Clinical trial results:
An International, Multicenter, Open-label, Randomized, Phase 3 Study of BLU-285 vs Regorafenib in subjects with Locally Advanced Unresectable or Metastatic Gastrointestinal Stromal Tumor (GIST)

Summary

EudraCT number	2017-003497-14
Trial protocol	GB FR SE HU DE NL AT ES BE CZ IT
Global end of trial date	15 September 2021

Results information

Result version number	v1 (current)
This version publication date	11 May 2022
First version publication date	11 May 2022

Trial information

Trial identification

Sponsor protocol code	BLU-285-1303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03465722
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Blueprint Medicines Corporation
Sponsor organisation address	45 Sidney Street, Cambridge, United States, MA 02139
Public contact	Project Director, Global Oncology, INC Research, +44 7717348365, shaun.bedford@syneoshealth.com
Scientific contact	Project Director, Global Oncology, INC Research, +44 7717348365, shaun.bedford@syneoshealth.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	15 September 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 September 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to demonstrate the efficacy of avapritinib based on progression-free survival (PFS) determined by central radiological assessment per (Modified) Response Evaluation Criteria in Solid Tumors (mRECIST), version 1.1 in subjects with advanced Gastrointestinal stromal tumor (GIST) following 2 or 3 regimens of prior treatment, including imatinib, compared to subjects treated with regorafenib.

Protection of trial subjects:

This trial was designed and monitored in accordance with 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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 March 2018
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	Singapore: 4
Country: Number of subjects enrolled	United States: 133
Country: Number of subjects enrolled	Netherlands: 8
Country: Number of subjects enrolled	Poland: 19
Country: Number of subjects enrolled	Spain: 25
Country: Number of subjects enrolled	Sweden: 13
Country: Number of subjects enrolled	United Kingdom: 24
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Czechia: 4
Country: Number of subjects enrolled	France: 42
Country: Number of subjects enrolled	Germany: 35
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Italy: 28
Country: Number of subjects enrolled	China: 74
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Korea, Republic of: 43
Country: Number of subjects enrolled	Australia: 10

Worldwide total number of subjects	476
EEA total number of subjects	180

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)	287
From 65 to 84 years	186
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Overall, 569 subjects were screened, of them, 476 subjects were randomized and enrolled in the study.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Avapritinib : 300 mg PO QD

Arm description:

Subjects received avapritinib 300 milligrams (mg) orally (PO) once daily (QD), continuously in 28-day cycles.

Arm type	Experimental
Investigational medicinal product name	Avapritinib
Investigational medicinal product code	BLU-285
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received avapritinib 300 milligrams (mg) orally (PO) once daily (QD), continuously in 28-day cycles.

Arm title	Regorafinib: 160 mg PO QD

Arm description:

Subjects received regorafenib 160 mg PO QD, for 3 weeks out of every 4 weeks (ie. 3 weeks on/1 week off) in 28-day cycles.

Arm type	Active comparator
Investigational medicinal product name	Regorafinib 160mg PO QD
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received regorafenib 160 mg PO QD, for 3 weeks out of every 4 weeks (ie. 3 weeks on/1 week off) in 28-day cycles.

Number of subjects in period 1	Avapritinib : 300 mg PO QD	Regorafinib: 160 mg PO QD
Started	240	236
Completed	0	0
Not completed	240	236
Consent withdrawn by subject	21	14
Administrative	33	32
Death	89	87
Lost to follow-up	5	3
Sponsor decision	91	98
Not treated	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Avapritinib : 300 mg PO QD
Reporting group description:	
Subjects received avapritinib 300 milligrams (mg) orally (PO) once daily (QD), continuously in 28-day cycles.	
Reporting group title	Regorafinib: 160 mg PO QD
Reporting group description:	
Subjects received regorafenib 160 mg PO QD, for 3 weeks out of every 4 weeks (ie. 3 weeks on/1 week off) in 28-day cycles.	

Reporting group values	Avapritinib : 300 mg PO QD	Regorafinib: 160 mg PO QD	Total
Number of subjects	240	236	476
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	61.1	61.0	
standard deviation	± 10.96	± 10.74	-
Gender categorical			
Units: Subjects			
Female	78	80	158
Male	162	156	318
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	64	64	128
Native Hawaiian or Other Pacific Islander	1	1	2
Black or African American	9	5	14
White	139	143	282
More than one race	0	0	0
Unknown or Not Reported	27	23	50
Body Mass Index (BMI)			
Both height and weight measurements are needed for body mass index calculation. Some subjects had missing height and/or weight measurements. Only subjects with both a height and a weight measurement are included in the body mass index calculation.			
Units: Kilogram per meter square			
arithmetic mean	25.50	24.69	
standard deviation	± 5.563	± 5.163	-

End points

End points reporting groups

Reporting group title	Avapritinib : 300 mg PO QD
Reporting group description:	
Subjects received avapritinib 300 milligrams (mg) orally (PO) once daily (QD), continuously in 28-day cycles.	
Reporting group title	Regorafinib: 160 mg PO QD
Reporting group description:	
Subjects received regorafenib 160 mg PO QD, for 3 weeks out of every 4 weeks (ie. 3 weeks on/1 week off) in 28-day cycles.	

Primary: Efficacy of Avapritinib Based on Progression-free Survival (PFS) Determined by Central Radiological Assessment Per Modified Response Evaluation Criteria in Solid Tumors (mRECIST), Version 1.1

End point title	Efficacy of Avapritinib Based on Progression-free Survival (PFS) Determined by Central Radiological Assessment Per Modified Response Evaluation Criteria in Solid Tumors (mRECIST), Version 1.1

End point description:

To demonstrate the efficacy of avapritinib based on progression-free survival (PFS) determined by central radiological assessment per modified Response Evaluation Criteria in Solid Tumors (mRECIST), version 1.1 in subjects with advanced GIST following 2 or 3 regimens of prior treatment with a tyrosine kinase inhibitor (TKI), including imatinib, compared to subjects treated with regorafenib. A progressively growing tumor must meet the following criteria: a) the target lesions must be greater or equal to 2cm in size and be a new GIST active lesion or b) the target lesions must be expanding on at least 2 sequential imaging studies. Intent-to-treat population that included all subject randomized to study.

End point type	Primary
End point timeframe:	
24 Months	

End point values	Avapritinib : 300 mg PO QD	Regorafinib: 160 mg PO QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240	236		
Units: Months				
median (confidence interval 95%)	4.2 (3.7 to 5.6)	5.6 (3.8 to 7.2)		

Statistical analyses

Statistical analysis title	stratified log-rank test

Statistical analysis description:

A stratified log-rank test was performed to compare the progression free survival of avapritinib versus regorafenib. The nominal 2-sided p-value was 0.055, indicating there was no significant difference between the two treatments in extending patients' progression free survival.

Comparison groups	Avapritinib : 300 mg PO QD v Regorafinib: 160 mg PO QD

Number of subjects included in analysis	476
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.055
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.247
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.992
upper limit	1.5666

Secondary: Objective Response Rate (ORR) Determined by Central Radiology Assessment Per mRECIST, Version 1.1

End point title	Objective Response Rate (ORR) Determined by Central Radiology Assessment Per mRECIST, Version 1.1

End point description:

To evaluate objective response rate (ORR) determined by central radiology assessment per mRECIST, version 1.1 in subjects with advanced GIST treated with avapritinib compared to subjects treated with regorafenib. A complete response (CR) per modified Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1) is defined as complete disappearance of all target lesions. A partial response (PR) is defined as at least 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum of diameters. Overall Response (OR) = CR + PR. Intent-to-treat population that included all subject randomized to study.

End point type	Secondary

End point timeframe:

24 Months

End point values	Avapritinib : 300 mg PO QD	Regorafinib: 160 mg PO QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240	236		
Units: Subjects				
Responder	41	17		
Non-Responder	199	219		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) in Subjects With Advanced GIST Treated With Avapritinib Compared to subjects Treated With Regorafenib

End point title	Overall Survival (OS) in Subjects With Advanced GIST Treated With Avapritinib Compared to subjects Treated With Regorafenib

End point description:

To evaluate overall survival (OS) in subjects with advanced GIST treated with avapritinib compared to subjects treated with regorafenib.
Here, "99999" indicates upper bound of the confidence interval is not estimable by the Kaplan-Meier analysis due to the short follow-up time. Intent-to-treat population that included all subject randomized to study. Since the primary endpoint of statiscally significant in PFS was not met subjects are not being followed for OS.

End point type	Secondary

End point timeframe:

24 Months

End point values	Avapritinib : 300 mg PO QD	Regorafinib: 160 mg PO QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240	236		
Units: Months				
median (confidence interval 95%)	19.2 (19.2 to 99999)	17.4 (15.8 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: European Organisation for Research and Treatment of Cancer Quality of Life (EORTC-QLQ-30). Change in Individual Scores in subjects With Advanced GIST Treated With Avapritinib Compared to subjects Treated With Regorafenib

End point title	European Organisation for Research and Treatment of Cancer Quality of Life (EORTC-QLQ-30). Change in Individual Scores in subjects With Advanced GIST Treated With Avapritinib Compared to subjects Treated With Regorafenib

End point description:

The Global Health Status Score is derived from question 29 and 30 on the EORTC-QLQ-C30 tool. The change in score was assessed between baseline and week 12 in subjects treated with advanced GIST treated with avapritinib compared to subjects treated with regorafenib. The Global Health Status Score score range is 0 to 100 with a higher score indicating better global health status. A positive change indicates improvement in global health status. Intent-to-treat population with both a baseline and a week 12 measurements.

End point type	Secondary

End point timeframe:

Difference between baseline and week 12 of treatment

End point values	Avapritinib : 300 mg PO QD	Regorafinib: 160 mg PO QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123[1]	138[2]		
Units: scores on a scale				
median (standard deviation)	-5.7 (± 24.29)	-4.4 (± 20.74)		

Notes:
[1] - “Subject Analysed” signifies those subjects who were evaluable at specified time points.
[2] - “Subject Analysed” signifies those subjects who were evaluable at specified time points.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the date of first study drug administration to 30 days after last study drug administration, approximately 6 months

Adverse event reporting additional description:

The total number of at risk subjects includes subjects that were randomized to treatment and received at least one dose of treatment. Subjects that were randomized by did not receive treatment were excluded from the safety analysis.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Avapritinib: 300 mg PO QD

Reporting group description:

Avapritinib: Avapritinib tablets for oral administration. Avapritinib will be dosed at 300 mg once daily, continuously.

Reporting group title	Regorafinib: 160 mg PO QD

Reporting group description:

Regorafenib tablets for oral administration. Regorafenib will be dosed at 160 mg once daily for 3 weeks out of every 4 weeks (ie. 3 weeks on/1 week off).

Serious adverse events	Avapritinib: 300 mg PO QD	Regorafinib: 160 mg PO QD	
Total subjects affected by serious adverse events			
subjects affected / exposed	106 / 239 (44.35%)	91 / 234 (38.89%)	
number of deaths (all causes)	14	13	
number of deaths resulting from adverse events	13	13	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	3 / 239 (1.26%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Adenocarcinoma of colon			

subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant ascites			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	1 / 239 (0.42%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Metastases to liver			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour necrosis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stromal tumour			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 1	
Liver carcinoma ruptured			

subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour fistulisation			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	0 / 239 (0.00%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal sarcoma			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour compression			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 239 (0.00%)	3 / 234 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 239 (0.42%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
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			

Disease progression			
subjects affected / exposed	3 / 239 (1.26%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 2	
Face oedema			
subjects affected / exposed	2 / 239 (0.84%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	2 / 239 (0.84%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	3 / 239 (1.26%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Pyrexia			
subjects affected / exposed	4 / 239 (1.67%)	7 / 234 (2.99%)	
occurrences causally related to treatment / all	1 / 4	4 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 239 (0.42%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	2 / 239 (0.84%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	3 / 239 (1.26%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hernia perforation			

subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammation			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 239 (0.00%)	3 / 234 (1.28%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Condition aggravated			
subjects affected / exposed	1 / 239 (0.42%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malaise			
subjects affected / exposed	0 / 239 (0.00%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			

subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (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			
Uterine haemorrhage			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
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			
Dyspnoea			
subjects affected / exposed	3 / 239 (1.26%)	5 / 234 (2.14%)	
occurrences causally related to treatment / all	0 / 3	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	3 / 239 (1.26%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	2 / 239 (0.84%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory distress			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 239 (0.42%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchitis chronic			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
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	0 / 239 (0.00%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 239 (0.00%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Insomnia			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			

subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Amylase increased			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	1 / 239 (0.42%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Spinal fracture			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental overdose			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Anastomotic stenosis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	2 / 239 (0.84%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			

subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	3 / 239 (1.26%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	2 / 239 (0.84%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 239 (0.84%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	1 / 239 (0.42%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Facial paresis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIIth nerve paralysis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic uraemic syndrome			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	27 / 239 (11.30%)	7 / 234 (2.99%)	
occurrences causally related to treatment / all	15 / 27	3 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			

subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal vein occlusion			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	5 / 239 (2.09%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	6 / 239 (2.51%)	5 / 234 (2.14%)	
occurrences causally related to treatment / all	3 / 6	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	5 / 239 (2.09%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	1 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	4 / 239 (1.67%)	5 / 234 (2.14%)	
occurrences causally related to treatment / all	0 / 4	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	4 / 239 (1.67%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
subjects affected / exposed	2 / 239 (0.84%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haemorrhage			

subjects affected / exposed	3 / 239 (1.26%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	13 / 239 (5.44%)	11 / 234 (4.70%)	
occurrences causally related to treatment / all	1 / 13	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	2 / 239 (0.84%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 239 (0.84%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	2 / 239 (0.84%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 239 (0.42%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			

subjects affected / exposed	1 / 239 (0.42%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal fistula			
subjects affected / exposed	2 / 239 (0.84%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	2 / 239 (0.84%)	3 / 234 (1.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intestinal perforation			
subjects affected / exposed	2 / 239 (0.84%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			

subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal toxicity			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia strangulated			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal haemorrhage			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 239 (0.00%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 1	
Small intestine ulcer			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			

subjects affected / exposed	2 / 239 (0.84%)	3 / 234 (1.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric mucosal lesion			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic haemorrhage			
subjects affected / exposed	3 / 239 (1.26%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	2 / 239 (0.84%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal hypertension			
subjects affected / exposed	2 / 239 (0.84%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (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 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			

subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatic pain			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Purpura			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash morbilliform			

subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin toxicity			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 239 (1.67%)	4 / 234 (1.71%)	
occurrences causally related to treatment / all	2 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Autoimmune nephritis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 239 (1.26%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Spinal pain			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	5 / 239 (2.09%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	2 / 239 (0.84%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 239 (0.84%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 239 (0.42%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			

subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (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	1 / 239 (0.42%)	3 / 234 (1.28%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis infectious			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			

subjects affected / exposed	2 / 239 (0.84%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	2 / 239 (0.84%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	1 / 239 (0.42%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 239 (0.42%)	0 / 234 (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 / 239 (0.42%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 239 (0.00%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypoglycaemia			
subjects affected / exposed	2 / 239 (0.84%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 2	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	Avapritinib: 300 mg PO QD	Regorafinib: 160 mg PO QD	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	218 / 239 (91.21%)	224 / 234 (95.73%)	
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	6 / 239 (2.51%)	13 / 234 (5.56%)	
occurrences (all)	6	13	
White blood cell count decreased			
subjects affected / exposed	42 / 239 (17.57%)	7 / 234 (2.99%)	
occurrences (all)	42	7	
Aspartate aminotransferase increased			
subjects affected / exposed	33 / 239 (13.81%)	33 / 234 (14.10%)	
occurrences (all)	33	33	
Weight decreased			
subjects affected / exposed	24 / 239 (10.04%)	53 / 234 (22.65%)	
occurrences (all)	24	53	
Blood creatinine increased			
subjects affected / exposed	21 / 239 (8.79%)	12 / 234 (5.13%)	
occurrences (all)	21	12	
Weight increased			
subjects affected / exposed	18 / 239 (7.53%)	4 / 234 (1.71%)	
occurrences (all)	18	4	
Alanine aminotransferase increased			
subjects affected / exposed	15 / 239 (6.28%)	29 / 234 (12.39%)	
occurrences (all)	15	29	
Nervous system disorders			
Dizziness			
subjects affected / exposed	32 / 239 (13.39%)	19 / 234 (8.12%)	
occurrences (all)	32	19	
Dysgeusia			
subjects affected / exposed	20 / 239 (8.37%)	11 / 234 (4.70%)	
occurrences (all)	20	11	
Memory impairment			

subjects affected / exposed	31 / 239 (12.97%)	5 / 234 (2.14%)	
occurrences (all)	31	5	
Headache			
subjects affected / exposed	29 / 239 (12.13%)	43 / 234 (18.38%)	
occurrences (all)	29	43	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	55 / 239 (23.01%)	13 / 234 (5.56%)	
occurrences (all)	55	13	
Mucosal inflammation			
subjects affected / exposed	3 / 239 (1.26%)	28 / 234 (11.97%)	
occurrences (all)	3	28	
Eye disorders			
Periorbital oedema			
subjects affected / exposed	68 / 239 (28.45%)	0 / 234 (0.00%)	
occurrences (all)	68	0	
Lacrimation increased			
subjects affected / exposed	45 / 239 (18.83%)	0 / 234 (0.00%)	
occurrences (all)	45	0	
Eyelid oedema			
subjects affected / exposed	35 / 239 (14.64%)	0 / 234 (0.00%)	
occurrences (all)	35	0	
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	21 / 239 (8.79%)	16 / 234 (6.84%)	
occurrences (all)	21	16	
Gastrooesophageal reflux disease			
subjects affected / exposed	16 / 239 (6.69%)	7 / 234 (2.99%)	
occurrences (all)	16	7	
Dry mouth			
subjects affected / exposed	7 / 239 (2.93%)	15 / 234 (6.41%)	
occurrences (all)	7	15	
Stomatitis			
subjects affected / exposed	7 / 239 (2.93%)	40 / 234 (17.09%)	
occurrences (all)	7	40	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	17 / 239 (7.11%)	13 / 234 (5.56%)	
occurrences (all)	17	13	
Dysphonia			
subjects affected / exposed	8 / 239 (3.35%)	71 / 234 (30.34%)	
occurrences (all)	8	71	
Skin and subcutaneous tissue disorders			
Hair colour changes			
subjects affected / exposed	33 / 239 (13.81%)	2 / 234 (0.85%)	
occurrences (all)	33	2	
Alopecia			
subjects affected / exposed	24 / 239 (10.04%)	38 / 234 (16.24%)	
occurrences (all)	24	38	
Dry skin			
subjects affected / exposed	10 / 239 (4.18%)	18 / 234 (7.69%)	
occurrences (all)	10	18	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	4 / 239 (1.67%)	143 / 234 (61.11%)	
occurrences (all)	4	143	
Rash maculo-papular			
subjects affected / exposed	7 / 239 (2.93%)	14 / 234 (5.98%)	
occurrences (all)	7	14	
Pruritus			
subjects affected / exposed	11 / 239 (4.60%)	15 / 234 (6.41%)	
occurrences (all)	11	15	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	12 / 239 (5.02%)	3 / 234 (1.28%)	
occurrences (all)	12	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 239 (3.77%)	16 / 234 (6.84%)	
occurrences (all)	9	16	
Myalgia			
subjects affected / exposed	7 / 239 (2.93%)	22 / 234 (9.40%)	
occurrences (all)	7	22	

Muscle spasms subjects affected / exposed occurrences (all)	6 / 239 (2.51%) 6	25 / 234 (10.68%) 25	
Infections and infestations Conjunctivitis subjects affected / exposed occurrences (all)	12 / 239 (5.02%) 12	0 / 234 (0.00%) 0	
Metabolism and nutrition disorders Hypoalbuminaemia subjects affected / exposed occurrences (all)	12 / 239 (5.02%) 12	16 / 234 (6.84%) 16	
Hypocalcaemia subjects affected / exposed occurrences (all)	15 / 239 (6.28%) 15	11 / 234 (4.70%) 11	
Hypomagnesaemia subjects affected / exposed occurrences (all)	11 / 239 (4.60%) 11	12 / 234 (5.13%) 12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 January 2018	• BLU-285 was updated to the newly approved generic name, avapritinib, and the stratification of subjects by mutation status was updated from Platelet-derived growth factor receptor alpha (PDGFRA) vs V-Kit Hardy-Zuckerman 4 Feline Sarcoma Viral Oncogene Homolog (KIT) to PDGFRA D842V mutation present or absent. • Study Objectives, Study Endpoints, and related sections of the Study Summary were updated and reorganized in response to feedback from the FDA. • Study Conduct, related sections of the Study Summary, and all other related sections of the protocol were updated to clarify the circumstances where avapritinib doses could be escalated from 300 mg QD to 400 mg QD, to specify that a washout period was required for Subjects who switched from treatment with regorafenib to treatment with avapritinib, and to provide additional details for avapritinib dose reductions and re-escalations.
02 August 2018	• Inclusion criterion, the subjects with ECOG PS of 2 were no longer to be included. • The Subjects with arterial thrombotic or embolic events within 6 months or venous thrombotic events within 14 days before randomization were excluded. • Exclude subjects with a brain aneurysm if it had not been removed or repaired. • Exclude subjects with known hypersensitivity to avapritinib, regorafenib, or the excipients in either study drug as a precautionary measure.
20 June 2019	Key modifications made to the protocol as a part of Amendment 3, are summarized below. • The planned interim analysis was removed in order to provide more mature PFS and OS data at the time of primary analysis of efficacy. This also allowed enrollment of an adequate number of patients in Asia. • The EORTC-QLQ-C30 physical functioning, pain, role functioning, and appetite loss scores were moved from key secondary to secondary objectives and endpoints and were no longer in the hierarchy of the sequential testing scheme. • Removed from the exploratory objectives and corresponding endpoints the correlation of clinical efficacy with other cancer-relevant gene mutant allele fractions and mutant allele fractions measured in ctDNA • Removed the option of escalating the avapritinib dose to 400 mg QD based on analyses of safety showing earlier onset and higher-grade AEs at 400 mg dose versus 300 mg dose. • Added in Section, Prohibited Concomitant Therapy, that patients who experienced centrally confirmed disease progression but subsequently underwent radiation therapy or surgery may continue to receive study treatment with avapritinib, if the treating investigator considered it to be in the patient's best medical interest. • Added brain imaging assessments at Week 12 (± 1 week) and Week 24 (± 1 week), and instructions to repeat as clinically indicated, ie, for unexpected neurologic AEs, in response to feedback from regulatory authorities. • Updated language used for AE and SAE definitions, recording, and reporting. • Removed the requirement that patients underwent at least 1 postbaseline tumor assessment by independent radiology reviewers to be included in the per-protocol population.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported