cytoplasmic antibody positive vasculitis | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ovarian cyst | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 3 / 288 (1.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vulvovaginal swelling | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute lung injury | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Aspiration | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cough | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 8 / 288 (2.78%) | 5 / 288 (1.74%) | |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemothorax | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 6 / 288 (2.08%) | 10 / 288 (3.47%) | |
| occurrences causally related to treatment / all | 0 / 6 | 1 / 10 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Painful respiration | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 288 (0.35%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax spontaneous | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary arterial hypertension | | | |
| subjects affected / exposed | 4 / 288 (1.39%) | 4 / 288 (1.39%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 2 / 288 (0.69%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 4 / 288 (1.39%) | 5 / 288 (1.74%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary fibrosis | | | |
| subjects affected / exposed | 4 / 288 (1.39%) | 4 / 288 (1.39%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 288 (0.35%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systemic sclerosis pulmonary | | | |
| subjects affected / exposed | 5 / 288 (1.74%) | 3 / 288 (1.04%) | |
| occurrences causally related to treatment / all | 0 / 6 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Major depression | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Delirium | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Cell marker increased | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Forced vital capacity decreased | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| White blood cell count decreased | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint dislocation | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postoperative ileus | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Hypertrophic cardiomyopathy | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Arrhythmia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 288 (0.69%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial flutter | | | |
| subjects affected / exposed | 3 / 288 (1.04%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery disease | | | |
| subjects affected / exposed | 2 / 288 (0.69%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocarditis | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Palpitations | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericarditis | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleuropericarditis | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Restrictive cardiomyopathy | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Right ventricular failure | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular fibrillation | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Carotid artery aneurysm | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral amyloid angiopathy | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral infarction | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral microhaemorrhage | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular disorder | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depressed level of consciousness | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Immune thrombocytopenic purpura | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombotic microangiopathy | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| Glaucoma | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Macular oedema | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retinal vein occlusion | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rhegmatogenous retinal detachment | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Colitis | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis ischaemic | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 288 (0.69%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematemesis | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematochezia | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus paralytic | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal mass | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal pseudo-obstruction | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine polyp | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 2 / 288 (0.69%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Bile duct stone | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug-induced liver injury | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 288 (0.35%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatocellular injury | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver disorder | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver injury | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Actinic keratosis | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Digital pitting scar | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Petechiae | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sclerema | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin ulcer | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 288 (0.69%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 3 / 288 (1.04%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder perforation | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Scleroderma renal crisis | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Urinary incontinence | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue | | | |

| | | | |
|---|-----------------|-----------------|--|
| disorders | | | |
| Arthritis | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bursitis | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drooping shoulder syndrome | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fistula | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 3 / 288 (1.04%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteonecrosis | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Polymyalgia rheumatica | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Scleroderma | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systemic scleroderma | | | |
| subjects affected / exposed | 2 / 288 (0.69%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Adenovirus infection | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Campylobacter gastroenteritis | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gangrene | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (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 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection | | | |
| subjects affected / exposed | 2 / 288 (0.69%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteomyelitis | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 288 (0.69%) | 10 / 288 (3.47%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 11 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 3 / 288 (1.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systemic candida | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tuberculosis | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fluid overload | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 288 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Placebo | Nintedanib | |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 239 / 288 (82.99%) | 270 / 288 (93.75%) | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 4 / 288 (1.39%) | 22 / 288 (7.64%) | |
| occurrences (all) | 4 | 30 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 288 (0.35%) | 16 / 288 (5.56%) | |
| occurrences (all) | 1 | 20 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 4 / 288 (1.39%) | 19 / 288 (6.60%) | |
| occurrences (all) | 4 | 22 | |
| Weight decreased | | | |
| subjects affected / exposed | 15 / 288 (5.21%) | 39 / 288 (13.54%) | |
| occurrences (all) | 15 | 41 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 15 / 288 (5.21%) | 19 / 288 (6.60%) | |
| occurrences (all) | 15 | 22 | |
| Headache | | | |
| subjects affected / exposed | 28 / 288 (9.72%) | 34 / 288 (11.81%) | |
| occurrences (all) | 40 | 49 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 21 / 288 (7.29%) | 33 / 288 (11.46%) | |
| occurrences (all) | 26 | 37 | |
| Pyrexia | | | |

| | | | |
|--|------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 13 / 288 (4.51%) 18 | 20 / 288 (6.94%) 22 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 21 / 288 (7.29%) | 36 / 288 (12.50%) | |
| occurrences (all) | 29 | 56 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 15 / 288 (5.21%) | 21 / 288 (7.29%) | |
| occurrences (all) | 22 | 41 | |
| Constipation | | | |
| subjects affected / exposed | 19 / 288 (6.60%) | 15 / 288 (5.21%) | |
| occurrences (all) | 19 | 15 | |
| Diarrhoea | | | |
| subjects affected / exposed | 92 / 288 (31.94%) | 218 / 288 (75.69%) | |
| occurrences (all) | 211 | 647 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 26 / 288 (9.03%) | 20 / 288 (6.94%) | |
| occurrences (all) | 30 | 25 | |
| Nausea | | | |
| subjects affected / exposed | 41 / 288 (14.24%) | 96 / 288 (33.33%) | |
| occurrences (all) | 49 | 213 | |
| Vomiting | | | |
| subjects affected / exposed | 31 / 288 (10.76%) | 78 / 288 (27.08%) | |
| occurrences (all) | 39 | 165 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 62 / 288 (21.53%) | 41 / 288 (14.24%) | |
| occurrences (all) | 80 | 46 | |
| Dyspnoea | | | |
| subjects affected / exposed | 27 / 288 (9.38%) | 23 / 288 (7.99%) | |
| occurrences (all) | 29 | 27 | |
| Epistaxis | | | |
| subjects affected / exposed | 16 / 288 (5.56%) | 8 / 288 (2.78%) | |
| occurrences (all) | 17 | 18 | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|-------------------------|-------------------------|--|
| Skin ulcer subjects affected / exposed occurrences (all) | 54 / 288 (18.75%) 87 | 56 / 288 (19.44%) 94 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 23 / 288 (7.99%) 28 | 23 / 288 (7.99%) 31 | |
| Back pain subjects affected / exposed occurrences (all) | 15 / 288 (5.21%) 15 | 20 / 288 (6.94%) 22 | |
| Myalgia subjects affected / exposed occurrences (all) | 11 / 288 (3.82%) 11 | 16 / 288 (5.56%) 17 | |
| Pain in extremity subjects affected / exposed occurrences (all) | 14 / 288 (4.86%) 15 | 15 / 288 (5.21%) 17 | |
| Infections and infestations | | | |
| Bronchitis subjects affected / exposed occurrences (all) | 27 / 288 (9.38%) 32 | 22 / 288 (7.64%) 32 | |
| Influenza subjects affected / exposed occurrences (all) | 15 / 288 (5.21%) 15 | 16 / 288 (5.56%) 16 | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 56 / 288 (19.44%) 77 | 43 / 288 (14.93%) 61 | |
| Respiratory tract infection subjects affected / exposed occurrences (all) | 16 / 288 (5.56%) 19 | 10 / 288 (3.47%) 14 | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 43 / 288 (14.93%) 63 | 39 / 288 (13.54%) 53 | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 28 / 288 (9.72%) 41 | 28 / 288 (9.72%) 42 | |
| Metabolism and nutrition disorders | | | |

| | | | |
|--|------------------------|------------------------|--|
| Decreased appetite subjects affected / exposed occurrences (all) | 14 / 288 (4.86%) 15 | 28 / 288 (9.72%) 33 | |
|--|------------------------|------------------------|--|

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--|
| 02 March 2016 | <p>The following main changes in the conduct of the trial were introduced by the amendment:</p> <ol style="list-style-type: none">1) To ensure regular pregnancy testing as requested by health authorities, information was added that women of childbearing potential had to perform a pregnancy test every 4 to 6 weeks. Once intervals between site visits were >6 weeks, home urine dipstick pregnancy tests were centrally provided and had to be performed at home.2) For Inclusion Criterion No. 5, the reference time point for the historical HRCT, which had to be performed within 12 months, was changed from Visit 2 to Visit 1, as Visit 1 represented the better predictable time point3) Exclusion Criterion No. 8 was updated to clarify that not only digital ulcers but also severe other ulcers could have led to the exclusion of a patient at the discretion of the investigator4) Exclusion Criterion No. 12 was updated to clarify that also severe gastrointestinal symptoms due to SSc could have led to the exclusion of a patient5) Exclusion Criterion No. 25 was added based on advice from regulatory agencies: patients with underlying chronic liver disease (Child Pugh A, B, C hepatic impairment)6) The restrictions regarding concomitant treatment with corticosteroids were modified.7) Patients on low dose corticosteroid therapy were eligible for the trial even if the dose of the corticosteroid medication was not stable8) The description of the method of measuring DLco was harmonised within the CTP, by removal of the adjustments for altitude and carboxyhaemoglobin incorrectly mentioned in one section of the CTP9) Addition of mycophenolate sodium to clarify that for 'mycophenolate' 2 possible salt forms are available. |
| 26 January 2017 | <p>1) For selection of trial population, it was added that recruitment of pts who were on stable dose of mycophenolate or methotrexate background medications could have been restricted, although enrolment was generally competitive 2) Numbers of sites & countries contributing pts worldwide were updated from approximately 170 sites to about 230 sites & from about 20 to 33 countries 3) Inclusion Criterion No. 4 was revised & requested SSc disease onset (defined by first non-Raynaud symptom) had to occur within 7 years instead of 5 years of Visit 1. This change was introduced to facilitate recruitment into trial, without compromising characterisation of trial population. 4) For Exclusion Criterion No. 4, reference time point to assess eligibility regarding airway obstruction (pre-bronchodilator FEV1/FVC <0.7) was changed from Visit 1 to Visit 2 to ensure consistency with all other lung function criteria 5) To Exclusion Criterion No. 18 & restrictions of concomitant trt required washout period of at least 8 weeks before Visit 2 was added for mycophenolate mofetil/sodium or methotrexate 6) In Exclusion Criterion No. 22 tubal occlusion was removed as an example for method of permanent sterilization, since according to Clinical Trial Facilitation Group recommendations (2014), woman who underwent tubal ligation is still to be considered 'of childbearing potential' 7) Exclusion Criterion No. 26 was added: pts with history of SSc renal crisis 8) For AE collection & reporting it was clarified that independent adjudication committee reviewed all fatal cases for primary causes of death. Data protection measures for committee & adjudication process were clarified too. 9) Absolute change from bl. at wk 52 in CRISP index score was added as secondary endpoint & removed from list of further endpoints; however, TSAP defined to analyse proportion of responders instead of absolute change from bl. 10) ATA status & bl. FVC% predicted were included as covariates in analysis of rate of decline in FVC in % predicted.</p> |

| | |
|------------------|---|
| 15 February 2018 | <p>The following main changes in the conduct of the trial were introduced by the amendment:</p> <ol style="list-style-type: none"> 1) The end of trial for patients on-treatment as well as for patients who prematurely discontinued trial medication and attended visits as planned was clarified. Details regarding the time point of the EOT Visit and requirements for Follow-up Visits were added. 2) The restrictions regarding concomitant treatment were modified. The definition of clinically significant deterioration was extended to other clinical parameters than mRSS and FVC 3) Clarification that based on the half-life of the trial drug, a safety analysis restricted to AEs that occurred between the start of treatment and up to 7 days after the date of the last dose of trial medication were analysed in addition |
|------------------|---|

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported