Clinical trial results:
An open-label extension trial to assess the long term safety of nintedanib in patients with 'Systemic Sclerosis associated Interstitial Lung Disease' (SSc-ILD)

Summary

EudraCT number	2016-003403-66
Trial protocol	NL ES PT GB FR DK BE AT CZ GR SE NO FI IT
Global end of trial date	25 January 2023

Results information

Result version number	v1 (current)
This version publication date	09 February 2024
First version publication date	09 February 2024

Trial information

Trial identification

Sponsor protocol code	1199-0225

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03313180
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, 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	03 March 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 January 2023
Global end of trial reached?	Yes
Global end of trial date	25 January 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial was to assess the long-term safety of nintedanib treatment in patients with SSc-ILD.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 December 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 5
Country: Number of subjects enrolled	Australia: 10
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Belgium: 16
Country: Number of subjects enrolled	Brazil: 4
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Chile: 4
Country: Number of subjects enrolled	China: 17
Country: Number of subjects enrolled	Czechia: 1
Country: Number of subjects enrolled	Denmark: 5
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	France: 38
Country: Number of subjects enrolled	Germany: 41
Country: Number of subjects enrolled	Greece: 7
Country: Number of subjects enrolled	India: 21
Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	Japan: 53
Country: Number of subjects enrolled	Malaysia: 4

Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	Netherlands: 14
Country: Number of subjects enrolled	Norway: 4
Country: Number of subjects enrolled	Poland: 14
Country: Number of subjects enrolled	Portugal: 10
Country: Number of subjects enrolled	Spain: 24
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	Thailand: 4
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	United States: 106
Worldwide total number of subjects	444
EEA total number of subjects	192

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)	341
From 65 to 84 years	103
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a prospective, open-label extension trial to assess long-term safety and tolerability of nintedanib in patients with Systemic Sclerosis associated Interstitial Lung Disease (SSc-ILD) who had completed treatment of the randomised, double-blind, placebo-controlled parent trial 1199.214 or trial 1199-0340.

Pre-assignment

Screening details:

Only patients with SSc-ILD who completed one of the parent trials on treatment (i.e., did not discontinue treatment early) were eligible and were included in this trial if they fulfilled all the inclusion criteria and did not present any of the exclusion criteria.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was an open-label extension trial and treatment allocation was not concealed throughout the trial.

Arms

Arm title	Nintedanib

Arm description:

Patients with Systemic Sclerosis associated Interstitial Lung Disease (SSc-ILD) who took part in the parent trials 1199.214 (Nintedanib or Placebo) or 1199-0340 (Nintedanib). Patients continued in this trial and received Nintedanib 150 mg (milligram) twice daily (bid) unless they had reduced their dose to 100 mg bid trial medication (Nintedanib or Placebo) in the parent trial. Patients receiving 100 mg bid trial medication at the end of the parent trial could receive either Nintedanib 100 mg bid or 150 mg bid at the discretion of the investigator.

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:

Nintedanib 150 mg (milligram) twice daily (bid) unless they had reduced their dose to 100 mg bid trial medication (nintedanib or placebo) in the parent trial.

Number of subjects in period 1	Nintedanib
Started	444
Completed	265
Not completed	179
Adverse event, serious fatal	20
Consent withdrawn by subject	39
Adverse event, non-fatal	100
Covid-19 related	2

Other than listed above	15
Lost to follow-up	3

Baseline characteristics

Reporting groups	
Reporting group title	Nintedanib
Reporting group description:	
Patients with Systemic Sclerosis associated Interstitial Lung Disease (SSc-ILD) who took part in the parent trials 1199.214 (Nintedanib or Placebo) or 1199-0340 (Nintedanib). Patients continued in this trial and received Nintedanib 150 mg (milligram) twice daily (bid) unless they had reduced their dose to 100 mg bid trial medication (Nintedanib or Placebo) in the parent trial. Patients receiving 100 mg bid trial medication at the end of the parent trial could receive either Nintedanib 100 mg bid or 150 mg bid at the discretion of the investigator.	

Reporting group values	Nintedanib	Total	
Number of subjects	444	444	
Age categorical			
Treated Set (TS): all patients who signed informed consent and received at least 1 dose of trial medication			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	341	341	
From 65-84 years	103	103	
85 years and over	0	0	
Age Continuous			
Treated Set (TS): all patients who signed informed consent and received at least 1 dose of trial medication			
Units: years			
arithmetic mean	55.0		
standard deviation	± 11.9	-	
Sex: Female, Male			
Treated Set (TS): all patients who signed informed consent and received at least 1 dose of trial medication			
Units: Participants			
Female	335	335	
Male	109	109	
Race (NIH/OMB)			
Treated Set (TS): all patients who signed informed consent and received at least 1 dose of trial medication			
Units: Subjects			
American Indian or Alaska Native	4	4	
Asian	110	110	
Native Hawaiian or Other Pacific Islander	2	2	
Black or African American	18	18	
White	308	308	
More than one race	2	2	
Unknown or Not Reported	0	0	

Ethnicity (NIH/OMB)			
Treated Set (TS): all patients who signed informed consent and received at least 1 dose of trial medication			
Units: Subjects			
Hispanic or Latino	38	38	
Not Hispanic or Latino	406	406	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Nintedanib

Reporting group description:

Patients with Systemic Sclerosis associated Interstitial Lung Disease (SSc-ILD) who took part in the parent trials 1199.214 (Nintedanib or Placebo) or 1199-0340 (Nintedanib). Patients continued in this trial and received Nintedanib 150 mg (milligram) twice daily (bid) unless they had reduced their dose to 100 mg bid trial medication (Nintedanib or Placebo) in the parent trial. Patients receiving 100 mg bid trial medication at the end of the parent trial could receive either Nintedanib 100 mg bid or 150 mg bid at the discretion of the investigator.

Primary: Number of patients with any adverse event (AE) over the course of the trial

End point title	Number of patients with any adverse event (AE) over the course of the trial[1]

End point description:

Number of patients with any adverse event (AE) over the course of the trial.

Treated Set (TS): all patients who signed informed consent and received at least 1 dose of trial medication

End point type	Primary

End point timeframe:

First trial medication intake up to last trial drug intake, plus 7 days residual effect period, up to approximate 60 months.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Results were analyzed descriptively, no statistical analyses was planned for this endpoint.

End point values	Nintedanib			
Subject group type	Reporting group			
Number of subjects analysed	444			
Units: Participants	441			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First trial medication intake up to last trial drug intake, plus 7 days residual effect period, up to ~59.9 months.

Adverse event reporting additional description:

Treated Set (TS): all patients who signed informed consent and received at least 1 dose of trial medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Nintedanib

Reporting group description:

Patients with Systemic Sclerosis associated Interstitial Lung Disease (SSc-ILD) who took part in the parent trials 1199.214 (Nintedanib or Placebo) or 1199-0340 (Nintedanib). Patients continued in this trial and received nintedanib 150 mg (milligram) twice daily (bid) unless they had reduced their dose to 100 mg bid trial medication (nintedanib or placebo) in the parent trial.
patients receiving 100 mg bid trial medication at the end of the parent trial could receive either nintedanib 100 mg bid or 150 mg bid at the discretion of the investigator.

Serious adverse events	Nintedanib		
Total subjects affected by serious adverse events			
subjects affected / exposed	198 / 444 (44.59%)		
number of deaths (all causes)	23		
number of deaths resulting from adverse events	19		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bowen's disease			
subjects affected / exposed	2 / 444 (0.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Acute myeloid leukaemia			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Adenoid cystic carcinoma			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Angiomyolipoma				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Basal cell carcinoma				
subjects affected / exposed	4 / 444 (0.90%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Breast cancer				
subjects affected / exposed	3 / 444 (0.68%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Tongue neoplasm malignant stage unspecified				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung adenocarcinoma				
subjects affected / exposed	3 / 444 (0.68%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Lung neoplasm malignant				
subjects affected / exposed	5 / 444 (1.13%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Malignant melanoma				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Meningioma				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metastases to bone				

subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metastases to gallbladder				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metastases to liver				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metastases to lymph nodes				
subjects affected / exposed	2 / 444 (0.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Non-small cell lung cancer				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Papillary thyroid cancer				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Parathyroid tumour benign				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small cell lung cancer metastatic				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Splenic marginal zone lymphoma				

subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of skin				
subjects affected / exposed	2 / 444 (0.45%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
T-cell type acute leukaemia				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Colon cancer				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Raynaud's phenomenon				
subjects affected / exposed	2 / 444 (0.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Arteriosclerosis				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				
subjects affected / exposed	2 / 444 (0.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Dry gangrene				

subjects affected / exposed	2 / 444 (0.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Extremity necrosis			
subjects affected / exposed	2 / 444 (0.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	2 / 444 (0.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral artery occlusion			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Peripheral ischaemia			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 444 (0.45%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Chest discomfort			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Disease progression			

subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
General physical health deterioration				
subjects affected / exposed	2 / 444 (0.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Non-cardiac chest pain				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Polyserositis				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	2 / 444 (0.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	2 / 444 (0.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Anti-neutrophil cytoplasmic antibody positive vasculitis				
subjects affected / exposed	2 / 444 (0.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				

Heavy menstrual bleeding				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ovarian cyst				
subjects affected / exposed	2 / 444 (0.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute pulmonary oedema				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Acute respiratory failure				
subjects affected / exposed	3 / 444 (0.68%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Cough				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Interstitial lung disease				
subjects affected / exposed	13 / 444 (2.93%)			
occurrences causally related to treatment / all	0 / 14			
deaths causally related to treatment / all	0 / 2			

Paranasal sinus discomfort			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleurisy			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleuritic pain			
subjects affected / exposed	2 / 444 (0.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumomediastinum			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	3 / 444 (0.68%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 1		
Pneumothorax spontaneous			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary arterial hypertension			
subjects affected / exposed	9 / 444 (2.03%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			

subjects affected / exposed	8 / 444 (1.80%)			
occurrences causally related to treatment / all	4 / 8			
deaths causally related to treatment / all	0 / 0			
Pulmonary fibrosis				
subjects affected / exposed	7 / 444 (1.58%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 0			
Pulmonary hypertension				
subjects affected / exposed	17 / 444 (3.83%)			
occurrences causally related to treatment / all	2 / 18			
deaths causally related to treatment / all	0 / 2			
Pulmonary mass				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	5 / 444 (1.13%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 1			
Sleep apnoea syndrome				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tracheal stenosis				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	9 / 444 (2.03%)			
occurrences causally related to treatment / all	0 / 9			
deaths causally related to treatment / all	0 / 0			
Investigations				
Alanine aminotransferase increased				

subjects affected / exposed	4 / 444 (0.90%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	3 / 444 (0.68%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Blood alkaline phosphatase increased				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ejection fraction decreased				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gamma-glutamyltransferase increased				
subjects affected / exposed	2 / 444 (0.45%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Hepatic enzyme increased				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Human metapneumovirus test positive				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Weight decreased				
subjects affected / exposed	3 / 444 (0.68%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural				

complications				
Fall				
subjects affected / exposed	2 / 444 (0.45%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Animal bite				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dislocation of vertebra				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal compression fracture				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spleen contusion				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sternal fracture				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thoracic vertebral fracture				

subjects affected / exposed	2 / 444 (0.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Upper limb fracture				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Cardiac failure				
subjects affected / exposed	7 / 444 (1.58%)			
occurrences causally related to treatment / all	0 / 9			
deaths causally related to treatment / all	0 / 2			
Cardiac arrest				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Acute left ventricular failure				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Angina unstable				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Arrhythmia				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Arteriosclerosis coronary artery				

subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	5 / 444 (1.13%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 0			
Atrial flutter				
subjects affected / exposed	2 / 444 (0.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Atrial tachycardia				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				
subjects affected / exposed	2 / 444 (0.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac failure chronic				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chordae tendinae rupture				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pericarditis				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Palpitations				

subjects affected / exposed	2 / 444 (0.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mitral valve incompetence				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Left ventricular failure				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Coronary artery occlusion				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Coronary artery disease				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Right ventricular failure				
subjects affected / exposed	3 / 444 (0.68%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Carpal tunnel syndrome				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral infarction				

subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cerebral ischaemia				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoaesthesia				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intracranial mass				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Paraesthesia				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sciatica				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral haematoma				

subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anaemia of chronic disease			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Autoimmune haemolytic anaemia			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphadenopathy			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Sudden hearing loss			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Blindness unilateral			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cataract			
subjects affected / exposed	2 / 444 (0.45%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

Glaucoma				
subjects affected / exposed	2 / 444 (0.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Retinal detachment				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Retinal tear				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vitreous detachment				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Colitis				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal pseudo-obstruction				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Inguinal hernia				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterocolitis				

subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Enteritis				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea haemorrhagic				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	4 / 444 (0.90%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Colitis ulcerative				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lower gastrointestinal haemorrhage				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	3 / 444 (0.68%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				

subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal prolapse				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumoperitoneum				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumatosis intestinalis				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis acute				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Liver injury				
subjects affected / exposed	5 / 444 (1.13%)			
occurrences causally related to treatment / all	4 / 5			
deaths causally related to treatment / all	0 / 0			
Hydrocholecystis				

subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic function abnormal				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Drug-induced liver injury				
subjects affected / exposed	4 / 444 (0.90%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Cholelithiasis				
subjects affected / exposed	2 / 444 (0.45%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Ischaemic skin ulcer				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sclerema				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin hypertrophy				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin lesion				

subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Skin necrosis				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin ulcer				
subjects affected / exposed	8 / 444 (1.80%)			
occurrences causally related to treatment / all	0 / 15			
deaths causally related to treatment / all	0 / 0			
Scleroderma associated digital ulcer				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	4 / 444 (0.90%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 1			
Glomerulonephritis rapidly progressive				
subjects affected / exposed	2 / 444 (0.45%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Endocrine disorders				
Adrenal insufficiency				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Musculoskeletal and connective tissue disorders			
Cervical spinal stenosis			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Connective tissue disorder			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Crowned dens syndrome			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myopathy			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Osteonecrosis of jaw			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Polymyalgia rheumatica			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Scleroderma			
subjects affected / exposed	4 / 444 (0.90%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 1		

Sjogren's syndrome				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Systemic scleroderma				
subjects affected / exposed	2 / 444 (0.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Trismus				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bronchitis				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchiolitis				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Arthritis bacterial				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis viral				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Haemophilus infection				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infected bunion				

subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infected skin ulcer			
subjects affected / exposed	2 / 444 (0.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	2 / 444 (0.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Intervertebral discitis			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Labyrinthitis			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Localised infection			
subjects affected / exposed	2 / 444 (0.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bronchitis viral			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
COVID-19			

subjects affected / exposed	9 / 444 (2.03%)			
occurrences causally related to treatment / all	0 / 10			
deaths causally related to treatment / all	0 / 1			
COVID-19 pneumonia				
subjects affected / exposed	3 / 444 (0.68%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridium colitis				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	2 / 444 (0.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Diarrhoea infectious				
subjects affected / exposed	2 / 444 (0.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Enteritis infectious				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Escherichia infection				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gallbladder abscess				

subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	3 / 444 (0.68%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pharyngotonsillitis				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	26 / 444 (5.86%)			
occurrences causally related to treatment / all	1 / 30			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pneumonia bacterial				
subjects affected / exposed	3 / 444 (0.68%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pneumonia mycoplasmal				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia viral				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Propionibacterium infection				

subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal infection				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Subperiosteal abscess				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	6 / 6			
deaths causally related to treatment / all	0 / 0			
Tooth abscess				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteomyelitis				
subjects affected / exposed	4 / 444 (0.90%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Cachexia				

subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Decreased appetite			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypocalcaemia			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	2 / 444 (0.45%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hypomagnesaemia			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Nintedanib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	425 / 444 (95.72%)		
Vascular disorders			
Raynaud's phenomenon			
subjects affected / exposed	18 / 444 (4.05%)		
occurrences (all)	19		
Hypertension			
subjects affected / exposed	23 / 444 (5.18%)		
occurrences (all)	27		
General disorders and administration site conditions			

Chest pain			
subjects affected / exposed	22 / 444 (4.95%)		
occurrences (all)	29		
Fatigue			
subjects affected / exposed	46 / 444 (10.36%)		
occurrences (all)	55		
Pyrexia			
subjects affected / exposed	28 / 444 (6.31%)		
occurrences (all)	35		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	83 / 444 (18.69%)		
occurrences (all)	106		
Dyspnoea			
subjects affected / exposed	47 / 444 (10.59%)		
occurrences (all)	57		
Oropharyngeal pain			
subjects affected / exposed	18 / 444 (4.05%)		
occurrences (all)	22		
Productive cough			
subjects affected / exposed	16 / 444 (3.60%)		
occurrences (all)	16		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	14 / 444 (3.15%)		
occurrences (all)	17		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	47 / 444 (10.59%)		
occurrences (all)	73		
Aspartate aminotransferase increased			
subjects affected / exposed	43 / 444 (9.68%)		
occurrences (all)	61		
Gamma-glutamyltransferase increased			

subjects affected / exposed	33 / 444 (7.43%)		
occurrences (all)	45		
Weight decreased			
subjects affected / exposed	63 / 444 (14.19%)		
occurrences (all)	81		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	16 / 444 (3.60%)		
occurrences (all)	18		
Limb injury			
subjects affected / exposed	22 / 444 (4.95%)		
occurrences (all)	25		
Nervous system disorders			
Dizziness			
subjects affected / exposed	24 / 444 (5.41%)		
occurrences (all)	30		
Headache			
subjects affected / exposed	55 / 444 (12.39%)		
occurrences (all)	80		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	24 / 444 (5.41%)		
occurrences (all)	28		
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	21 / 444 (4.73%)		
occurrences (all)	23		
Dyspepsia			
subjects affected / exposed	20 / 444 (4.50%)		
occurrences (all)	25		
Diarrhoea			
subjects affected / exposed	338 / 444 (76.13%)		
occurrences (all)	1100		
Constipation			
subjects affected / exposed	20 / 444 (4.50%)		
occurrences (all)	27		

Abdominal pain upper subjects affected / exposed occurrences (all)	24 / 444 (5.41%) 37		
Abdominal pain subjects affected / exposed occurrences (all)	52 / 444 (11.71%) 85		
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	43 / 444 (9.68%) 50		
Nausea subjects affected / exposed occurrences (all)	122 / 444 (27.48%) 168		
Vomiting subjects affected / exposed occurrences (all)	100 / 444 (22.52%) 161		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	20 / 444 (4.50%) 27		
Skin ulcer subjects affected / exposed occurrences (all)	110 / 444 (24.77%) 261		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	75 / 444 (16.89%) 106		
Back pain subjects affected / exposed occurrences (all)	41 / 444 (9.23%) 43		
Pain in extremity subjects affected / exposed occurrences (all)	31 / 444 (6.98%) 39		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	46 / 444 (10.36%) 69		

Urinary tract infection subjects affected / exposed occurrences (all)	43 / 444 (9.68%) 80		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	76 / 444 (17.12%) 116		
Respiratory tract infection subjects affected / exposed occurrences (all)	27 / 444 (6.08%) 41		
Nasopharyngitis subjects affected / exposed occurrences (all)	82 / 444 (18.47%) 130		
Influenza subjects affected / exposed occurrences (all)	23 / 444 (5.18%) 23		
Herpes zoster subjects affected / exposed occurrences (all)	19 / 444 (4.28%) 21		
COVID-19 subjects affected / exposed occurrences (all)	68 / 444 (15.32%) 80		
Viral infection subjects affected / exposed occurrences (all)	17 / 444 (3.83%) 30		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	33 / 444 (7.43%) 36		
Hypokalaemia subjects affected / exposed occurrences (all)	21 / 444 (4.73%) 29		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 August 2017	The changes to the CTP included clarifications and corrections to the schedule of assessments, the frequency of Thyroid-stimulating hormone (TSH) testing, the creatinine clearance measurement formula, and procedures to be followed in case of pregnancy in a trial patient or their partner.
17 August 2018	The following main changes, clarifications, and corrections of inconsistencies were implemented: . Patients who completed trial 1199-0340 (approximately 14 patients) were added to the pool of patients who could enter the present trial . Selexipag was added to the list of oral or parenteral therapies for pulmonary hypertension; patients treated for pulmonary hypertension were highly recommended to discontinue nintedanib in Safety and Efficacy of Nintedanib in Systemic Sclerosis (SENSCIS-ON) . Clarification of the collected blood volume for safety laboratory tests (110 (milliliter) mL in the first year and 45 mL during any subsequent year) . An inconsistency in the list of procedures to be done at dose-modification visits was corrected to include safety laboratory testing . The length of the Residual Effect Period (REP) was corrected from 28 days to 7 days, based on the half-life of nintedanib
13 August 2020	The following changes, clarifications, and corrections of inconsistencies were implemented: . The introduction was updated to ensure it reflected current knowledge and recent data on the medical background relevant to this trial . The benefit-risk assessment was updated to reflect new information on the Covid-19 pandemic . The duration of the trial design was clarified, the end of the trial was more precisely described, and it was documented that the trial could last beyond availability of marketed drug . The numbers of wallets provided at Visits 5 and 6 were corrected . The recommendations for cases of hepatic injury were changed: o The wording regarding withdrawal and interruption of trial medication was revised for clarification. It was also noted that trial medication could be resumed if clear evidence of an alternative cause for hepatic injury was identified. It was specified that this was only possible after consultation with the sponsor and if prior to restart, liver laboratory values were normal. Liver laboratory values had to be monitored weekly for the first 4 weeks after reintroduction and every 2 weeks for the following 8 weeks. . Following the first wave of the Covid-19 pandemic, the visit schedule was modified for exceptional circumstance (such as a pandemic) to allow flexibility in visit conduct to ensure patients safety by ensuring continuous treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported