Clinical trial results:
A Phase III Randomized, Double-Blind, Placebo-Controlled Clinical Trial of BBI608 plus Weekly Paclitaxel vs. Placebo plus Weekly Paclitaxel in Adult Patients with Advanced, Previously Treated Gastric and Gastro-Esophageal Junction Adenocarcinoma

Summary

EudraCT number	2014-000774-18
Trial protocol	ES LT HU DE PL GB IT BE CZ EE BG
Global end of trial date	20 September 2017

Results information

Result version number	v1 (current)
This version publication date	12 October 2019
First version publication date	12 October 2019

Trial information

Trial identification

Sponsor protocol code	BBI608-336

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02178956
WHO universal trial number (UTN)	U1111-1161-0304

Notes:

Sponsors

Sponsor organisation name	Boston Biomedical, Inc.
Sponsor organisation address	640 Memorial Drive, Cambridge, United States, MA 02139
Public contact	Clinical Trials Office, Boston Biomedical, Inc., +1 6176746800, 608-336@bostonbiomedical.com
Scientific contact	Clinical Trials Office, Boston Biomedical, Inc., +1 6176746800, 608-336@bostonbiomedical.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	21 August 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 September 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare overall survival (OS) of subjects with pre-treated, advanced gastric and gastro-esophageal junction (GEJ) adenocarcinoma treated with Napabucasin (BBI608) plus weekly paclitaxel versus placebo plus weekly paclitaxel. OS is defined as the time from randomization until death from any cause.

Protection of trial subjects:

This study was designed, monitored, and executed in accordance with the applicable standard operating procedures (SOPs), 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. Informed consent was obtained from each patient (or patient's legally authorized representative) before the patient was admitted to the study. At each study center, the protocol and informed consent form (ICF) for this study were reviewed and approved by a duly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC) before patients were screened for entry.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 September 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	36 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 29
Country: Number of subjects enrolled	Romania: 17
Country: Number of subjects enrolled	Spain: 56
Country: Number of subjects enrolled	United Kingdom: 43
Country: Number of subjects enrolled	Belgium: 32
Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	Czech Republic: 5
Country: Number of subjects enrolled	Estonia: 8
Country: Number of subjects enrolled	France: 29
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Hungary: 29
Country: Number of subjects enrolled	Italy: 25
Country: Number of subjects enrolled	Lithuania: 26
Country: Number of subjects enrolled	Australia: 49

Country: Number of subjects enrolled	Brazil: 34
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	Israel: 8
Country: Number of subjects enrolled	Japan: 74
Country: Number of subjects enrolled	Russian Federation: 53
Country: Number of subjects enrolled	Korea, Republic of: 32
Country: Number of subjects enrolled	United States: 43
Country: Number of subjects enrolled	China: 93
Worldwide total number of subjects	714
EEA total number of subjects	315

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)	440
From 65 to 84 years	271
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 264 investigational sites across 22 countries.

Pre-assignment

Screening details:

In this study, 714 subjects with Gastric and GEJ Adenocarcinoma were randomized across the 2 treatment groups Napabucasin (BBI608) plus weekly paclitaxel or placebo plus weekly paclitaxel. All subjects underwent inclusion exclusion criteria assessment and all eligible participants signed the informed consent.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Napabucasin plus Paclitaxel

Arm description:

Randomized subjects in this study received Napabucasin orally, at 480 mg two times daily (960 mg total daily dose). In each cycle (28 days), Napabucasin was taken daily continuously for 4 weeks. Napabucasin was administered twice daily, one hour prior or two hours after meals, with the first dose taken in the morning and doses separated by approximately 12 hours.

Arm type	Experimental
Investigational medicinal product name	Napabucasin
Investigational medicinal product code	
Other name	BBI608
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects in this study received Napabucasin orally, at 480 mg two times daily (960 mg total daily dose). In each cycle (28 days), Napabucasin was taken daily continuously for 4 weeks . Napabucasin was administered twice daily, one hour prior or two hours after meals, with the first dose taken in the morning and doses separated by approximately 12 hours.

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects in this study received Paclitaxel 80 mg/m2 intravenous (IV) administered weekly, on Day 1, 8, and 15 of each 28 day study cycle.

Arm title	Placebo plus Paclitaxel

Arm description:

Randomized subjects received placebo orally, two times daily and Paclitaxel 80 mg/m2 IV, once weekly on Day 1, 8, and 15 of each 28 day study cycle. Placebo was taken daily continuously for 4 weeks.

Arm type	Active comparator

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received matched placebo. Placebo was administered twice daily, approximately one hour prior or two hours after meals, with the first dose taken in the morning and the second dose given approximately 12 hours later.

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Participants in this study received Paclitaxel 80 mg/m2 IV administered weekly, on day 1, 8, and 15 of each 28 day study cycle.

Number of subjects in period 1	Napabucasin plus Paclitaxel	Placebo plus Paclitaxel
Started	357	357
Completed	357	357

Baseline characteristics

Reporting groups	
Reporting group title	Napabucasin plus Paclitaxel
Reporting group description:	
Randomized subjects in this study received Napabucasin orally, at 480 mg two times daily (960 mg total daily dose). In each cycle (28 days), Napabucasin was taken daily continuously for 4 weeks. Napabucasin was administered twice daily, one hour prior or two hours after meals, with the first dose taken in the morning and doses separated by approximately 12 hours.	
Reporting group title	Placebo plus Paclitaxel
Reporting group description:	
Randomized subjects received placebo orally, two times daily and Paclitaxel 80 mg/m2 IV, once weekly on Day 1, 8, and 15 of each 28 day study cycle. Placebo was taken daily continuously for 4 weeks.	

Reporting group values	Napabucasin plus Paclitaxel	Placebo plus Paclitaxel	Total
Number of subjects	357	357	714
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	60.79	59.89	
standard deviation	± 11.513	± 11.123	-
Gender categorical Units: Subjects			
Female	96	103	199
Male	261	254	515
Race Units: Subjects			
White or Caucasian	237	240	477
Black or African American	2	3	5
Asian	107	102	209
American Indian	0	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
Other	9	9	18
Missing	2	2	4
ECOG Performance Status Grade Units: Subjects			
Grade 0	128	134	262
Grade 1	229	222	451
Grade 2	0	0	0
Grade 3	0	0	0
Grade 4	0	0	0
Missing	0	1	1
Location of Primary Tumor Units: Subjects			
Gastric Adenocarcinoma	258	275	533
Gastro-esophageal junction (GEJ)	99	82	181
Pathological Diagnosis			

Units: Subjects			
HER2 Positive	66	53	119
HER2 Negative	200	199	399
HER2 Unknown	91	105	196
Stage at Screening Units: Subjects			
Stage IV (metastatic)	339	342	681
Locally Advanced and unresectable	18	15	33
Disease Measurability Units: Subjects			
Yes	289	283	572
No	68	74	142
Weight Units: kilogram(s)			
arithmetic mean	66.8	67.2	
standard deviation	± 16.36	± 17.05	-
Height Units: Centimeter			
arithmetic mean	168.8	168.1	
standard deviation	± 9.21	± 9.17	-
BMI Units: kilogram(s)/square meter			
arithmetic mean	23.3	23.6	
standard deviation	± 4.48	± 4.71	-

End points

End points reporting groups

Reporting group title	Napabucasin plus Paclitaxel
Reporting group description:	
Randomized subjects in this study received Napabucasin orally, at 480 mg two times daily (960 mg total daily dose). In each cycle (28 days), Napabucasin was taken daily continuously for 4 weeks. Napabucasin was administered twice daily, one hour prior or two hours after meals, with the first dose taken in the morning and doses separated by approximately 12 hours.	
Reporting group title	Placebo plus Paclitaxel
Reporting group description:	
Randomized subjects received placebo orally, two times daily and Paclitaxel 80 mg/m2 IV, once weekly on Day 1, 8, and 15 of each 28 day study cycle. Placebo was taken daily continuously for 4 weeks.	

Primary: Overall Survival (OS)- Time to event

End point title	Overall Survival (OS)- Time to event
End point description:	
Overall Survival (OS), defined as the time from randomization until death from any cause, in subjects with pre-treated advanced gastric/GEJ adenocarcinoma treated with Napabucasin plus weekly paclitaxel versus placebo plus weekly paclitaxel.	
End point type	Primary
End point timeframe:	
From randomization until death from any cause	

End point values	Napabucasin plus Paclitaxel	Placebo plus Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	357	357		
Units: Months				
median (confidence interval 95%)				
50% (Median)	6.93 (6.28 to 7.69)	7.36 (6.64 to 8.15)		

Statistical analyses

Statistical analysis title	Overall Survival
Comparison groups	Napabucasin plus Paclitaxel v Placebo plus Paclitaxel
Number of subjects included in analysis	714
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8596
Method	Log-Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.01

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.2

Secondary: Overall survival in the predefined biomarker-positive population

End point title	Overall survival in the predefined biomarker-positive population

End point description:

To compare OS in the biomarker-positive population [those subjects with pSTAT3 positivity on immunohistochemical (IHC) staining of Formalin Fixed Paraffin Embedded (FFPE) archival tissue] with pre-treated advanced gastric/GEJ adenocarcinoma treated with Napabucasin plus weekly paclitaxel versus placebo plus weekly paclitaxel.

End point type	Secondary

End point timeframe:

From randomization until death from any cause (maximum up to 36 months)

End point values	Napabucasin plus Paclitaxel	Placebo plus Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	126		
Units: Months				
median (confidence interval 95%)				
50% (Median)	7.39 (6.08 to 8.11)	7.13 (5.55 to 8.80)		

Statistical analyses

Statistical analysis title	OS in the biomarker-positive population
Comparison groups	Napabucasin plus Paclitaxel v Placebo plus Paclitaxel
Number of subjects included in analysis	260
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5689
Method	Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.21

Secondary: Progression-Free Survival (PFS) - Time to Event

End point title	Progression-Free Survival (PFS) - Time to Event

End point description:

Progression-Free Survival (PFS), defined as the time from randomization until the first objective observation of disease progression or death from any cause, in subjects with pre-treated advanced gastric/GEJ adenocarcinoma treated with Napabucasin plus weekly paclitaxel versus placebo plus weekly paclitaxel.

End point type	Secondary

End point timeframe:

From randomization until the first objective observation of disease progression or death from any cause (maximum up to 36 months)

End point values	Napabucasin plus Paclitaxel	Placebo plus Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	357	357		
Units: months				
median (confidence interval 95%)				
50% (Median)	3.55 (3.22 to 3.68)	3.65 (3.45 to 3.71)		

Statistical analyses

Statistical analysis title	Analysis of Progression-Free Survival
Comparison groups	Napabucasin plus Paclitaxel v Placebo plus Paclitaxel
Number of subjects included in analysis	714
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9679
Method	Log rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.17

Secondary: PFS in the biomarker-positive population of subjects- Percentage of subjects with event

End point title	PFS in the biomarker-positive population of subjects- Percentage of subjects with event

End point description:

To compare PFS in the biomarker-positive population of patients [those subjects with pSTAT3 positivity on immunohistochemical (IHC) staining of Formalin Fixed Paraffin-Embedded (FFPE) archival tissue] with pre-treated advanced gastric/GEJ adenocarcinoma treated with Napabucasin plus weekly paclitaxel versus placebo plus weekly paclitaxel.

End point type	Secondary

End point timeframe:

From randomization until the first objective observation of disease progression or death from any cause.

End point values	Napabucasin plus Paclitaxel	Placebo plus Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	126		
Units: percentage of subjects				
number (not applicable)				
Disease Progression	72.4	73.8		
Death Without Disease Progression	11.2	17.5		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS in the biomarker-positive population of subjects- Time to event

End point title	PFS in the biomarker-positive population of subjects- Time to event

End point description:

To compare PFS in the biomarker-positive population of patients [those subjects with pSTAT3 positivity on immunohistochemical (IHC) staining of Formalin Fixed Paraffin-Embedded (FFPE) archival tissue] with pre-treated advanced gastric/GEJ adenocarcinoma treated with Napabucasin plus weekly paclitaxel versus placebo plus weekly paclitaxel.

End point type	Secondary

End point timeframe:

From randomization until the first objective observation of disease progression or death from any cause.

End point values	Napabucasin plus Paclitaxel	Placebo plus Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	126		
Units: Months				
median (confidence interval 95%)				
50% (Median)	3.55 (2.86 to 3.68)	3.35 (2.07 to 3.68)		

Statistical analyses

Statistical analysis title	PFS in the biomarker-positive population
Comparison groups	Napabucasin plus Paclitaxel v Placebo plus Paclitaxel

Number of subjects included in analysis	260
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8018
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.25

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

Objective Response Rate (ORR), defined as the proportion of subjects with a documented complete response or partial response (CR + PR) based on RECIST 1.1 criteria, in subjects with pre-treated advanced gastric/GEJ adenocarcinoma treated with Napabucasin plus weekly paclitaxel versus placebo plus weekly paclitaxel. Subjects with measurable disease by RECIST 1.1 at randomization were included in the analysis of ORR.

End point type	Secondary

End point timeframe:

From randomization until disease progression or the end of study (maximum up to 36 months)

End point values	Napabucasin plus Paclitaxel	Placebo plus Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289[1]	283[2]		
Units: proportion of subjects				
number (confidence interval 95%)	0.16 (0.12 to 0.21)	0.18 (0.14 to 0.23)		

Notes:

[1] - Number of Subjects with Measurable Disease

[2] - Number of Subjects with Measurable Disease

Statistical analyses

Statistical analysis title	Difference in ORR

Statistical analysis description:

BBI608 + Paclitaxel

Comparison groups	Napabucasin plus Paclitaxel v Placebo plus Paclitaxel

Number of subjects included in analysis	572
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7358
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.04

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)

End point description:

To compare the Disease Control Rate (DCR), defined as the proportion of subjects with a documented complete response, partial response and stable disease (CR + PR + SD) based on RECIST 1.1 criteria, in subjects with pre-treated advanced gastric/GEJ adenocarcinoma treated with Napabucasin plus weekly paclitaxel versus placebo plus weekly paclitaxel.

End point type	Secondary

End point timeframe:

From randomization until disease progression or the end of study (maximum up to 36 months)

End point values	Napabucasin plus Paclitaxel	Placebo plus Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289[3]	283[4]		
Units: Proportion of subjects				
number (confidence interval 95%)	0.55 (0.49 to 0.61)	0.58 (0.52 to 0.64)		

Notes:

[3] - Number of Subjects with Measurable Disease

[4] - Number of Subjects with Measurable Disease

Statistical analyses

Statistical analysis title	Difference in DCR

Statistical analysis description:

BBI608 + Paclitaxel

Comparison groups	Napabucasin plus Paclitaxel v Placebo plus Paclitaxel
Number of subjects included in analysis	572
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6555
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.03

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	0.05

Secondary: Number of subjects with adverse events

End point title	Number of subjects with adverse events

End point description:

To evaluate the safety profile of Napabucasin administered daily plus weekly paclitaxel in subjects with pre-treated advanced gastric/GEJ adenocarcinoma, with safety assessed according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE version 4.0). TEAE: Treatment emergent adverse event.

End point type	Secondary

End point timeframe:

SAEs were collected from time of consent to randomization for all consented subjects. For randomized patients, AEs (including SAEs) were collected from time of consent until 30 days after last dose.

End point values	Napabucasin plus Paclitaxel	Placebo plus Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	357	350		
Units: Subjects				
Subjects with at least one TEAE	352	338		
Subjects with TEAE related to Paclitaxel	292	293		
Subjects with TEAE related to Napabucasin/Placebo	322	224		
Subjects with TEAR related to study drug	339	305		
Subjects with serious TEAE	125	101		
Subjects with TEAE resulting in death	17	14		
TEAE leading to dose modification-Paclitaxel	216	192		
TEAE leadingtodosemodification-Napabucasin/placebo	255	132		
TEAE leading to dose modification-study drugs	292	211		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From consent to 30 days after last dose of protocol therapy for randomized patients

Adverse event reporting additional description:

An AE was the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. Data reported are TEAEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Napabucasin plus Paclitaxel

Reporting group description:

Participants received Napabucasin 480 mg orally twice daily plus Paclitaxel 80mg/m intravenously for once weekly

Reporting group title	Placebo plus Paclitaxel

Reporting group description:

Randomized participants received placebo Orally, two times daily and Paclitaxel 80 mg/m2 IV, once weekly on day 1, 8, and 15 of each 28 day study cycle.

Serious adverse events	Napabucasin plus Paclitaxel	Placebo plus Paclitaxel	
Total subjects affected by serious adverse events			
subjects affected / exposed	125 / 357 (35.01%)	101 / 350 (28.86%)	
number of deaths (all causes)	17	13	
number of deaths resulting from adverse events	2	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric cancer			
subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			
subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			

subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Embolism			
subjects affected / exposed	2 / 357 (0.56%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 357 (0.56%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Circulatory collapse			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemorrhage			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			

subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	6 / 357 (1.68%)	6 / 350 (1.71%)	
occurrences causally related to treatment / all	2 / 7	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	4 / 357 (1.12%)	3 / 350 (0.86%)	
occurrences causally related to treatment / all	2 / 4	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	5 / 357 (1.40%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	4 / 6	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General physical health deterioration			
subjects affected / exposed	3 / 357 (0.84%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	1 / 2	0 / 1	
Death			
subjects affected / exposed	0 / 357 (0.00%)	3 / 350 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Adverse event			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyperthermia			
subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stent malfunction			

subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
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 / 357 (0.84%)	7 / 350 (2.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 3	
Pneumonitis			
subjects affected / exposed	0 / 357 (0.00%)	3 / 350 (0.86%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 357 (0.28%)	2 / 350 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia aspiration			
subjects affected / exposed	1 / 357 (0.28%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal obstruction			
subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 357 (0.00%)	2 / 350 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	2 / 357 (0.56%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

White blood cell count decreased			
subjects affected / exposed	1 / 357 (0.28%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood urea increased			
subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			

subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	4 / 357 (1.12%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	1 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Myocardial infarction			
subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Palpitations			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	3 / 357 (0.84%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Brain oedema			
subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	6 / 357 (1.68%)	5 / 350 (1.43%)	
occurrences causally related to treatment / all	3 / 8	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 357 (0.28%)	2 / 350 (0.57%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	2 / 357 (0.56%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Agranulocytosis			
subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microangiopathic haemolytic anaemia			
subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neutropenia			
subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
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	14 / 357 (3.92%)	2 / 350 (0.57%)	
occurrences causally related to treatment / all	6 / 15	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	8 / 357 (2.24%)	5 / 350 (1.43%)	
occurrences causally related to treatment / all	2 / 9	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diarrhoea			
subjects affected / exposed	10 / 357 (2.80%)	3 / 350 (0.86%)	
occurrences causally related to treatment / all	13 / 14	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	3 / 357 (0.84%)	5 / 350 (1.43%)	
occurrences causally related to treatment / all	0 / 3	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	5 / 357 (1.40%)	3 / 350 (0.86%)	
occurrences causally related to treatment / all	1 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastric haemorrhage			
subjects affected / exposed	4 / 357 (1.12%)	3 / 350 (0.86%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 0	
Ascites			
subjects affected / exposed	3 / 357 (0.84%)	3 / 350 (0.86%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nausea			
subjects affected / exposed	6 / 357 (1.68%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	4 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	2 / 357 (0.56%)	4 / 350 (1.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abdominal pain upper			
subjects affected / exposed	4 / 357 (1.12%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			

subjects affected / exposed	2 / 357 (0.56%)	3 / 350 (0.86%)	
occurrences causally related to treatment / all	1 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	3 / 357 (0.84%)	2 / 350 (0.57%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haematemesis			
subjects affected / exposed	1 / 357 (0.28%)	3 / 350 (0.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
subjects affected / exposed	2 / 357 (0.56%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 357 (0.56%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	2 / 357 (0.56%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric stenosis			
subjects affected / exposed	1 / 357 (0.28%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	2 / 357 (0.56%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			

subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal obstruction			
subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haemorrhage			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jejunal stenosis			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			

subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ileus			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal haemorrhage			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oesophageal obstruction			
subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (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 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	1 / 357 (0.28%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	1 / 357 (0.28%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cholecystitis acute			

subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypertransaminasaemia			
subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	3 / 357 (0.84%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 357 (0.28%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal injury			
subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (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	2 / 357 (0.56%)	3 / 350 (0.86%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	5 / 357 (1.40%)	4 / 350 (1.14%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	4 / 357 (1.12%)	3 / 350 (0.86%)	
occurrences causally related to treatment / all	2 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 357 (0.84%)	2 / 350 (0.57%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			

subjects affected / exposed	2 / 357 (0.56%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	3 / 357 (0.84%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 357 (0.56%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			
subjects affected / exposed	2 / 357 (0.56%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	1 / 357 (0.28%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 357 (0.00%)	2 / 350 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 357 (0.00%)	2 / 350 (0.57%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			

subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyonephrosis			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	5 / 357 (1.40%)	2 / 350 (0.57%)	
occurrences causally related to treatment / all	6 / 6	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	5 / 357 (1.40%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	2 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 357 (0.56%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 357 (0.00%)	2 / 350 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid retention			
subjects affected / exposed	1 / 357 (0.28%)	0 / 350 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 357 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Napabucasin plus Paclitaxel	Placebo plus Paclitaxel	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	349 / 357 (97.76%)	336 / 350 (96.00%)	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	48 / 357 (13.45%)	53 / 350 (15.14%)	
occurrences (all)	113	118	
White blood cell count decreased			

subjects affected / exposed	35 / 357 (9.80%)	43 / 350 (12.29%)	
occurrences (all)	122	123	
Weight decreased			
subjects affected / exposed	41 / 357 (11.48%)	23 / 350 (6.57%)	
occurrences (all)	50	33	
Blood alkaline phosphatase increased			
subjects affected / exposed	22 / 357 (6.16%)	10 / 350 (2.86%)	
occurrences (all)	33	15	
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	46 / 357 (12.89%)	38 / 350 (10.86%)	
occurrences (all)	70	52	
Peripheral sensory neuropathy			
subjects affected / exposed	37 / 357 (10.36%)	47 / 350 (13.43%)	
occurrences (all)	59	72	
Dysgeusia			
subjects affected / exposed	27 / 357 (7.56%)	15 / 350 (4.29%)	
occurrences (all)	33	15	
Paraesthesia			
subjects affected / exposed	17 / 357 (4.76%)	22 / 350 (6.29%)	
occurrences (all)	24	38	
Dizziness			
subjects affected / exposed	19 / 357 (5.32%)	19 / 350 (5.43%)	
occurrences (all)	22	21	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	109 / 357 (30.53%)	92 / 350 (26.29%)	
occurrences (all)	225	158	
Asthenia			
subjects affected / exposed	72 / 357 (20.17%)	71 / 350 (20.29%)	
occurrences (all)	173	130	
Pyrexia			
subjects affected / exposed	55 / 357 (15.41%)	38 / 350 (10.86%)	
occurrences (all)	91	51	
Oedema peripheral			

subjects affected / exposed	38 / 357 (10.64%)	31 / 350 (8.86%)	
occurrences (all)	46	40	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	123 / 357 (34.45%)	117 / 350 (33.43%)	
occurrences (all)	337	307	
Neutropenia			
subjects affected / exposed	37 / 357 (10.36%)	49 / 350 (14.00%)	
occurrences (all)	96	106	
Leukopenia			
subjects affected / exposed	22 / 357 (6.16%)	19 / 350 (5.43%)	
occurrences (all)	87	63	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	304 / 357 (85.15%)	126 / 350 (36.00%)	
occurrences (all)	858	250	
Nausea			
subjects affected / exposed	176 / 357 (49.30%)	123 / 350 (35.14%)	
occurrences (all)	356	209	
Vomiting			
subjects affected / exposed	132 / 357 (36.97%)	95 / 350 (27.14%)	
occurrences (all)	249	164	
Abdominal pain			
subjects affected / exposed	136 / 357 (38.10%)	90 / 350 (25.71%)	
occurrences (all)	252	149	
Constipation			
subjects affected / exposed	61 / 357 (17.09%)	78 / 350 (22.29%)	
occurrences (all)	79	111	
Abdominal pain upper			
subjects affected / exposed	31 / 357 (8.68%)	40 / 350 (11.43%)	
occurrences (all)	39	56	
Abdominal distension			
subjects affected / exposed	27 / 357 (7.56%)	24 / 350 (6.86%)	
occurrences (all)	40	31	
Dysphagia			

subjects affected / exposed	19 / 357 (5.32%)	21 / 350 (6.00%)	
occurrences (all)	27	32	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	35 / 357 (9.80%)	34 / 350 (9.71%)	
occurrences (all)	41	37	
Dyspnoea			
subjects affected / exposed	28 / 357 (7.84%)	32 / 350 (9.14%)	
occurrences (all)	31	36	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	73 / 357 (20.45%)	94 / 350 (26.86%)	
occurrences (all)	88	109	
Rash			
subjects affected / exposed	13 / 357 (3.64%)	18 / 350 (5.14%)	
occurrences (all)	15	24	
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	47 / 357 (13.17%)	3 / 350 (0.86%)	
occurrences (all)	49	3	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	30 / 357 (8.40%)	27 / 350 (7.71%)	
occurrences (all)	37	36	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	29 / 357 (8.12%)	31 / 350 (8.86%)	
occurrences (all)	32	41	
Arthralgia			
subjects affected / exposed	17 / 357 (4.76%)	28 / 350 (8.00%)	
occurrences (all)	30	48	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	28 / 357 (7.84%)	11 / 350 (3.14%)	
occurrences (all)	35	13	
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	128 / 357 (35.85%)	103 / 350 (29.43%)	
occurrences (all)	238	162	
Hypoalbuminaemia			
subjects affected / exposed	20 / 357 (5.60%)	18 / 350 (5.14%)	
occurrences (all)	37	27	
Hypokalaemia			
subjects affected / exposed	27 / 357 (7.56%)	9 / 350 (2.57%)	
occurrences (all)	49	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 May 2014	Amendment 1: Inclusion criteria: amendment to 2 barrier methods to satisfy the requirement of adequate measures to avoid pregnancy.
16 June 2014	Amendment 2: The allowance of prior docetaxel treatment in the first line setting was removed. The fourth stratification factor was amended to "prior taxane therapy (yes vs. no)".
30 June 2014	Amendment 3: EORTC QLQ-C30 evaluation after protocol treatment discontinuation amended to avoid patients who went off study therapy to have additional visits to obtain quality of life questionnaires. Language pertaining to tumor evaluation scanning options added to standardize the method of tumor measurement among the patients. Language pertaining to SAE reporting and paclitaxel overdose was added to clarify the details of data collection for medical monitoring and pharmacovigilance purposes. Clarification of the acceptable number of unstained slides in combination with cores of tumor tissue, if tumor blocks were not available. Language was changed to remove inclusion of patient initials from tissue samples collected during the study. The roles and responsibilities of the DSMB were clarified.
05 August 2014	Amendment 4: Inclusion criteria; changed to 6 months after the last dose of paclitaxel and 30 days after the final dose of napabucasin/placebo to satisfy the SmPC recommendations for paclitaxel use. Accordingly, adequate contraception was redefined to include 6 months and 30 days of abstinence following the final dose of paclitaxel and napabucasin/placebo, respectively. Addition of language to report pregnancies occurring up to 6 months following the last dose of paclitaxel and to clarify a definition of true abstinence. Clarification of language to allow the Investigator to have unilateral right to unblind the patient in circumstances of medical emergency requiring unblinding. Addition of the recommendation to hold the bowel regimen for a specified period of time unless absence of bowel movement was noted in the first 2 days of protocol; this was to avoid the development of diarrhoea while on study drug. For the management of napabucasin-related AEs, dose holiday was extended to 3 days, based on the phase II trial of napabucasin in combination with paclitaxel.
09 February 2015	Amendment 5: The duration of treatment was amended to avoid imbalance in paclitaxel treatment between patients treated with active agent napabucasin and patients treated with placebo. The period of required contraception was expanded to 90 days after the final dose of napabucasin/placebo for male patients in response to the French regulatory authority. It was clarified that if pregnancies occurred before 90 days after the final dose for male patients, the event was to be reported to the Sponsor. The following changes/clarifications were made, based on the SmPC: severe hepatic impairment and history of severe hypersensitivity to paclitaxel or to any of the excipients, including macrogolglycerol ricinoleate were included in the exclusion criteria; clarification that paclitaxel is a tetratogen, embryotoxic and a mutagen with mandatory contraception to 6 months following the last dose of paclitaxel; a cautionary note that male patients should seek advice on cryopreservation of sperm before paclitaxel treatment; inclusion of a cautionary note pertaining to the co-administration of paclitaxel and/or napabucasin with specific cytochrome inhibitors and inducers. Clarification that immediate unblinding without the need to prior sponsor notification was permissible in instances where emergent unblinding was necessary for patient safety, as per the UK regulatory agency. Serial blood sampling reduced based on the recommendations of the preclinical team.

01 May 2015	Amendment 6: The total sample size was increased from 680 to 700 to accommodate the 5% expected patient yearly dropout rate. The background information about Ramucirumab's approval by the Food and Drug Administration was included. It was clarified in the inclusion criteria that all 3 Siewert types of GEJ adenocarcinoma would be eligible. Treatment failure on first line therapy was expanded to include patients progressing within ≤ 6 months of last dose of therapy. Also, the criterion was further clarified. The number of slides of archival tumor sample was amended. Uncontrolled intercurrent illness definition was clarified. Prior cancer history exclusion criterion was clarified to define species of other prior malignant conditions. Instructions for protocol-defined administration of paclitaxel were specified. Management of severe hematologic AEs was amended to include the Medical Monitor. Patient compliance was clarified as measurement against drug dose prescribed by the investigator. In Appendix I, data collection following protocol treatment discontinuation was modified. The timing of blood collection was amended.
06 December 2016	Amendment 7: The statistical calculations for the interim analysis were changed to correct an error made in the previous calculation. The biomarker-positive definition was revised to specify patients with p-STAT3 positivity on IHC staining of archival tissue. Safety profile text was moved to the end of list to main consistency with secondary and exploratory objectives in rest of protocol. Information in pre-medication recommendation was updated in line with current Investigator Brochure. For sensitivity analysis of the primary endpoint, factors used in the Cox proportional hazards model were modified to prevent treatment effect bias. In the correlative study section, analysis of duration of response was removed and the complete set of stratification factors was included for consistency with data collected. The procedure for unblinding was clarified. Regarding Appendix VI, changes were made as a clarification to define specifics of other prior malignant conditions; modified was done to state that unblinding would not be allowed for informational purposes or to permit participation in other clinical trials. Additionally, the necessity of specifying a reason for unblinding in the process of the unblinding request was stipulated. This change was made to clarify the procedures for unblinding study participants.
21 July 2017	Amendment 8: The study was amended following the results of the planned interim analysis at 380 events to allow unblinding of the study and continued treatment as the discretion of the investigator. Additionally, the study is planned to terminate by 15 September 2017.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
28 July 2017	On 28 July 2017 the sponsor decided to terminate this trial prior to its anticipated ending per protocol due to lack of efficacy as determined by a planned Interim Analysis of two-thirds of the study's total planned events. The DSMB determined that the study was unlikely to reach its primary endpoint of superior overall survival for napabucasin plus paclitaxel versus paclitaxel alone. Boston Biomedical accepted the recommendation to unblind the study and continued to follow all endpoints as defined in the protocol until study termination on 20 September 2017.	-

Notes:

Limitations and caveats

None reported