Clinical trial results:
A double-blind, randomised, placebo controlled Phase III study of nintedanib plus Best Supportive Care (BSC) versus placebo plus BSC in patients with colorectal cancer refractory to standard therapies

Summary

EudraCT number	2012-000095-42
Trial protocol	LU IT SE AT DK BE DE PT NL PL FR
Global end of trial date	15 September 2016

Results information

Result version number	v2 (current)
This version publication date	14 November 2021
First version publication date	06 August 2017
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	1199.52

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02149108
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	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 8002430127, clintriage.rdg@boehringer-ingelheim.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	14 June 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 May 2016
Global end of trial reached?	Yes
Global end of trial date	15 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate efficacy and safety of Nintedanib plus BSC vs. placebo plus BSC in patients with metastatic colorectal cancer after failure of previous treatment with standard chemotherapy and biological agents.

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. If a subject continued to take trial medication, close monitoring was adhered to and all adverse events recorded. Rules were implemented in all trials whereby doses would be reduced if required. There were 2 dose reductions planned in the protocol: From 200 mg bid to 150 mg bid; then from 150 mg bid to 100 mg bid. In case a patient had these 2 dose reductions and , thereafter had an adverse event that require further dose reduction, the patient should be withdrawn as no further dose reduction was allowed. Symptomatic treatment of tumour associated symptoms were allowed throughout.

Background therapy: -

Evidence for comparator:

Placebo soft gelatin capsule matching that of Nintedanib twice daily (b.i.d.) administered orally of 21-day treatment course was the active comparator.

Actual start date of recruitment	14 October 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 23
Country: Number of subjects enrolled	Australia: 37
Country: Number of subjects enrolled	Austria: 27
Country: Number of subjects enrolled	Belgium: 61
Country: Number of subjects enrolled	Canada: 32
Country: Number of subjects enrolled	Czechia: 33
Country: Number of subjects enrolled	Denmark: 16
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	Hong Kong: 15
Country: Number of subjects enrolled	Israel: 12
Country: Number of subjects enrolled	Italy: 104
Country: Number of subjects enrolled	Japan: 112
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 73
Country: Number of subjects enrolled	Luxembourg: 3

Country: Number of subjects enrolled	Mexico: 8
Country: Number of subjects enrolled	Netherlands: 11
Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	Portugal: 30
Country: Number of subjects enrolled	Russian Federation: 21
Country: Number of subjects enrolled	Spain: 97
Country: Number of subjects enrolled	Sweden: 11
Country: Number of subjects enrolled	Taiwan: 29
Country: Number of subjects enrolled	Turkey: 39
Country: Number of subjects enrolled	United Kingdom: 64
Country: Number of subjects enrolled	United States: 54
Worldwide total number of subjects	949
EEA total number of subjects	430

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)	542
From 65 to 84 years	405
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The "completed" patients were on treatment (2 patients on Placebo, 3 patients on Nintedanib) at the data cut-off date 14JUN2016. The "NOT Completed" patients were off-treatment (380 patients on Placebo, 383 patients on Nintedanib) at the data cut-off date 14JUN2016.
Enrolled=949 subjects were enrolled, randomised (entered) =768 and treated=765.

Pre-assignment

Screening details:

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

Period 1

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

Blinding implementation details:

Patients, investigators, the sponsor’s trial team, and everyone involved in the analysis or with an interest in this trial remained blinded with regard to the randomised treatment assignments until after database lock.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo soft gelatin capsule matching that of Nintedanib twice daily (b.i.d.) administered orally of 21-day treatment course. If required the dose of placebo, could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

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

Dosage and administration details:

Placebo soft gelatin capsule matching that of Nintedanib twice daily (b.i.d.) administered orally of 21-day treatment course. If required the dose of placebo, could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

Arm title	Nintedanib

Arm description:

Nintedanib 200 mg twice daily (b.i.d.) administered orally in the form of a soft gelatin capsule of 21-day treatment course. If required the dose of Nintedanib, could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

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 200 mg twice daily (b.i.d.) administered orally in the form of a soft gelatin capsule of 21-day treatment course. If required the dose of Nintedanib, could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

Number of subjects in period 1[1]	Placebo	Nintedanib
Started	382	386
Completed	2	3
Not completed	380	383
Adverse event, serious fatal	11	12
Other not defined above	-	2
Adverse event, non-fatal	28	38
Progressive Disease (PD)	324	318
Refusal to continue trial medication	15	11
Lost to follow-up	1	-
Not treated	1	2

Notes:

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

Justification: Justification: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one of the trial medication. No Statistical analysis

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo soft gelatin capsule matching that of Nintedanib twice daily (b.i.d.) administered orally of 21-day treatment course. If required the dose of placebo, could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.	
Reporting group title	Nintedanib
Reporting group description:	
Nintedanib 200 mg twice daily (b.i.d.) administered orally in the form of a soft gelatin capsule of 21-day treatment course. If required the dose of Nintedanib, could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.	

Reporting group values	Placebo	Nintedanib	Total
Number of subjects	382	386	768
Age categorical Units: Subjects			
All	382	386	768
Age Continuous			
Randomised Set (RS): This patient set included all patients who were randomised to receive treatment, whether treated or not.			
Units: years			
arithmetic mean	61.1	61.0	
standard deviation	± 10.8	± 11.3	-
Gender, Male/Female Units: Subjects			
Female	164	150	314
Male	218	236	454

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo soft gelatin capsule matching that of Nintedanib twice daily (b.i.d.) administered orally of 21-day treatment course. If required the dose of placebo, could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

Reporting group title	Nintedanib

Reporting group description:

Nintedanib 200 mg twice daily (b.i.d.) administered orally in the form of a soft gelatin capsule of 21-day treatment course. If required the dose of Nintedanib, could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

Primary: Progression-Free Survival (PFS) by Central Review Assessment

End point title	Progression-Free Survival (PFS) by Central Review Assessment

End point description:

PFS by central review assessment was defined as the time from the date of randomisation to the date of disease progression according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 or death from any cause, whichever occurred first. Median, 95% Confidence Interval were calculated from an unadjusted Kaplan−Meier curve for each treatment arm.
Randomised Set: This patient set included all patients who were randomised to receive treatment, whether treated or not.

End point type	Primary

End point timeframe:

From randomisation until cut-off date 14JUN2016.

End point values	Placebo	Nintedanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	382[1]	386[2]		
Units: Months				
median (confidence interval 95%)	1.38 (1.38 to 1.41)	1.51 (1.45 to 2.17)		

Notes:

[1] - RS

[2] - RS

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Nintedanib

Number of subjects included in analysis	768
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.0001 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.69

Notes:

[3] - Hazard ratio <1 favors Nintedanib.

[4] - Hazard ratio, confidence interval and p−value obtained from log−rank test stratified by regorafenib pre−treatment (yes vs no), time from onset metastatic disease until randomisation (less than 24 months vs 24 months or more) and region.

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from randomisation to the time of death from any cause. Median, 95% Confidence Interval were calculated from an unadjusted Kaplan−Meier curve for each treatment arm. Randomised Set: This patient set included all patients who were randomised to receive treatment, whether treated or not.

End point type	Primary

End point timeframe:

From randomisation until cut-off date 14JUN2016.

End point values	Placebo	Nintedanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	382[5]	386[6]		
Units: Months				
median (confidence interval 95%)	6.05 (5.22 to 6.97)	6.44 (5.98 to 7.10)		

Notes:

[5] - RS

[6] - RS

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Nintedanib
Number of subjects included in analysis	768
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.8659 [8]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.01

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.19

Notes:

[7] - Hazard ratio below 1 favors Nintedanib.

[8] - Hazard ratio, confidence interval and p−value obtained from log−rank test stratified by regorafenib pre−treatment (yes vs no), time from onset metastatic disease until randomisation (less than 24 months vs 24 months or more) and region.

Secondary: Objective Tumour Response (Complete Response (CR)) + Partial Response (PR) by Central Review Assessment

End point title	Objective Tumour Response (Complete Response (CR)) + Partial Response (PR) by Central Review Assessment

End point description:

Objective tumour response was defined as best overall response of CR or PR determined by central review assessment.
Randomised Set: This patient set included all patients who were randomised to receive treatment, whether treated or not.

End point type	Secondary

End point timeframe:

From randomisation until cut-off date 14JUN2016.

End point values	Placebo	Nintedanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	382[9]	386[10]		
Units: Percentage of participants				
Objective response	0	0		

Notes:

[9] - RS

[10] - RS

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control (Complete Response + Partial Response + Stable Disease) by Central Review Assessment

End point title	Disease Control (Complete Response + Partial Response + Stable Disease) by Central Review Assessment

End point description:

Disease control was defined as best overall response of CR, PR, or Stable Disease (SD).
Randomised Set: This patient set included all patients who were randomised to receive treatment, whether treated or not.

End point type	Secondary

End point timeframe:

From randomisation until cut-off date 14JUN2016.

End point values	Placebo	Nintedanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	382[11]	386[12]		
Units: Percentage of participants				
number (not applicable)	10.5	25.6		

Notes:

[11] - RS

[12] - RS

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Nintedanib
Number of subjects included in analysis	768
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	< 0.0001 [14]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	2
upper limit	4.47

Notes:

[13] - An odds ratio >1 indicates benefit to Nintedanib.

[14] - Odds ratio and p−value are obtained from logistic regression model adjusted for regorafenib pre−treatment (yes vs no), time from onset metastatic disease until randomization in the trial (less than 24 months vs. 24 months or more) and region.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

1 patient who was randomised to the Placebo was not treated. Consequently, number of subjects that started is 382 but only 381 reported that includes only treated patients.
2 patients were randomised to the Nintedanib were not treated. Consequently, number of subjects that started is 386 but only 384 reported that includes only treated patients.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Nintedanib

Reporting group description:

Nintedanib 200 mg twice daily (b.i.d.) administered orally in the form of a soft gelatin capsule of 21-day treatment course. If required the dose of Nintedanib, could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

Reporting group title	Placebo

Reporting group description:

Placebo soft gelatin capsule matching that of Nintedanib twice daily (b.i.d.) administered orally of 21-day treatment course. If required the dose of placebo, could be reduced to 150 mg b.i.d. or 100 mg b.i.d. (according to the protocol-defined dose-reduction scheme). No dose increase was allowed after a dose reduction.

Serious adverse events	Nintedanib	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	149 / 384 (38.80%)	133 / 381 (34.91%)	
number of deaths (all causes)	55	51	
number of deaths resulting from adverse events	55	51	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bowen's disease			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			

subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial tumour haemorrhage			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malignant ascites			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	27 / 384 (7.03%)	24 / 381 (6.30%)	
occurrences causally related to treatment / all	0 / 27	0 / 24	
deaths causally related to treatment / all	0 / 27	0 / 24	
Metastases to central nervous system			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	1 / 384 (0.26%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to spine			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour associated fever			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			

subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	1 / 384 (0.26%)	5 / 381 (1.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour perforation			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 384 (0.26%)	2 / 381 (0.52%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 384 (1.04%)	3 / 381 (0.79%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	

Chest pain			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Condition aggravated			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Death			
subjects affected / exposed	2 / 384 (0.52%)	4 / 381 (1.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 4	
Fatigue			
subjects affected / exposed	2 / 384 (0.52%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 384 (0.00%)	3 / 381 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Generalised oedema			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			

subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	3 / 384 (0.78%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
subjects affected / exposed	5 / 384 (1.30%)	3 / 381 (0.79%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 5	0 / 1	
Pyrexia			
subjects affected / exposed	3 / 384 (0.78%)	4 / 381 (1.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis in device			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			

Pelvic pain			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acquired diaphragmatic eventration			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aspiration			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	12 / 384 (3.13%)	12 / 381 (3.15%)	
occurrences causally related to treatment / all	1 / 12	0 / 12	
deaths causally related to treatment / all	0 / 5	0 / 3	
Haemoptysis			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	3 / 384 (0.78%)	6 / 381 (1.57%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumothorax			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary embolism			
subjects affected / exposed	1 / 384 (0.26%)	2 / 381 (0.52%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Respiratory distress			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord polyp			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Confusional state			
subjects affected / exposed	1 / 384 (0.26%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Delirium			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 384 (1.82%)	3 / 381 (0.79%)	
occurrences causally related to treatment / all	7 / 7	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Aspartate aminotransferase increased			
subjects affected / exposed	6 / 384 (1.56%)	5 / 381 (1.31%)	
occurrences causally related to treatment / all	6 / 6	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	2 / 384 (0.52%)	6 / 381 (1.57%)	
occurrences causally related to treatment / all	1 / 2	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 384 (0.00%)	2 / 381 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	2 / 384 (0.52%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Liver function test increased			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	2 / 384 (0.52%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 384 (0.26%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Spinal compression fracture			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site haemorrhage			
subjects affected / exposed	2 / 384 (0.52%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 384 (0.00%)	2 / 381 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ataxia			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	1 / 384 (0.26%)	3 / 381 (0.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral haemorrhage			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			

subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	2 / 384 (0.52%)	2 / 381 (0.52%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	1 / 384 (0.26%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	2 / 384 (0.52%)	2 / 381 (0.52%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peroneal nerve palsy			

subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sensory loss			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 384 (0.52%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	2 / 384 (0.52%)	4 / 381 (1.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abdominal hernia			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	6 / 384 (1.56%)	4 / 381 (1.05%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 384 (0.26%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 384 (0.26%)	4 / 381 (1.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Constipation			
subjects affected / exposed	2 / 384 (0.52%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 384 (0.52%)	2 / 381 (0.52%)	
occurrences causally related to treatment / all	2 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	2 / 384 (0.52%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocutaneous fistula			

subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fistula of small intestine			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal hypomotility			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	5 / 384 (1.30%)	2 / 381 (0.52%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated inguinal hernia			
subjects affected / exposed	2 / 384 (0.52%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal obstruction			
subjects affected / exposed	6 / 384 (1.56%)	6 / 381 (1.57%)	
occurrences causally related to treatment / all	0 / 6	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal prolapse			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			

subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal stenosis			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	2 / 384 (0.52%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 384 (0.00%)	2 / 381 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mallory-Weiss syndrome			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	3 / 384 (0.78%)	4 / 381 (1.05%)	
occurrences causally related to treatment / all	2 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			

subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal obstruction			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal tenesmus			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Subileus			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	5 / 384 (1.30%)	2 / 381 (0.52%)	
occurrences causally related to treatment / all	3 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stenosis			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			

subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	2 / 384 (0.52%)	4 / 381 (1.05%)	
occurrences causally related to treatment / all	1 / 2	0 / 4	
deaths causally related to treatment / all	1 / 1	0 / 3	
Drug-induced liver injury			
subjects affected / exposed	4 / 384 (1.04%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	6 / 6	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	1 / 384 (0.26%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	2 / 384 (0.52%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Jaundice			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	1 / 384 (0.26%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver disorder			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	7 / 384 (1.82%)	3 / 381 (0.79%)	
occurrences causally related to treatment / all	0 / 7	0 / 3	
deaths causally related to treatment / all	0 / 5	0 / 0	
Focal segmental glomerulosclerosis			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	4 / 384 (1.04%)	5 / 381 (1.31%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Micturition disorder			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	3 / 384 (0.78%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal impairment			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 384 (0.26%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	4 / 384 (1.04%)	5 / 381 (1.31%)	
occurrences causally related to treatment / all	0 / 4	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fistula			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 384 (0.00%)	2 / 381 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 384 (0.00%)	3 / 381 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			

subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	3 / 384 (0.78%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oral candidiasis			

subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	2 / 384 (0.52%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 384 (0.78%)	5 / 381 (1.31%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Postoperative wound infection			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	4 / 384 (1.04%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Small intestine gangrene			

subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	6 / 384 (1.56%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	1 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection pseudomonal			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 384 (0.00%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	6 / 384 (1.56%)	5 / 381 (1.31%)	
occurrences causally related to treatment / all	1 / 6	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dehydration			
subjects affected / exposed	4 / 384 (1.04%)	1 / 381 (0.26%)	
occurrences causally related to treatment / all	2 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			

subjects affected / exposed	0 / 384 (0.00%)	3 / 381 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	1 / 384 (0.26%)	0 / 381 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Nintedanib	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	351 / 384 (91.41%)	309 / 381 (81.10%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	90 / 384 (23.44%)	23 / 381 (6.04%)	
occurrences (all)	111	25	
Aspartate aminotransferase increased			
subjects affected / exposed	90 / 384 (23.44%)	44 / 381 (11.55%)	
occurrences (all)	108	47	
Blood alkaline phosphatase increased			
subjects affected / exposed	28 / 384 (7.29%)	22 / 381 (5.77%)	
occurrences (all)	33	22	
Weight decreased			
subjects affected / exposed	35 / 384 (9.11%)	13 / 381 (3.41%)	
occurrences (all)	35	13	

Blood bilirubin increased			
subjects affected / exposed	26 / 384 (6.77%)	15 / 381 (3.94%)	
occurrences (all)	27	18	
Vascular disorders			
Hypertension			
subjects affected / exposed	42 / 384 (10.94%)	15 / 381 (3.94%)	
occurrences (all)	43	16	
Nervous system disorders			
Headache			
subjects affected / exposed	25 / 384 (6.51%)	19 / 381 (4.99%)	
occurrences (all)	30	24	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	23 / 384 (5.99%)	22 / 381 (5.77%)	
occurrences (all)	26	23	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	113 / 384 (29.43%)	89 / 381 (23.36%)	
occurrences (all)	127	95	
Asthenia			
subjects affected / exposed	54 / 384 (14.06%)	46 / 381 (12.07%)	
occurrences (all)	60	50	
Oedema peripheral			
subjects affected / exposed	22 / 384 (5.73%)	28 / 381 (7.35%)	
occurrences (all)	25	28	
Pain			
subjects affected / exposed	9 / 384 (2.34%)	21 / 381 (5.51%)	
occurrences (all)	9	21	
Pyrexia			
subjects affected / exposed	53 / 384 (13.80%)	45 / 381 (11.81%)	
occurrences (all)	61	58	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	65 / 384 (16.93%)	59 / 381 (15.49%)	
occurrences (all)	69	60	
Abdominal pain upper			

subjects affected / exposed	25 / 384 (6.51%)	21 / 381 (5.51%)	
occurrences (all)	28	22	
Constipation			
subjects affected / exposed	65 / 384 (16.93%)	57 / 381 (14.96%)	
occurrences (all)	73	60	
Diarrhoea			
subjects affected / exposed	175 / 384 (45.57%)	57 / 381 (14.96%)	
occurrences (all)	301	76	
Vomiting			
subjects affected / exposed	149 / 384 (38.80%)	71 / 381 (18.64%)	
occurrences (all)	229	93	
Nausea			
subjects affected / exposed	163 / 384 (42.45%)	103 / 381 (27.03%)	
occurrences (all)	202	129	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	42 / 384 (10.94%)	48 / 381 (12.60%)	
occurrences (all)	47	48	
Dyspnoea			
subjects affected / exposed	35 / 384 (9.11%)	40 / 381 (10.50%)	
occurrences (all)	37	43	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	20 / 384 (5.21%)	14 / 381 (3.67%)	
occurrences (all)	21	14	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	30 / 384 (7.81%)	22 / 381 (5.77%)	
occurrences (all)	33	22	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	34 / 384 (8.85%)	12 / 381 (3.15%)	
occurrences (all)	38	14	
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	21 / 384 (5.47%)	6 / 381 (1.57%)	
occurrences (all)	22	6	
Back pain			
subjects affected / exposed	33 / 384 (8.59%)	30 / 381 (7.87%)	
occurrences (all)	37	32	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	128 / 384 (33.33%)	96 / 381 (25.20%)	
occurrences (all)	143	100	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 July 2014	In the amendment 1 primary endpoint PFS and key secondary endpoint OS were changed to coprimary endpoints to reflect the clinical benefit for patients in this trial. As the trial was already powered for OS, no other changes in the trial design or patient number were needed. All relevant sections of the Clinical Trial Protocol (CTP) were adapted accordingly. The subgroup analysis 'previous treatment with TAS-102 (yes vs. no)' was added for both coprimary endpoints. The amendment 1 also clarified that analyses to describe the pattern of time to death would be described, while accounting for the extent and influence of postprogression anticancer treatments. The amendment 1 added the analysis on exposure-response relationship to the CTP.
13 March 2015	The amendment 2 clarified that previous treatment for Colo Rectal Cancer (CRC) with TAS-102, if available to the patient according to local standards, was allowed in this trial. Further clarifications regarding dose reduction in the case of diarrhoea, treatment interruption in case of haematological AEs, and the threshold for liver enzymes not being dependent on CTCAE were provided. The information about history of CRC that should be obtained and recorded in the electronic Case Report Form (eCRF) was extended by 'reasons for not administering regorafenib'. For the HRQoL analysis, it was clarified that the main HRQoL endpoints in this trial are the changes in mean scores over the duration of the median follow-up period for the physical functioning scale and global health status (QoL scale measured on the EORTC QCL-C30 questionnaire using longitudinal models). These are mixed-effects growth curve models with the average profile over time for each HRQoL endpoint described using a piecewise linear model. A mean score per patient for each HRQoL endpoint will be calculated from the area under the estimated growth curve up to the median follow-up time. An additional responder analysis will compare the proportions of patients in each treatment group that achieved an average 10-point increase from the baseline score over the follow-up time for each HRQoL endpoint of interest.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported