Clinical trial results:
An open-label extension trial of the long-term safety of nintedanib in patients with Progressive Fibrosing Interstitial Lung Disease (PF-ILD)

Summary

EudraCT number	2018-000525-32
Trial protocol	ES PL GB DE BE IT
Global end of trial date	30 August 2022

Results information

Result version number	v1 (current)
This version publication date	03 September 2023
First version publication date	03 September 2023

Trial information

Trial identification

Sponsor protocol code	1199-0248

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03820726
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	12 October 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 August 2022
Global end of trial reached?	Yes
Global end of trial date	30 August 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this clinical trial was to assess long-term tolerability and safety of treatment with oral nintedanib in patients with Progressive Fibrosing-Interstitial Lung Disease (PF-ILD) who completed (and did not prematurely discontinue trial medication in) the Phase III parent trial, INBUILD® (1199-0247) NCT02999178.

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	20 June 2019
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: 21
Country: Number of subjects enrolled	Belgium: 16
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Chile: 27
Country: Number of subjects enrolled	China: 13
Country: Number of subjects enrolled	France: 42
Country: Number of subjects enrolled	Germany: 30
Country: Number of subjects enrolled	Italy: 19
Country: Number of subjects enrolled	Japan: 65
Country: Number of subjects enrolled	Poland: 24
Country: Number of subjects enrolled	Russian Federation: 27
Country: Number of subjects enrolled	Korea, Republic of: 25
Country: Number of subjects enrolled	Spain: 31
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	United States: 73
Worldwide total number of subjects	436
EEA total number of subjects	162

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)	173
From 65 to 84 years	258
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

A phase III, open label, extension trial. The study aimed to evaluate the long-term tolerability and safety of oral nintedanib treatment in patients with Progressive Fibrosing Interstitial Lung Disease (PF-ILD) who have completed (and did not prematurely discontinue trial medication in) the phase III parent trial, 1199.247 (INBUILD®) NCT02999178.

Pre-assignment

Screening details:

Only patients with PF-ILD who completed the parent trial (INBUILD®) 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	Entered
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was an open-label trial, single-arm, treatment allocation was not concealed throughout the trial. The Case Report Form (CRF) contained information on actual treatment.
The previous treatment received in INBUILD® (active drug or placebo) remained unknown to the investigator and patient until after the final database lock of INBUILD®

Arms

Arm title	Nintedanib (Experimental)

Arm description:

Patients taking 150 milligram (mg) bid blinded trial medication (active drug or placebo) at the end of INBUILD® started treatment with nintedanib 150 mg bid in this extension trial. Patients taking 100 mg bid blinded trial medication (active drug or placebo) at the end of INBUILD® started treatment with nintedanib in this extension trial either at 100 mg bid or at an increased dose of 150 mg bid at the discretion of the investigator orally as soft gelatine capsule, twice daily (bid), together with a glass of water (~250 mL), in a dose interval of 12 hours. With an optional dose reduction to 100 mg bid temporarily or permanently to manage adverse events (AEs). The treatment had a duration of 96 weeks or until nintedanib was made available to the patients outside of the clinical trial. Treatment was stopped if any reason for withdrawal was met.

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:

Participants were administered 150 milligram (mg) nintedanib orally as soft gelatine capsule, twice daily (bid), together with a glass of water (~250 mL), in a dose interval of 12 hours. With an optional dose reduction to 100 mg bid temporarily or permanently to manage adverse events (AEs).

Number of subjects in period 1	Nintedanib (Experimental)
Started	435
Completed	434
Not completed	1
Patient not treated	1

Period 2

Period 2 title	Treated
Is this the baseline period?	Yes[1]
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This was an open-label trial, treatment allocation was not concealed throughout the trial. The CRF contained information on actual treatment.
The previous treatment received in INBUILD® (active drug or placebo) remained unknown to the investigator and patient until after the final database lock of INBUILD®.

Arms

Arm title	Nintedanib

Arm description:

Patients taking 150 milligram (mg) bid blinded trial medication (active drug or placebo) at the end of INBUILD® started treatment with nintedanib 150 mg bid in this extension trial. Patients taking 100 mg bid blinded trial medication (active drug or placebo) at the end of INBUILD® started treatment with nintedanib in this extension trial either at 100 mg bid or at an increased dose of 150 mg bid at the discretion of the investigator orally as soft gelatine capsule, twice daily (bid), together with a glass of water (~250 mL), in a dose interval of 12 hours. With an optional dose reduction to 100 mg bid temporarily or permanently to manage adverse events (AEs). The treatment had a duration of 96 weeks or until nintedanib was made available to the patients outside of the clinical trial. Treatment was stopped if any reason for withdrawal was met.

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:

Participants were administered 150 milligram (mg) nintedanib orally as soft gelatine capsule, twice daily (bid), together with a glass of water (~250 mL), in a dose interval of 12 hours. With an optional dose reduction to 100 mg bid temporarily or permanently to manage adverse events (AEs).

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 are the randomised subjects, period 2 the treated, baseline characteristics are reported for the treated subjects.

Number of subjects in period 2[2]	Nintedanib
Started	434
Completed	224
Not completed	210
Consent withdrawn by subject	37
Adverse event, non-fatal	146
Protocol deviation	1
Lost to follow-up	3
Other than listed	23

Notes:

[2] - 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: Out of 436 subjects enrolled only 435 subjects entered the study.

Baseline characteristics

Reporting groups	
Reporting group title	Nintedanib
Reporting group description:	
Patients taking 150 milligram (mg) bid blinded trial medication (active drug or placebo) at the end of INBUILD® started treatment with nintedanib 150 mg bid in this extension trial. Patients taking 100 mg bid blinded trial medication (active drug or placebo) at the end of INBUILD® started treatment with nintedanib in this extension trial either at 100 mg bid or at an increased dose of 150 mg bid at the discretion of the investigator orally as soft gelatine capsule, twice daily (bid), together with a glass of water (~250 mL), in a dose interval of 12 hours. With an optional dose reduction to 100 mg bid temporarily or permanently to manage adverse events (AEs). The treatment had a duration of 96 weeks or until nintedanib was made available to the patients outside of the clinical trial. Treatment was stopped if any reason for withdrawal was met.	

Reporting group values	Nintedanib	Total	
Number of subjects	434	434	
Age categorical			
Treated Set (TS): This set included all patients who were dispensed trial medication (nintedanib) and were documented to have taken at least 1 dose of open-label trial medication (nintedanib).			
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)	172	172	
From 65-84 years	257	257	
85 years and over	5	5	
Age Continuous			
Treated Set (TS): This set included all patients who were dispensed trial medication (nintedanib) and were documented to have taken at least 1 dose of open-label trial medication (nintedanib).			
Units: years			
arithmetic mean	65.9		
standard deviation	± 9.9	-	
Sex: Female, Male			
Treated Set (TS): This set included all patients who were dispensed trial medication (nintedanib) and were documented to have taken at least 1 dose of open-label trial medication (nintedanib).			
Units: Participants			
Female	211	211	
Male	223	223	
Race (NIH/OMB)			
Treated Set (TS): This set included all patients who were dispensed trial medication (nintedanib) and were documented to have taken at least 1 dose of open-label trial medication (nintedanib).			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	108	108	
Native Hawaiian or Other Pacific Islander	1	1	
Black or African American	4	4	

White	279	279	
More than one race	1	1	
Unknown or Not Reported	41	41	
Ethnicity (NIH/OMB)			
Treated Set (TS): This set included all patients who were dispensed trial medication (nintedanib) and were documented to have taken at least 1 dose of open-label trial medication (nintedanib).			
Units: Subjects			
Hispanic or Latino	65	65	
Not Hispanic or Latino	328	328	
Unknown or Not Reported	41	41	

End points

End points reporting groups

Reporting group title	Nintedanib (Experimental)

Reporting group description:

Patients taking 150 milligram (mg) bid blinded trial medication (active drug or placebo) at the end of INBUILD® started treatment with nintedanib 150 mg bid in this extension trial. Patients taking 100 mg bid blinded trial medication (active drug or placebo) at the end of INBUILD® started treatment with nintedanib in this extension trial either at 100 mg bid or at an increased dose of 150 mg bid at the discretion of the investigator orally as soft gelatine capsule, twice daily (bid), together with a glass of water (~250 mL), in a dose interval of 12 hours. With an optional dose reduction to 100 mg bid temporarily or permanently to manage adverse events (AEs). The treatment had a duration of 96 weeks or until nintedanib was made available to the patients outside of the clinical trial. Treatment was stopped if any reason for withdrawal was met.

Reporting group title	Nintedanib

Reporting group description:

Patients taking 150 milligram (mg) bid blinded trial medication (active drug or placebo) at the end of INBUILD® started treatment with nintedanib 150 mg bid in this extension trial. Patients taking 100 mg bid blinded trial medication (active drug or placebo) at the end of INBUILD® started treatment with nintedanib in this extension trial either at 100 mg bid or at an increased dose of 150 mg bid at the discretion of the investigator orally as soft gelatine capsule, twice daily (bid), together with a glass of water (~250 mL), in a dose interval of 12 hours. With an optional dose reduction to 100 mg bid temporarily or permanently to manage adverse events (AEs). The treatment had a duration of 96 weeks or until nintedanib was made available to the patients outside of the clinical trial. Treatment was stopped if any reason for withdrawal was met.

Primary: Number of participants with any adverse events

End point title	Number of participants with any adverse events[1]

End point description:

Number of participants with adverse events over the course of the extension trial, AEs defined as any untoward medical occurrence in a patient administered with the investigational product and which does not necessarily have to have a causal relationship with this treatment. Treated Set (TS): This set included all patients who were dispensed trial medication (nintedanib) and were documented to have taken at least 1 dose of open-label trial medication (nintedanib).

End point type	Primary

End point timeframe:

From first nintedanib intake until last nintedanib intake + 28 days of Residual effect period (REP), up to 1195 days.

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: The Primary endpoint was planned to be only analyzed descriptively.

End point values	Nintedanib			
Subject group type	Reporting group			
Number of subjects analysed	434			
Units: Participants	417			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first nintedanib intake until last nintedanib intake + 28 days of Residual effect period (REP), up to 1195 days.

Adverse event reporting additional description:

Treated Set (TS): This set included all patients who were dispensed trial medication (nintedanib) and were documented to have taken at least 1 dose of open-label trial medication (nintedanib).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Nintedanib

Reporting group description:

Patients taking 150 milligram (mg) bid blinded trial medication (active drug or placebo) at the end of INBUILD® started treatment with nintedanib 150 mg bid in this extension trial. Patients taking 100 mg bid blinded trial medication (active drug or placebo) at the end of INBUILD® started treatment with nintedanib in this extension trial either at 100 mg bid or at an increased dose of 150 mg bid at the discretion of the investigator orally as soft gelatine capsule, twice daily (bid), together with a glass of water (~250 mL), in a dose interval of 12 hours. With an optional dose reduction to 100 mg bid temporarily or permanently to manage adverse events (AEs). The treatment had a duration of 96 weeks or until nintedanib was made available to the patients outside of the clinical trial. Treatment was stopped if any reason for withdrawal was met.

Serious adverse events	Nintedanib		
Total subjects affected by serious adverse events			
subjects affected / exposed	234 / 434 (53.92%)		
number of deaths (all causes)	83		
number of deaths resulting from adverse events	77		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Carcinoid tumour pulmonary			
subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	3 / 434 (0.69%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Bowen's disease			

subjects affected / exposed	2 / 434 (0.46%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Chronic lymphocytic leukaemia				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung neoplasm malignant				
subjects affected / exposed	2 / 434 (0.46%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Myelodysplastic syndrome				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neuroendocrine tumour of the lung				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatic carcinoma				
subjects affected / exposed	2 / 434 (0.46%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of lung				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Squamous cell carcinoma of skin				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colon cancer				

subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Extremity necrosis			
subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Air embolism			
subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Aortic stenosis			
subjects affected / exposed	1 / 434 (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 / 434 (0.46%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Neurogenic shock			
subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vein disorder			
subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral ischaemia			
subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			

Pyrexia				
subjects affected / exposed	2 / 434 (0.46%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Asthenia				
subjects affected / exposed	3 / 434 (0.69%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	4 / 434 (0.92%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 1			
Death				
subjects affected / exposed	4 / 434 (0.92%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 4			
Disease progression				
subjects affected / exposed	5 / 434 (1.15%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 3			
General physical health deterioration				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Impaired healing				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Multiple organ dysfunction syndrome				
subjects affected / exposed	2 / 434 (0.46%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 2			
Sudden death				

subjects affected / exposed	2 / 434 (0.46%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Reproductive system and breast disorders			
Uterine haemorrhage			
subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Lower respiratory tract inflammation			
subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute respiratory distress syndrome			
subjects affected / exposed	2 / 434 (0.46%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Acute respiratory failure			
subjects affected / exposed	15 / 434 (3.46%)		
occurrences causally related to treatment / all	0 / 17		
deaths causally related to treatment / all	0 / 7		
Chronic respiratory failure			
subjects affected / exposed	2 / 434 (0.46%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Chylothorax			
subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	12 / 434 (2.76%)		
occurrences causally related to treatment / all	1 / 13		
deaths causally related to treatment / all	0 / 1		

Hypercapnia			
subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypersensitivity pneumonitis			
subjects affected / exposed	6 / 434 (1.38%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	3 / 434 (0.69%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 2		
Idiopathic interstitial pneumonia			
subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Interstitial lung disease			
subjects affected / exposed	35 / 434 (8.06%)		
occurrences causally related to treatment / all	0 / 40		
deaths causally related to treatment / all	0 / 10		
Lung disorder			
subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Organising pneumonia			
subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pneumomediastinum			
subjects affected / exposed	2 / 434 (0.46%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			

subjects affected / exposed	9 / 434 (2.07%)			
occurrences causally related to treatment / all	0 / 12			
deaths causally related to treatment / all	0 / 0			
Pulmonary arterial hypertension				
subjects affected / exposed	3 / 434 (0.69%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	3 / 434 (0.69%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Pulmonary fibrosis				
subjects affected / exposed	20 / 434 (4.61%)			
occurrences causally related to treatment / all	0 / 23			
deaths causally related to treatment / all	0 / 3			
Pulmonary hypertension				
subjects affected / exposed	14 / 434 (3.23%)			
occurrences causally related to treatment / all	0 / 14			
deaths causally related to treatment / all	0 / 0			
Pulmonary mass				
subjects affected / exposed	2 / 434 (0.46%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Respiratory distress				
subjects affected / exposed	2 / 434 (0.46%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	17 / 434 (3.92%)			
occurrences causally related to treatment / all	0 / 18			
deaths causally related to treatment / all	0 / 8			
Sleep apnoea syndrome				

subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung infiltration				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Depression				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Confusional state				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Delirium				
subjects affected / exposed	3 / 434 (0.69%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Mixed anxiety and depressive disorder				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Alanine aminotransferase increased				
subjects affected / exposed	2 / 434 (0.46%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Liver function test increased				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oxygen consumption increased				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Platelet count decreased				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Weight decreased				
subjects affected / exposed	3 / 434 (0.69%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Accidental overdose				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Compression fracture				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	3 / 434 (0.69%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Femoral neck fracture				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Femur fracture				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	2 / 434 (0.46%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Humerus fracture				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvic fracture				
subjects affected / exposed	2 / 434 (0.46%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Poisoning				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Post procedural haematoma				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Postoperative ileus				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Postoperative wound complication				

subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Procedural pneumothorax				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal fracture				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Right ventricular failure				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Angina pectoris				
subjects affected / exposed	2 / 434 (0.46%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	7 / 434 (1.61%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 0			
Atrial flutter				
subjects affected / exposed	2 / 434 (0.46%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bradycardia				

subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	4 / 434 (0.92%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 3			
Cardiac failure				
subjects affected / exposed	7 / 434 (1.61%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 0			
Cardiac failure acute				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardio-respiratory arrest				
subjects affected / exposed	5 / 434 (1.15%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 5			
Cor pulmonale chronic				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	3 / 434 (0.69%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 1			
Pericarditis				

subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Prinzmetal angina				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sinus arrest				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ventricular fibrillation				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Nervous system disorders				
Cerebral infarction				
subjects affected / exposed	2 / 434 (0.46%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cerebral ischaemia				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	5 / 434 (1.15%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 2			
Ischaemic stroke				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lacunar infarction				

subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mental impairment			
subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	3 / 434 (0.69%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Vascular parkinsonism			
subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytosis			
subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Age-related macular degeneration			
subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cataract			
subjects affected / exposed	2 / 434 (0.46%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Glaucoma			

subjects affected / exposed	2 / 434 (0.46%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Normal tension glaucoma				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diplopia				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Faecaloma				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	5 / 434 (1.15%)			
occurrences causally related to treatment / all	5 / 5			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				

subjects affected / exposed	3 / 434 (0.69%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Haemorrhoids				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	2 / 434 (0.46%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis acute				
subjects affected / exposed	2 / 434 (0.46%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumatosis intestinalis				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumoperitoneum				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				

subjects affected / exposed	3 / 434 (0.69%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastritis erosive				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholecystitis acute				
subjects affected / exposed	2 / 434 (0.46%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cholelithiasis				
subjects affected / exposed	2 / 434 (0.46%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Drug-induced liver injury				
subjects affected / exposed	3 / 434 (0.69%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Gallbladder rupture				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic cirrhosis				

subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic cytolysis				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic function abnormal				
subjects affected / exposed	2 / 434 (0.46%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Liver injury				
subjects affected / exposed	2 / 434 (0.46%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Biliary colic				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Angioedema				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dermatomyositis				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Calculus urinary				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chronic kidney disease				

subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hydronephrosis				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
IgA nephropathy				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nephrolithiasis				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary renal syndrome				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Renal failure				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute kidney injury				
subjects affected / exposed	3 / 434 (0.69%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Endocrine disorders				
Adrenal insufficiency				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Inappropriate antidiuretic hormone secretion				

subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc protrusion			
subjects affected / exposed	3 / 434 (0.69%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	2 / 434 (0.46%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Osteonecrosis of jaw			
subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Polymyalgia rheumatica			
subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rheumatoid arthritis			
subjects affected / exposed	2 / 434 (0.46%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Sjogren's syndrome			
subjects affected / exposed	2 / 434 (0.46%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Systemic scleroderma			

subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Chronic tonsillitis			
subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abscess limb			
subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anal abscess			
subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Appendicitis perforated			
subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atypical mycobacterial pneumonia			
subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bacterial infection			
subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			

subjects affected / exposed	4 / 434 (0.92%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 1			
COVID-19				
subjects affected / exposed	12 / 434 (2.76%)			
occurrences causally related to treatment / all	0 / 12			
deaths causally related to treatment / all	0 / 4			
COVID-19 pneumonia				
subjects affected / exposed	7 / 434 (1.61%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 5			
Coronavirus infection				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	2 / 434 (0.46%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Device related infection				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Enterococcal sepsis				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Escherichia bacteraemia				

subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	2 / 434 (0.46%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Localised infection				
subjects affected / exposed	1 / 434 (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 / 434 (0.69%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumocystis jirovecii pneumonia				

subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	36 / 434 (8.29%)			
occurrences causally related to treatment / all	0 / 40			
deaths causally related to treatment / all	0 / 4			
Pneumonia aspiration				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia bacterial				
subjects affected / exposed	4 / 434 (0.92%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 1			
Pneumonia pneumococcal				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	5 / 434 (1.15%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 1			
Sepsis				
subjects affected / exposed	4 / 434 (0.92%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 1			
Cytomegalovirus viraemia				
subjects affected / exposed	1 / 434 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				

subjects affected / exposed	4 / 434 (0.92%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Abnormal loss of weight			
subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Decreased appetite			
subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	2 / 434 (0.46%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 434 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malnutrition			

subjects affected / exposed	1 / 434 (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	371 / 434 (85.48%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	43 / 434 (9.91%)		
occurrences (all)	56		
Weight decreased			
subjects affected / exposed	69 / 434 (15.90%)		
occurrences (all)	75		
Gamma-glutamyltransferase increased			
subjects affected / exposed	31 / 434 (7.14%)		
occurrences (all)	35		
Aspartate aminotransferase increased			
subjects affected / exposed	37 / 434 (8.53%)		
occurrences (all)	44		
Vascular disorders			
Hypertension			
subjects affected / exposed	27 / 434 (6.22%)		
occurrences (all)	29		
Nervous system disorders			
Headache			
subjects affected / exposed	31 / 434 (7.14%)		
occurrences (all)	32		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	22 / 434 (5.07%)		
occurrences (all)	22		
Abdominal pain			

subjects affected / exposed	29 / 434 (6.68%)		
occurrences (all)	33		
Nausea			
subjects affected / exposed	75 / 434 (17.28%)		
occurrences (all)	97		
Vomiting			
subjects affected / exposed	54 / 434 (12.44%)		
occurrences (all)	76		
Diarrhoea			
subjects affected / exposed	256 / 434 (58.99%)		
occurrences (all)	502		
Constipation			
subjects affected / exposed	23 / 434 (5.30%)		
occurrences (all)	25		
Respiratory, thoracic and mediastinal disorders			
Productive cough			
subjects affected / exposed	25 / 434 (5.76%)		
occurrences (all)	29		
Dyspnoea			
subjects affected / exposed	61 / 434 (14.06%)		
occurrences (all)	69		
Cough			
subjects affected / exposed	73 / 434 (16.82%)		
occurrences (all)	86		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	24 / 434 (5.53%)		
occurrences (all)	26		
Back pain			
subjects affected / exposed	30 / 434 (6.91%)		
occurrences (all)	31		
Infections and infestations			
Bronchitis			
subjects affected / exposed	48 / 434 (11.06%)		
occurrences (all)	68		
COVID-19			

subjects affected / exposed	22 / 434 (5.07%)		
occurrences (all)	22		
Nasopharyngitis			
subjects affected / exposed	38 / 434 (8.76%)		
occurrences (all)	54		
Respiratory tract infection			
subjects affected / exposed	25 / 434 (5.76%)		
occurrences (all)	30		
Urinary tract infection			
subjects affected / exposed	28 / 434 (6.45%)		
occurrences (all)	36		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	45 / 434 (10.37%)		
occurrences (all)	50		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 September 2020	The following main changes were introduced by the amendment: A clarification was added that dose reduction was also possible at Visit 1, if required to manage AEs identified at the end of the parent trial. The wording regarding withdrawal and interruption of trial medication in the management of liver enzyme elevations was clarified. Furthermore it was added that trial medication could be resumed in the case that clear evidence for an alternative cause for the hepatic injury was identified and resolved and the conditions for this and monitoring requirements after reintroduction were specified. A clarification was added that blood pressure and pulse rate should ideally be taken prior to blood sampling. The requirement to report SAEs by fax was replaced with requirement to report SAEs according to the country-specific reporting process. A risk assessment due to the COVID-19 pandemic situation was added to the benefit/risk assessment. Specifications were added for modification of visits in exceptional circumstances in the context of the COVID-19 pandemic. Site visits could be replaced with home or remote visits; as a minimum, at least AEs, concomitant treatments, and details on interruption of trial medication were to be collected. Instead of the planned central laboratory assessments, local laboratory assessments could be performed. If dose reduction was required for management of liver enzyme elevations but patients could not come to site and/or patient safety and follow-up safety laboratory testing could not be guaranteed, treatment had to be interrupted. Shipping of trial medication from site/depot to patients was permitted instead of dispensation on site.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported