



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 Sclerosisassociated 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
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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
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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
Protocol deviation	2	2
Adverse event, non-fatal	20	28
Consent withdrawn by subject	7	5
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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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.
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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
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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
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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
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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
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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
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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
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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 ^[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
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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
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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
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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
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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 CRIS				
number (not applicable)	11.8	12.2		

Notes:

[21] - Treated set

[22] - Treated set

Statistical analyses

Statistical analysis title	Statistical Analysis I
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Statistical analysis description:

The comparison between both treatment groups was performed using a Cochran-Mantel-Haenszel test. CRIS 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
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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
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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
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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
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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
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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 (\pm 0.04)	0.03 (\pm 0.05)		

Notes:

[25] - Treated set

[26] - Treated set

Statistical analyses

Statistical analysis title	Statistical Analysis I
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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
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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
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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 (\pm 0.024)	0.054 (\pm 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
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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
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End point timeframe:

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 (\pm 0.41)	0.99 (\pm 0.42)		

Notes:

[29] - Treated set

[30] - Treated set

Statistical analyses

Statistical analysis title	Statistical Analysis I
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.1
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Reporting groups

Reporting group title	Placebo
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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
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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	
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	
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	
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	
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	
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	
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	
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	
Psychiatric disorders			
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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 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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	

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	

Weight decreased subjects affected / exposed occurrences (all)	15 / 288 (5.21%) 15	39 / 288 (13.54%) 41	
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	4 / 288 (1.39%) 4	19 / 288 (6.60%) 22	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea subjects affected / exposed occurrences (all)	27 / 288 (9.38%) 29	23 / 288 (7.99%) 27	
Cough subjects affected / exposed occurrences (all)	62 / 288 (21.53%) 80	41 / 288 (14.24%) 46	
Epistaxis subjects affected / exposed occurrences (all)	16 / 288 (5.56%) 17	8 / 288 (2.78%) 18	
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	28 / 288 (9.72%) 40	34 / 288 (11.81%) 49	
Dizziness subjects affected / exposed occurrences (all)	15 / 288 (5.21%) 15	19 / 288 (6.60%) 22	
General disorders and administration site conditions			
Pyrexia subjects affected / exposed occurrences (all)	13 / 288 (4.51%) 18	20 / 288 (6.94%) 22	
Fatigue subjects affected / exposed occurrences (all)	21 / 288 (7.29%) 26	33 / 288 (11.46%) 37	
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	21 / 288 (7.29%) 29	36 / 288 (12.50%) 56	
Constipation subjects affected / exposed	19 / 288 (6.60%)	15 / 288 (5.21%)	

occurrences (all)	19	15	
Abdominal pain upper			
subjects affected / exposed	15 / 288 (5.21%)	21 / 288 (7.29%)	
occurrences (all)	22	41	
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	
Vomiting			
subjects affected / exposed	31 / 288 (10.76%)	78 / 288 (27.08%)	
occurrences (all)	39	165	
Nausea			
subjects affected / exposed	41 / 288 (14.24%)	96 / 288 (33.33%)	
occurrences (all)	49	213	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	54 / 288 (18.75%)	56 / 288 (19.44%)	
occurrences (all)	87	94	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	23 / 288 (7.99%)	23 / 288 (7.99%)	
occurrences (all)	28	31	
Back pain			
subjects affected / exposed	15 / 288 (5.21%)	20 / 288 (6.94%)	
occurrences (all)	15	22	
Myalgia			
subjects affected / exposed	11 / 288 (3.82%)	16 / 288 (5.56%)	
occurrences (all)	11	17	
Pain in extremity			
subjects affected / exposed	14 / 288 (4.86%)	15 / 288 (5.21%)	
occurrences (all)	15	17	
Metabolism and nutrition disorders			

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

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 CRIS 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
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported