Clinical trial results:
RANDOMIZED, DOUBLE-BLIND, PHASE 3 STUDY EVALUATING TAS-102 PLUS BEST SUPPORTIVE CARE (BSC) VERSUS PLACEBO PLUS BSC IN PATIENTS WITH METASTATIC GASTRIC CANCER REFRACTORY TO STANDARD TREATMENTS

Summary

EudraCT number	2015-002683-16
Trial protocol	GB DE BE ES IE PT CZ PL IT
Global end of trial date	19 December 2019

Results information

Result version number	v2 (current)
This version publication date	12 September 2024
First version publication date	12 April 2020
Version creation reason	• Correction of full data set Updates are required to fix the data discrepancies.
Summary attachment (see zip file)	TAS-120-302 CSR Synopsis (2015-002683-16_CSR Synopsis_04Dec2018.pdf)

Trial information

Trial identification

Sponsor protocol code	TO-TAS-102-302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02500043
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Taiho Oncology, Inc
Sponsor organisation address	101 Carnegie Center, Suite 101, Princeton, New Jersey, United States, NJ 08540
Public contact	Taiho Oncology, Inc , Taiho Pharma Europe, Ltd, +1 844-878-2446, medicalinformation@taihooncology.com
Scientific contact	Taiho Oncology, Inc , Taiho Pharma Europe, Ltd, +1 844-878-2446, medicalinformation@taihooncology.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	28 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 April 2018
Global end of trial reached?	Yes
Global end of trial date	19 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Overall survival (OS)

Protection of trial subjects:

This study was designed and conducted in accordance with the Sponsor procedures, which comply with the ethical principles of Good Clinical Practice (GCP) as required by the major regulatory authorities and in accordance with the Declaration of Helsinki, ICH E6 Guideline for GCP, and local regulations.

The protocol and amendments, Informed Consent Form (ICF), and the Investigator's Brochure (IB) provided to the Investigators, and any other documents that pertained to patient information (eg, patient diaries), recruitment methods, and advertisements received Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval before the first patient was enrolled at the investigational site. When necessary, all protocol amendments and changes to the ICF were submitted by the Investigator to the IRB/IEC for approval. The Investigators notified the IRB/IEC of deviations from the protocol or serious adverse events occurring at the site according to local policies and IRB/IEC requirements, as well as other adverse event reports, in accordance with local procedures.

The Investigator or a designee under the Investigator's responsibility (according to applicable regulatory requirements) fully informed patients of all pertinent aspects of the clinical study. All participants were informed to the fullest extent possible about the study in a language and in terms they were able to understand.

Prior to participation in the trial, the written ICF was signed and personally dated by the patient or by the patient's legal representative and by the person who conducted the informed consent discussion. A copy of the signed and dated ICF was provided to the patient.

Background therapy:

Best Supportive Care according to local clinical practice i.e.:
- regimens including fluoropyrimidines, platinum derivatives, and either a taxane- and/or irinotecan-containing regimen;
- a anti-HER2+ therapy for patients whose tumors are HER2-neupositive (HER2+);
- pre- or post-operative adjuvant chemotherapy or chemoradiotherapy,

Evidence for comparator:

This present study was designed as a randomized, double-blind, Phase 3 study comparing TAS-102 plus best supportive care (BSC) to placebo plus BSC in patients with metastatic gastric cancer who have received at least 2 prior regimens for advanced disease and were refractory or unable to tolerate their last prior therapy.

A placebo-controlled design was considered appropriate as there are currently no standard therapies for patients with metastatic gastric cancer who have failed first- and second-line therapies.

Actual start date of recruitment	11 February 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 66
Country: Number of subjects enrolled	United States: 26
Country: Number of subjects enrolled	Turkey: 43
Country: Number of subjects enrolled	France: 24
Country: Number of subjects enrolled	Japan: 73
Country: Number of subjects enrolled	Israel: 12
Country: Number of subjects enrolled	Russian Federation: 46
Country: Number of subjects enrolled	Belarus: 30
Country: Number of subjects enrolled	Poland: 14
Country: Number of subjects enrolled	Portugal: 39
Country: Number of subjects enrolled	Romania: 8
Country: Number of subjects enrolled	Spain: 40
Country: Number of subjects enrolled	United Kingdom: 45
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Czech Republic: 9
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Ireland: 8
Worldwide total number of subjects	507
EEA total number of subjects	277

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)	279
From 65 to 84 years	226
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Patients were randomized at 110 centers in 17 countries.
A total of 625 patients signed informed consent for participation in the study.

Pre-assignment

Screening details:

All patients had to complete the following study procedures prior to a confirmation of eligibility: -Medical History, -Histologic Confirmation, -Human Epidermal Growth Factor Receptor 2 (HER2) Status, -Physical Examination, -Baseline Signs and Symptoms, -Height, Vital Signs, Weight, -ECOG performance status and - Clinical Laboratory Evaluations

Pre-assignment period milestones

Number of subjects started	625[1]
Intermediate milestone: Number of subjects	Screening - Confirmation of Eligibility: 507
Number of subjects completed	507

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screen failure: 111
Reason: Number of subjects	Consent withdrawn by subject: 1
Reason: Number of subjects	Other: 4
Reason: Number of subjects	Death: 1
Reason: Number of subjects	Protocol deviation: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 625 subjects were screened and the same was showed as started in the pre-assignment period.

Period 1

Period 1 title	Baseline Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Baseline

Arm description:

Baseline period; screening for participation in the study

Arm type	Screening
Investigational medicinal product name	TAS-102
Investigational medicinal product code	FTD, F3TdR, F3dThd
Other name	5-TRIFLUOROTHYMIDINE
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

TAS-102 is formulated as an immediate-release film-coated tablet, which is supplied in 2 strengths:
• The 15 mg white, round tablet
• The 20 mg pale-red, round tablet

The total dose is 70 mg/m2 milligram(s)/square meter, per day within 1 hour after completion of

morning and evening meals, for 5 days a week with 2 days rest for 2 weeks, followed by a 14-day rest. This treatment cycle will be repeated every 4 weeks.

Number of subjects in period 1	Baseline
Started	507
Sign ICF	507
Enrollment	507
Medical History	507
Histological Confirmation	507
HER2 status (if available)	507
Physical Examination	507
Baseline Signs & Symptoms	507
Height	507
Vital Signs & Weight	507
ECOG Performance Status	507
Hematology	507
Serum Chemistry	507
Urinalysis	507
Pregnancy Test	507
Tumor Measurements	507
Quality of Life Assessment	507
Concomitant Medications	507
Completed	507

Period 2

Period 2 title	Treatment Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Blinding implementation details:

Eligible patients who met all of the inclusion and none of the exclusion criteria were centrally randomized (2:1) to TAS-102 plus BSC (experimental arm) or placebo plus BSC (control arm) using a

dynamic allocation method (biased coin) via an Interactive Voice/Web Response System (IXRS). Randomization was stratified by: region (Rest of World (ROW) vs Japan); ECOG performance status (0 vs 1); and prior treatment with ramucirumab (yes vs no).

Arms

Are arms mutually exclusive?	Yes
Arm title	TAS-102 plus BSC

Arm description:

Experimental arm, evaluating the efficacy and safety of TAS-102 (Investigational Medicinal Product) plus Best Supportive Care (BSC)

Arm type	Experimental
Investigational medicinal product name	TAS-102
Investigational medicinal product code	FTD, F3TdR, F3dThd
Other name	5-TRIFLUOROTHYMIDINE
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

TAS-102 is formulated as an immediate-release film-coated tablet, which is supplied in 2 strengths:
• The 15 mg white, round tablet
• The 20 mg pale-red, round tablet

The total dose is 70 mg/m2 milligram(s)/square meter, per day within 1 hour after completion of morning and evening meals, for 5 days a week with 2 days rest for 2 weeks, followed by a 14-day rest. This treatment cycle will be repeated every 4 weeks.

Arm title	Placebo plus BSC

Arm description:

Experimental arm, evaluating the efficacy and safety of placebo plus Best Supportive Care (BSC)

Arm type	Placebo
Investigational medicinal product name	TAS-102
Investigational medicinal product code	FTD, F3TdR, F3dThd
Other name	5-TRIFLUOROTHYMIDINE
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

TAS-102 is formulated as an immediate-release film-coated tablet, which is supplied in 2 strengths:
• The 15 mg white, round tablet
• The 20 mg pale-red, round tablet

The total dose is 70 mg/m2 milligram(s)/square meter, per day within 1 hour after completion of morning and evening meals, for 5 days a week with 2 days rest for 2 weeks, followed by a 14-day rest. This treatment cycle will be repeated every 4 weeks.

Number of subjects in period 2	TAS-102 plus BSC	Placebo plus BSC
Started	337	170
Randomization	337	170
Physical Examination	337	170
Vital Signs & Weight	337	170
ECOG Performance Status	337	170

Hematology	337	170
Serum Chemistry	337	170
Tumor Measurements	337	170
Quality of Life Assessment	337	170
Concomitant Medications	337	170
AE/SAE Assessment	337	170
TAS-102 or Placebo treatment	337	170
Survival Status	337	170
Completed	335	168
Not completed	2	2
Adverse event, serious fatal	1	-
Consent withdrawn by subject	-	2
Protocol deviation	1	-

Period 3

Period 3 title	End of Treatment Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	End of Study
Arm description: End of Treatment	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 3	End of Study
Started	503
Physical Examination	22
Vital Signs & Weight	22
ECOG Performance Status	22
Hematology	22
Serum Chemistry	22
Pregnancy Test	22
Tumor Measurements	22

Quality of Life Assessment	22
Concomitant Medications	22
AE/SAE Assessment	22
Survival Status	22
Completed	22
Not completed	481
Clinical progression	89
Consent withdrawn by subject	18
Physician decision	14
Radiological progression	302
Adverse event, non-fatal	44
Death	13
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Baseline Period

Reporting group description: -

Reporting group values	Baseline Period	Total	
Number of subjects	507	507	
Age categorical Units: Subjects			
Adults (18-64 years)	279	279	
From 65-84 years	226	226	
85 years and over	2	2	
Age continuous Units: years			
arithmetic mean	62.5		
full range (min-max)	24 to 89	-	
Gender categorical Units: Subjects			
Female	138	138	
Male	369	369	
Race Units: Subjects			
White	357	357	
Black/African American	3	3	
Asian	80	80	
Not collectable	62	62	
Other	5	5	
Region Units: Subjects			
Japan	73	73	
United States	26	26	
European Union	408	408	
Baseline renal function Units: Subjects			
Normal (CrCl ≥ 90 mL/min)	202	202	
Mild impairment (CrCl 60-89 mL/min)	212	212	
Moderate impairment (CrCl 30-59 mL/min)	86	86	
Severe impairment (CrCl < 30 mL/min)	3	3	
Not recorded	4	4	
Body Surface Area Units: m2			
arithmetic mean	1.749		
full range (min-max)	1.20 to 2.52	-	

Subject analysis sets	
Subject analysis set title	Intention to treat (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description: ITT population - patients who were randomized	
Subject analysis set title	TAS-102 + BSC
Subject analysis set type	Full analysis
Subject analysis set description: Subjects randomised to TAS-102 + BSC group	
Subject analysis set title	Placebo + BSC
Subject analysis set type	Full analysis
Subject analysis set description: Subjects randomised to Placebo + BSC group	

Reporting group values	Intention to treat (ITT)	TAS-102 + BSC	Placebo + BSC
Number of subjects	507	337	170
Age categorical Units: Subjects			
Adults (18-64 years)	279	183	96
From 65-84 years	226	152	74
85 years and over	2	2	0
Age continuous Units: years			
arithmetic mean	62.5	62.8	62.0
full range (min-max)	24 to 89	24 to 89	32 to 82
Gender categorical Units: Subjects			
Female	138	85	53
Male	369	252	117
Race Units: Subjects			
White	357	244	113
Black/African American	3	1	2
Asian	80	51	29
Not collectable	62	38	24
Other	5	3	2
Region Units: Subjects			
Japan	73	46	27
United States	26	21	5
European Union	408	270	138
Baseline renal function Units: Subjects			
Normal (CrCl ≥ 90 mL/min)	202	134	68
Mild impairment (CrCl 60-89 mL/min)	212	141	71
Moderate impairment (CrCl 30-59 mL/min)	86	58	28
Severe impairment (CrCl < 30 mL/min)	3	2	1
Not recorded	4	2	2

Body Surface Area Units: m2			
arithmetic mean	1.749	1.747	1.754
full range (min-max)	1.20 to 2.52	1.20 to 2.37	1.29 to 2.52

End points

End points reporting groups

Reporting group title	Baseline

Reporting group description:

Baseline period; screening for participation in the study

Reporting group title	TAS-102 plus BSC

Reporting group description:

Experimental arm, evaluating the efficacy and safety of TAS-102 (Investigational Medicinal Product) plus Best Supportive Care (BSC)

Reporting group title	Placebo plus BSC

Reporting group description:

Experimental arm, evaluating the efficacy and safety of placebo plus Best Supportive Care (BSC)

Reporting group title	End of Study

Reporting group description:

End of Treatment

Subject analysis set title	Intention to treat (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

ITT population - patients who were randomized

Subject analysis set title	TAS-102 + BSC
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects randomised to TAS-102 + BSC group

Subject analysis set title	Placebo + BSC
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects randomised to Placebo + BSC group

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall Survival (OS) was the primary endpoint of this study and was defined as the time from the date of randomization to the death date. In the absence of death confirmation or for patients alive on the survival cut-off date, survival was censored at the date of last study follow-up or the cut-off date, whichever was earlier.

End point type	Primary

End point timeframe:

The overall survival (OS) cut-off date used for the primary analysis was based on the survival data obtained through the date of the 384th death observed in the study (27 Mar 2018).

End point values	TAS-102 plus BSC	Placebo plus BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	170		
Units: Subjects				
Total patients	337	170		
Not censored (dead)	244	140		
Censored	93	30		
Overall Survival by Region: Japan	46	27		
Overall Survival by Region: Rest of World	291	143		
Overall Survival by ECOG status at baseline: 0	123	68		
Overall Survival by ECOG status at baseline: 1	214	102		
OS by Prior treatment with ramucirumab: Yes	114	55		
OS by Prior treatment with ramucirumab: No	223	115		

Statistical analyses

Statistical analysis title	Overall Survival (months)

Statistical analysis description:

Overall Survival (OS) in the Intent to Treat (ITT) population will be compared between the 2 treatment groups using the stratified log-rank test.

Comparison groups	TAS-102 plus BSC v Placebo plus BSC
Number of subjects included in analysis	507
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0006
Method	t-test, 2-sided
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6917
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5597
upper limit	0.8548
Variability estimate	Standard deviation

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)

End point description:

Progression free survival was defined as the time from the date of randomization until the date of the investigator-assessed radiological disease progression or death due to any cause. Patients who were alive with no disease progression as of the analysis cut-off date were censored at the date of the last tumor assessment. Patients who received non-study cancer treatment before disease progression, or patients with clinical but not radiological evidence of progression was censored at the date of the last evaluable tumor assessment before the non-study cancer treatment was initiated.

End point type	Secondary

End point timeframe:

PFS was defined as the time from the date of randomization until the date of the investigator-assessed radiological disease progression or death due to any cause as of the pre-specified cut-off date of 31 Mar 2018 for non-survival data.

End point values	TAS-102 plus BSC	Placebo plus BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	170		
Units: Subjects				
Total patients	337	170		
PFS Events	287	156		
Progressed	209	113		
Death	78	43		
Censored	50	14		
Discontinued follow-up	12	1		
Initiated anti-tumor therapy	8	6		
Missed visit (> 91 days since last response)	10	3		
Follow-up ongoing at the time of analysis	20	4		
PFS by Region: Japan	46	27		
PFS by Region: Rest of World	291	143		
PFS by ECOG Performance Status at Baseline: 0	123	68		
PFS by ECOG Performance Status at Baseline: 1	214	102		
PFS by Prior Treatment with Ramucirumab: Yes	114	55		
PFS by Prior Treatment with Ramucirumab: No	223	115		

Statistical analyses

Statistical analysis title	Progression-Free Survival

Statistical analysis description:

Progression-free survival (PFS) was defined as the time from the date of randomization until the date of the investigator-assessed radiological disease progression or death due to any cause as of the pre-specified cut-off date of 31 Mar 2018 for non-survival data.

Comparison groups	TAS-102 plus BSC v Placebo plus BSC
Number of subjects included in analysis	507
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Hazard ratio (HR)
Point estimate	0.5723

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4674
upper limit	0.7008
Variability estimate	Standard deviation

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AE) were reported from the first dose of study medication through the period of patient follow-up (30 days after the last dose of study medication or until the start of new anti-tumor therapy, whichever was earlier).

Adverse event reporting additional description:

All adverse event reporting were performed using the as-treated (AT) analysis population.

The Common Terminology Criteria for Adverse Events (CTCAE Version 4.03) terms was used to assess severity/provide the grade for each adverse event (AE) that was reported.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	Placebo plus BSC

Reporting group description:

Adverse Events occurring in subjects within the placebo group

Reporting group title	TAS-102 plus BSC

Reporting group description:

Adverse Events occurring in subjects within the treatment (TAS-102) group

Serious adverse events	Placebo plus BSC	TAS-102 plus BSC	
Total subjects affected by serious adverse events			
subjects affected / exposed	70 / 168 (41.67%)	143 / 335 (42.69%)	
number of deaths (all causes)	142	253	
number of deaths resulting from adverse events	19	45	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous system			
subjects affected / exposed	0 / 168 (0.00%)	2 / 335 (0.60%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Tumour haemorrhage			
subjects affected / exposed	1 / 168 (0.60%)	2 / 335 (0.60%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain neoplasm			

subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangiosis carcinomatosa			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Malignant ascites			
subjects affected / exposed	2 / 168 (1.19%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm malignant			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cancer pain			
subjects affected / exposed	1 / 168 (0.60%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric cancer metastatic			
subjects affected / exposed	1 / 168 (0.60%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Shock haemorrhagic			
subjects affected / exposed	0 / 168 (0.00%)	2 / 335 (0.60%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	2 / 2	
Lymphoedema			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			

subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 168 (0.60%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	15 / 168 (8.93%)	21 / 335 (6.27%)	
occurrences causally related to treatment / all	15 / 15	21 / 21	
deaths causally related to treatment / all	11 / 11	17 / 17	
Fatigue			
subjects affected / exposed	0 / 168 (0.00%)	2 / 335 (0.60%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 168 (0.00%)	2 / 335 (0.60%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	3 / 168 (1.79%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	1 / 168 (0.60%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pain			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			

subjects affected / exposed	1 / 168 (0.60%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
subjects affected / exposed	1 / 168 (0.60%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial hyperplasia			
subjects affected / exposed	1 / 168 (0.60%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 168 (0.60%)	5 / 335 (1.49%)	
occurrences causally related to treatment / all	1 / 1	5 / 5	
deaths causally related to treatment / all	1 / 1	2 / 2	
Pulmonary embolism			
subjects affected / exposed	2 / 168 (1.19%)	5 / 335 (1.49%)	
occurrences causally related to treatment / all	2 / 2	5 / 5	
deaths causally related to treatment / all	0 / 0	3 / 3	
Dyspnoea			
subjects affected / exposed	2 / 168 (1.19%)	4 / 335 (1.19%)	
occurrences causally related to treatment / all	2 / 2	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory failure			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 168 (0.00%)	2 / 335 (0.60%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
White blood cell count decreased			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bilirubin conjugated increased			
subjects affected / exposed	1 / 168 (0.60%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	1 / 168 (0.60%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 168 (0.60%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 168 (0.60%)	2 / 335 (0.60%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	2 / 2	
Atrial fibrillation			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cerebral haemorrhage			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hemiparesis			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
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 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cerebrovascular accident			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	1 / 168 (0.60%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 168 (0.60%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 168 (2.38%)	13 / 335 (3.88%)	
occurrences causally related to treatment / all	4 / 4	13 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 168 (0.00%)	7 / 335 (2.09%)	
occurrences causally related to treatment / all	0 / 0	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 168 (0.00%)	4 / 335 (1.19%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 168 (0.00%)	4 / 335 (1.19%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular			

coagulation			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 168 (0.00%)	2 / 335 (0.60%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 168 (0.60%)	9 / 335 (2.69%)	
occurrences causally related to treatment / all	1 / 1	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	6 / 168 (3.57%)	8 / 335 (2.39%)	
occurrences causally related to treatment / all	6 / 6	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 168 (0.00%)	6 / 335 (1.79%)	
occurrences causally related to treatment / all	0 / 0	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	

Dysphagia			
subjects affected / exposed	2 / 168 (1.19%)	6 / 335 (1.79%)	
occurrences causally related to treatment / all	2 / 2	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 168 (0.60%)	4 / 335 (1.19%)	
occurrences causally related to treatment / all	1 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	
Intestinal obstruction			
subjects affected / exposed	3 / 168 (1.79%)	4 / 335 (1.19%)	
occurrences causally related to treatment / all	3 / 3	4 / 4	
deaths causally related to treatment / all	1 / 1	0 / 0	
Ascites			
subjects affected / exposed	7 / 168 (4.17%)	3 / 335 (0.90%)	
occurrences causally related to treatment / all	7 / 7	3 / 3	
deaths causally related to treatment / all	1 / 1	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	3 / 168 (1.79%)	3 / 335 (0.90%)	
occurrences causally related to treatment / all	3 / 3	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 168 (0.00%)	3 / 335 (0.90%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	2 / 168 (1.19%)	3 / 335 (0.90%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 168 (0.60%)	2 / 335 (0.60%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			

subjects affected / exposed	0 / 168 (0.00%)	2 / 335 (0.60%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 168 (1.19%)	2 / 335 (0.60%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Nausea			
subjects affected / exposed	0 / 168 (0.00%)	2 / 335 (0.60%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal obstruction			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			

subjects affected / exposed	1 / 168 (0.60%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric stenosis			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	1 / 168 (0.60%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 168 (0.60%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal obstruction			
subjects affected / exposed	1 / 168 (0.60%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Melaena			
subjects affected / exposed	1 / 168 (0.60%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal pain			
subjects affected / exposed	1 / 168 (0.60%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	1 / 168 (0.60%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 168 (0.60%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcerative gastritis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 168 (0.00%)	2 / 335 (0.60%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	2 / 2	
Jaundice			
subjects affected / exposed	0 / 168 (0.00%)	2 / 335 (0.60%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	1 / 168 (0.60%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			

subjects affected / exposed	1 / 168 (0.60%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis toxic			
subjects affected / exposed	1 / 168 (0.60%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 168 (0.60%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Joint swelling			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	3 / 168 (1.79%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Neutropenic sepsis			
subjects affected / exposed	0 / 168 (0.00%)	4 / 335 (1.19%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia			
subjects affected / exposed	2 / 168 (1.19%)	4 / 335 (1.19%)	
occurrences causally related to treatment / all	2 / 2	4 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	
Septic shock			
subjects affected / exposed	0 / 168 (0.00%)	3 / 335 (0.90%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	3 / 3	
Infection			
subjects affected / exposed	1 / 168 (0.60%)	2 / 335 (0.60%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Influenza			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 168 (0.60%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 168 (0.60%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			

subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Typhoid fever			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary sepsis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	1 / 168 (0.60%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 168 (0.60%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	4 / 168 (2.38%)	11 / 335 (3.28%)	
occurrences causally related to treatment / all	4 / 4	11 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	1 / 168 (0.60%)	2 / 335 (0.60%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	1 / 1	2 / 2	
Dehydration			
subjects affected / exposed	1 / 168 (0.60%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alkalosis hypochloraemic			
subjects affected / exposed	0 / 168 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cachexia			
subjects affected / exposed	1 / 168 (0.60%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 168 (0.60%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	1 / 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	Placebo plus BSC	TAS-102 plus BSC	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	151 / 168 (89.88%)	319 / 335 (95.22%)	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 168 (0.60%)	50 / 335 (14.93%)	
occurrences (all)	1	139	
Blood alkaline phosphatase increased			
subjects affected / exposed	14 / 168 (8.33%)	30 / 335 (8.96%)	
occurrences (all)	15	35	
Platelet count decreased			
subjects affected / exposed	6 / 168 (3.57%)	28 / 335 (8.36%)	
occurrences (all)	11	43	
White blood cell count decreased			
subjects affected / exposed	0 / 168 (0.00%)	23 / 335 (6.87%)	
occurrences (all)	0	59	
Aspartate aminotransferase increased			
subjects affected / exposed	13 / 168 (7.74%)	21 / 335 (6.27%)	
occurrences (all)	15	26	
Weight decreased			
subjects affected / exposed	12 / 168 (7.14%)	20 / 335 (5.97%)	
occurrences (all)	13	21	
Blood bilirubin increased			
subjects affected / exposed	7 / 168 (4.17%)	17 / 335 (5.07%)	
occurrences (all)	9	28	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	30 / 168 (17.86%)	142 / 335 (42.39%)	
occurrences (all)	52	250	
Neutropenia			
subjects affected / exposed	6 / 168 (3.57%)	128 / 335 (38.21%)	
occurrences (all)	9	314	
Leukopenia			

subjects affected / exposed	3 / 168 (1.79%)	57 / 335 (17.01%)	
occurrences (all)	14	116	
Thrombocytopenia			
subjects affected / exposed	2 / 168 (1.19%)	32 / 335 (9.55%)	
occurrences (all)	2	45	
Lymphopenia			
subjects affected / exposed	8 / 168 (4.76%)	20 / 335 (5.97%)	
occurrences (all)	21	42	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	35 / 168 (20.83%)	87 / 335 (25.97%)	
occurrences (all)	41	136	
Asthenia			
subjects affected / exposed	37 / 168 (22.02%)	65 / 335 (19.40%)	
occurrences (all)	45	97	
Pyrexia			
subjects affected / exposed	8 / 168 (4.76%)	23 / 335 (6.87%)	
occurrences (all)	9	37	
Oedema peripheral			
subjects affected / exposed	12 / 168 (7.14%)	17 / 335 (5.07%)	
occurrences (all)	12	17	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	53 / 168 (31.55%)	123 / 335 (36.72%)	
occurrences (all)	64	201	
Vomiting			
subjects affected / exposed	34 / 168 (20.24%)	80 / 335 (23.88%)	
occurrences (all)	48	104	
Diarrhoea			
subjects affected / exposed	24 / 168 (14.29%)	73 / 335 (21.79%)	
occurrences (all)	28	118	
Abdominal pain			
subjects affected / exposed	27 / 168 (16.07%)	50 / 335 (14.93%)	
occurrences (all)	34	75	
Constipation			

subjects affected / exposed	25 / 168 (14.88%)	44 / 335 (13.13%)	
occurrences (all)	31	54	
Abdominal pain upper			
subjects affected / exposed	14 / 168 (8.33%)	22 / 335 (6.57%)	
occurrences (all)	15	27	
Ascites			
subjects affected / exposed	10 / 168 (5.95%)	16 / 335 (4.78%)	
occurrences (all)	18	24	
Abdominal distension			
subjects affected / exposed	9 / 168 (5.36%)	13 / 335 (3.88%)	
occurrences (all)	9	15	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	16 / 168 (9.52%)	21 / 335 (6.27%)	
occurrences (all)	16	24	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	10 / 168 (5.95%)	11 / 335 (3.28%)	
occurrences (all)	10	12	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	9 / 168 (5.36%)	25 / 335 (7.46%)	
occurrences (all)	10	31	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	49 / 168 (29.17%)	109 / 335 (32.54%)	
occurrences (all)	54	165	
Hypoalbuminaemia			
subjects affected / exposed	10 / 168 (5.95%)	21 / 335 (6.27%)	
occurrences (all)	11	28	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 February 2016	Various sections of the protocol was amended (namely Inclusion/Exclusion criteria etc) in response to Health Authority requests and in order to make changes for consistency and/or clarification.
05 May 2016	The following sections of the study protocol were updated in response to Health Authority requests, and in order to make changes for consistency and/or clarification: - Section 8.8.1, Prohibited Medications and Therapies - Section 9.2.4.3, Dose Modification in Response to Hematologic Toxicities - Section 9.5, Study Drug Accountability - Section 12.1.1, Adverse Events

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported