Clinical trial results:
A Phase III Study of BBI-608 in combination with 5-Fluorouracil, Leucovorin, Irinotecan (FOLFIRI) in Adult Patients with Previously Treated Metastatic Colorectal Cancer (CRC)

Summary

EudraCT number	2016-001627-31
Trial protocol	DE NL BE CZ ES IT
Global end of trial date	11 June 2021

Results information

Result version number	v1 (current)
This version publication date	17 July 2022
First version publication date	17 July 2022

Trial information

Trial identification

Sponsor protocol code	CanStem303C

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02753127
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sumitomo Pharma Oncology, Inc.
Sponsor organisation address	84 Waterford Drive, Marlborough, United States, 01752
Public contact	Clinical Trial Office, Sumitomo Pharma Oncology, Inc. , +1 6176746800, CanStem303C@bostonbiomedical.com
Scientific contact	Clinical Trial Office, Sumitomo Pharma Oncology, Inc. , +1 6176746800, CanStem303C@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	19 January 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 April 2020
Global end of trial reached?	Yes
Global end of trial date	11 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

• To compare overall survival (OS) in the General Population patients treated with BBI-608 plus biweekly FOLFIRI (Arm 1) versus biweekly FOLFIRI (Arm 2)
• To compare OS in the pSTAT3-positive (pSTAT3(+)) Subpopulation patients treated with BBI-608 plus biweekly FOLFIRI (Arm 1) versus biweekly FOLFIRI (Arm 2)

Protection of trial subjects:

The study was conducted in accordance with International Conference on Harmonization-Good Clinical Practice (ICH-GCP) Guidelines, and applicable local laws and national regulations relevant to the use of new therapeutic agents in the country of conduct. Patients who could not given informed consent (i.e. mentally incompetent persons, or those physically incapacitated such as comatose persons) were not recruited to this study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 June 2016
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	Netherlands: 37
Country: Number of subjects enrolled	Spain: 136
Country: Number of subjects enrolled	Belgium: 40
Country: Number of subjects enrolled	Czechia: 37
Country: Number of subjects enrolled	France: 41
Country: Number of subjects enrolled	Germany: 26
Country: Number of subjects enrolled	Italy: 51
Country: Number of subjects enrolled	Australia: 60
Country: Number of subjects enrolled	Canada: 36
Country: Number of subjects enrolled	China: 121
Country: Number of subjects enrolled	Hong Kong: 12
Country: Number of subjects enrolled	Israel: 18
Country: Number of subjects enrolled	Japan: 126
Country: Number of subjects enrolled	Korea, Republic of: 83
Country: Number of subjects enrolled	Singapore: 17
Country: Number of subjects enrolled	United States: 412

Worldwide total number of subjects	1253
EEA total number of subjects	368

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)	796
From 65 to 84 years	456
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

1253 participants were randomized globally between October 2016 and March 2019.

Pre-assignment

Screening details:

Baseline evaluations were performed for all patients <14 days prior to randomization to determine study eligibility. A total of 1717 screenings were recorded

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	Napabucasin + FOLFIRI ± Bevacizumab

Arm description:

Napabucasin 240 mg will be administered orally, twice daily, with doses separated by approximately 12 hours (480 mg total daily dose).
Addition of bevacizumab to the FOLFIRI regimen will be permissible. FOLFIRI chemotherapy infusion will start at least 2 hours following the first daily dose of napabucasin and will be administered every 2 weeks. This regimen will be repeated on Day 1 of every 14 day cycle.

Arm type	Experimental
Investigational medicinal product name	Napabucasin
Investigational medicinal product code	
Other name	BBI608, BBI-608
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Napabucasin was administered orally, twice daily, with doses separated by approximately 12 hours. Napabucasin administration began 2-5 days prior to the first FOLFIRI with Bevacizumab infusion.

Investigational medicinal product name	5-FU
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intracavernous use

Dosage and administration details:

5-FU 400 mg/m2 bolus will be administered intravenously immediately following irinotecan/leucovorin infusion, followed by 5-FU 1200 mg/m2/day (total 2400 mg/m2) continuous infusion. This regimen will be repeated on Day 1 of every 14-day cycle.

Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5-FU 400 mg/m2 bolus will be administered intravenously immediately following irinotecan/leucovorin infusion, followed by 5-FU 1200 mg/m2/day (total 2400 mg/m2) continuous infusion. This regimen will be repeated on Day 1 of every 14-day cycle.

Investigational medicinal product name	leucovorin
Investigational medicinal product code	
Other name	Levoleucovorin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5-FU 400 mg/m2 bolus will be administered intravenously immediately following irinotecan/leucovorin infusion, followed by 5-FU 1200 mg/m2/day (total 2400 mg/m2) continuous infusion. This regimen will be repeated on Day 1 of every 14-day cycle.

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab (5 mg/kg) infusion should start at least 2 hours following the first dose of BBI-608 starting on Cycle 1 Day 1 and will be administered every 2 weeks.

Arm title	FOLFIRI ± Bevacizumab

Arm description:

Addition of bevacizumab to the FOLFIRI regimen will be permissible. FOLFIRI chemotherapy infusion will be administered every 2 weeks. Irinotecan/leucovorin infusion will follow bevacizumab infusion in selected patients to receive standard dose of bevacizumab (5 mg/kg). Irinotecan 180 mg/m^2 together with leucovorin 400 mg/m^2 will be administered intravenously, over approximately 90 minutes and 2 hours, respectively, starting on Day 1 of Cycle 1, following bevacizumab infusion. 5-FU 400 mg/m^2 bolus will be administered intravenously immediately following irinotecan/leucovorin infusion, followed by 5-FU 1200 mg/m^2/day (total 2400 mg/m^2) continuous infusion. This regimen will be repeated on Day 1 of every 14 day cycle.

Arm type	Active comparator
Investigational medicinal product name	5-FU
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intracavernous use

Dosage and administration details:

5-FU 400 mg/m2 bolus will be administered intravenously immediately following irinotecan/leucovorin infusion, followed by 5-FU 1200 mg/m2/day (total 2400 mg/m2) continuous infusion. This regimen will be repeated on Day 1 of every 14-day cycle.

Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5-FU 400 mg/m2 bolus will be administered intravenously immediately following irinotecan/leucovorin infusion, followed by 5-FU 1200 mg/m2/day (total 2400 mg/m2) continuous infusion. This regimen will be repeated on Day 1 of every 14-day cycle.

Investigational medicinal product name	leucovorin
Investigational medicinal product code	
Other name	Levoleucovorin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5-FU 400 mg/m2 bolus will be administered intravenously immediately following irinotecan/leucovorin infusion, followed by 5-FU 1200 mg/m2/day (total 2400 mg/m2) continuous infusion. This regimen will be repeated on Day 1 of every 14-day cycle.

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravascular use

Dosage and administration details:

Bevacizumab (5 mg/kg) infusion should start at least 2 hours following the first dose of BBI-608 starting on Cycle 1 Day 1 and will be administered every 2 weeks.

Number of subjects in period 1	Napabucasin + FOLFIRI ± Bevacizumab	FOLFIRI ± Bevacizumab
Started	624	629
Completed	571	561
Not completed	53	68
Consent withdrawn by subject	37	47
Hospice	-	2
Unknown	3	8
Lost to follow-up	13	11

Baseline characteristics

Reporting groups

Reporting group title	Napabucasin + FOLFIRI ± Bevacizumab

Reporting group description:

Napabucasin 240 mg will be administered orally, twice daily, with doses separated by approximately 12 hours (480 mg total daily dose).
Addition of bevacizumab to the FOLFIRI regimen will be permissible. FOLFIRI chemotherapy infusion will start at least 2 hours following the first daily dose of napabucasin and will be administered every 2 weeks. This regimen will be repeated on Day 1 of every 14 day cycle.

Reporting group title	FOLFIRI ± Bevacizumab

Reporting group description:

Addition of bevacizumab to the FOLFIRI regimen will be permissible. FOLFIRI chemotherapy infusion will be administered every 2 weeks. Irinotecan/leucovorin infusion will follow bevacizumab infusion in selected patients to receive standard dose of bevacizumab (5 mg/kg). Irinotecan 180 mg/m^2 together with leucovorin 400 mg/m^2 will be administered intravenously, over approximately 90 minutes and 2 hours, respectively, starting on Day 1 of Cycle 1, following bevacizumab infusion. 5-FU 400 mg/m^2 bolus will be administered intravenously immediately following irinotecan/leucovorin infusion, followed by 5-FU 1200 mg/m^2/day (total 2400 mg/m^2) continuous infusion. This regimen will be repeated on Day 1 of every 14 day cycle.

Reporting group values	Napabucasin + FOLFIRI ± Bevacizumab	FOLFIRI ± Bevacizumab	Total
Number of subjects	624	629	1253
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	393	403	796
From 65-84 years	231	225	456
85 years and over	0	1	1
Age continuous Units: years			
median	61.0	61.0	
full range (min-max)	26 to 84	21 to 86	-
Gender categorical Units: Subjects			
Female	240	254	494
Male	384	375	759

Subject analysis sets

Subject analysis set title	Intent-to-Treat Analysis Set in the General Population, Arm 1
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All participants who were randomized to Arm1 to receive napabucasin administered orally, twice daily in combination with FOLFIRI ± Bevacizumab

Subject analysis set title	Intent-to-Treat Analysis Set in the General Population, Arm 2
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All participants who were randomized to Arm 2 to receive FOLFIRI ± Bevacizumab

Subject analysis set title	Intent-to-Treat Analysis Set in the pSTAT3(+) , Arm 1
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All participants who were randomized to Arm 1 to receive napabucasin administered orally, twice daily in combination with Napabucasin + FOLFIRI ± Bevacizumab and were assessed to have positive pSTAT3 status based on their biomarker data.

Subject analysis set title	Intent-to-Treat Analysis Set in the pSTAT3(+) , Arm 2
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All participants who were randomized to Arm 2 to receive FOLFIRI ± Bevacizumab and were assessed to have positive pSTAT3 status based on their biomarker data.

Subject analysis set title	Safety Analysis Set in the General Population (SAS-GP) Arm 1
Subject analysis set type	Safety analysis

Subject analysis set description:

All participants who were randomized to Arm1 to receive napabucasin administered orally, twice daily in combination with FOLFIRI ± Bevacizumab and received at least 1 dose of study drug (BBI-608 and/or FOLFIRI).

Subject analysis set title	Safety Analysis Set in the General Population (SAS-GP) Arm 2
Subject analysis set type	Safety analysis

Subject analysis set description:

All participants who were randomized to Arm 2 to receive FOLFIRI ± Bevacizumab and received at least 1 dose of FOLFIRI.

Subject analysis set title	QoL Analysis Set in the General Population (QoL-GP), Arm 1
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All participants who were randomized to Arm 1 to receive napabucasin administered orally, twice daily in combination with Napabucasin + FOLFIRI ± Bevacizumab and have at least 1 QoL assessment in the General Population. QoL-GP will be used for QoL endpoint analysis in the General Population. QoL assessments from 14 days prior to randomization and afterward are considered.

Subject analysis set title	QoL Analysis Set in the General Population (QoL-GP), Arm 2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All participants who were randomized to Arm 2 to receive FOLFIRI ± Bevacizumab and have at least 1 QoL assessment in the General Population. QoL-GP will be used for QoL endpoint analysis in the General Population. QoL assessments from 14 days prior to randomization and afterward are considered.

Reporting group values	Intent-to-Treat Analysis Set in the General Population, Arm 1	Intent-to-Treat Analysis Set in the General Population, Arm 2	Intent-to-Treat Analysis Set in the pSTAT3(+) , Arm 1
Number of subjects	624	629	275
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0

Adults (18-64 years)	393	403	181
From 65-84 years	231	225	94
85 years and over	0	1	0
Age continuous			
Units: years			
median	61.0	61.0	61.0
full range (min-max)	26 to 84	21 to 86	26 to 81
Gender categorical			
Units: Subjects			
Female	240	254	105
Male	384	375	170

Reporting group values	Intent-to-Treat Analysis Set in the pSTAT3(+) , Arm 2	Safety Analysis Set in the General Population (SAS-GP) Arm 1	Safety Analysis Set in the General Population (SAS-GP) Arm 2
Number of subjects	272	622	610
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	171	392	391
From 65-84 years	101	230	218
85 years and over	0	0	1
Age continuous			
Units: years			
median	60.0		
full range (min-max)	21 to 83		
Gender categorical			
Units: Subjects			
Female	124		
Male	148		

Reporting group values	QoL Analysis Set in the General Population (QoL-GP), Arm 1	QoL Analysis Set in the General Population (QoL-GP), Arm 2	
Number of subjects	622	626	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	392	401	

From 65-84 years	230	224	
85 years and over	0	1	

Age continuous Units: years median full range (min-max)			
Gender categorical Units: Subjects			
Female Male			

End points

End points reporting groups

Reporting group title	Napabucasin + FOLFIRI ± Bevacizumab

Reporting group description:

Napabucasin 240 mg will be administered orally, twice daily, with doses separated by approximately 12 hours (480 mg total daily dose).
Addition of bevacizumab to the FOLFIRI regimen will be permissible. FOLFIRI chemotherapy infusion will start at least 2 hours following the first daily dose of napabucasin and will be administered every 2 weeks. This regimen will be repeated on Day 1 of every 14 day cycle.

Reporting group title	FOLFIRI ± Bevacizumab

Reporting group description:

Addition of bevacizumab to the FOLFIRI regimen will be permissible. FOLFIRI chemotherapy infusion will be administered every 2 weeks. Irinotecan/leucovorin infusion will follow bevacizumab infusion in selected patients to receive standard dose of bevacizumab (5 mg/kg). Irinotecan 180 mg/m^2 together with leucovorin 400 mg/m^2 will be administered intravenously, over approximately 90 minutes and 2 hours, respectively, starting on Day 1 of Cycle 1, following bevacizumab infusion. 5-FU 400 mg/m^2 bolus will be administered intravenously immediately following irinotecan/leucovorin infusion, followed by 5-FU 1200 mg/m^2/day (total 2400 mg/m^2) continuous infusion. This regimen will be repeated on Day 1 of every 14 day cycle.

Subject analysis set title	Intent-to-Treat Analysis Set in the General Population, Arm 1
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All participants who were randomized to Arm1 to receive napabucasin administered orally, twice daily in combination with FOLFIRI ± Bevacizumab

Subject analysis set title	Intent-to-Treat Analysis Set in the General Population, Arm 2
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All participants who were randomized to Arm 2 to receive FOLFIRI ± Bevacizumab

Subject analysis set title	Intent-to-Treat Analysis Set in the pSTAT3(+) , Arm 1
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All participants who were randomized to Arm 1 to receive napabucasin administered orally, twice daily in combination with Napabucasin + FOLFIRI ± Bevacizumab and were assessed to have positive pSTAT3 status based on their biomarker data.

Subject analysis set title	Intent-to-Treat Analysis Set in the pSTAT3(+) , Arm 2
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All participants who were randomized to Arm 2 to receive FOLFIRI ± Bevacizumab and were assessed to have positive pSTAT3 status based on their biomarker data.

Subject analysis set title	Safety Analysis Set in the General Population (SAS-GP) Arm 1
Subject analysis set type	Safety analysis

Subject analysis set description:

All participants who were randomized to Arm1 to receive napabucasin administered orally, twice daily in combination with FOLFIRI ± Bevacizumab and received at least 1 dose of study drug (BBI-608 and/or FOLFIRI).

Subject analysis set title	Safety Analysis Set in the General Population (SAS-GP) Arm 2
Subject analysis set type	Safety analysis

Subject analysis set description:

All participants who were randomized to Arm 2 to receive FOLFIRI ± Bevacizumab and received at least 1 dose of FOLFIRI.

Subject analysis set title	QoL Analysis Set in the General Population (QoL-GP), Arm 1
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All participants who were randomized to Arm 1 to receive napabucasin administered orally, twice daily in combination with Napabucasin + FOLFIRI ± Bevacizumab and have at least 1 QoL assessment in the General Population. QoL-GP will be used for QoL endpoint analysis in the General Population. QoL assessments from 14 days prior to randomization and afterward are considered.

Subject analysis set title	QoL Analysis Set in the General Population (QoL-GP), Arm 2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All participants who were randomized to Arm 2 to receive FOLFIRI ± Bevacizumab and have at least 1 QoL assessment in the General Population. QoL-GP will be used for QoL endpoint analysis in the General Population. QoL assessments from 14 days prior to randomization and afterward are considered.

Primary: Overall Survival (OS) General population

End point title	Overall Survival (OS) General population

End point description:

Overall survival was defined as the time from randomization until death from any cause.
Patients who are alive at the time of the interim or the final analyses or who have become lost to follow-up will be censored on the date the patient was last known to be alive.

End point type	Primary

End point timeframe:

Randomization to Date of Death from any cause or database cutoff date (28 Apr 2020) (Approximately 43 months)

End point values	Napabucasin + FOLFIRI ± Bevacizumab	FOLFIRI ± Bevacizumab	Intent-to-Treat Analysis Set in the General Population, Arm 1	Intent-to-Treat Analysis Set in the General Population, Arm 2
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	624	629	624	629
Units: Months				
median (confidence interval 95%)	14.29 (13.34 to 15.70)	13.83 (12.42 to 15.28)	14.29 (13.34 to 15.7)	13.83 (12.42 to 15.28)

Statistical analyses

Statistical analysis title	Statistical Test of Hypothesis
Comparison groups	Napabucasin + FOLFIRI ± Bevacizumab v FOLFIRI ± Bevacizumab
Number of subjects included in analysis	1253
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3629
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.976
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.854
upper limit	1.117

Primary: Overall Survival pSTAT3(+) Subpopulation patients

End point title	Overall Survival pSTAT3(+) Subpopulation patients

End point description:

Overall survival was defined as the time from randomization until death from any cause.
Patients who are alive at the time of the interim or the final analyses or who have become lost to follow-up will be censored on the date the patient was last known to be alive.

End point type	Primary

End point timeframe:

Randomization to Date of Death from any cause or database cutoff date (28 Apr 2020) (Approximately 43 months)

End point values	Napabucasin + FOLFIRI ± Bevacizumab	FOLFIRI ± Bevacizumab	Intent-to-Treat Analysis Set in the pSTAT3(+) , Arm 1	Intent-to-Treat Analysis Set in the pSTAT3(+) , Arm 2
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	275	272	275	272
Units: Months				
median (confidence interval 95%)	13.17 (11.30 to 15.31)	12.12 (11.24 to 14.06)	13.17 (11.30 to 15.31)	12.12 (11.24 to 14.06)

Statistical analyses

Statistical analysis title	Statistical Test of Hypothesis, pSTAT3(+)
Comparison groups	Intent-to-Treat Analysis Set in the pSTAT3(+) , Arm 1 v Intent-to-Treat Analysis Set in the pSTAT3(+) , Arm 2
Number of subjects included in analysis	547
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3782
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.969
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.797
upper limit	1.179

Secondary: Progression Free Survival (pSTAT3(+) Subpopulation patients)

End point title	Progression Free Survival (pSTAT3(+) Subpopulation patients)

End point description:

PFS is defined as the time from randomization to the first objective documentation of disease

progression per RECIST 1.1 (PD) or death, whichever comes first.

End point type	Secondary

End point timeframe:

Randomization to Date of Death or until the date of first documented objective disease progression or database cutoff date (28 Apr 2020) (Approximately 43 months)

End point values	Napabucasin + FOLFIRI ± Bevacizumab	FOLFIRI ± Bevacizumab	Intent-to-Treat Analysis Set in the pSTAT3(+) , Arm 1	Intent-to-Treat Analysis Set in the pSTAT3(+) , Arm 2
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	275	272	275	272
Units: Months				
median (confidence interval 95%)	5.39 (4.14 to 5.62)	5.55 (4.44 to 5.91)	5.39 (4.14 to 5.62)	5.55 (4.44 to 5.91)

Statistical analyses

Statistical analysis title	Statistical Test of Hypothesis, pSTAT3(+)
Comparison groups	Intent-to-Treat Analysis Set in the pSTAT3(+) , Arm 1 v Intent-to-Treat Analysis Set in the pSTAT3(+) , Arm 2
Number of subjects included in analysis	547
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7434
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.064
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.883
upper limit	1.283

Secondary: Progression Free Survival (General population)

End point title	Progression Free Survival (General population)

End point description:

PFS is defined as the time from randomization to the first objective documentation of disease progression per RECIST 1.1 (PD) or death, whichever comes first.

End point type	Secondary

End point timeframe:

Randomization to Date of Death or until the date of first documented objective disease progression or database cutoff date (28 Apr 2020) (Approximately 43 months)

End point values	Napabucasin + FOLFIRI ± Bevacizumab	FOLFIRI ± Bevacizumab	Intent-to-Treat Analysis Set in the General Population, Arm 1	Intent-to-Treat Analysis Set in the General Population, Arm 2
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	624	629	624	629
Units: Months				
median (confidence interval 95%)	5.55 (5.39 to 5.78)	5.62 (5.45 to 6.34)	5.55 (5.39 to 5.78)	5.62 (5.45 to 6.34)

Statistical analyses

Statistical analysis title	Statistical Test of Hypothesis, General population
Comparison groups	Napabucasin + FOLFIRI ± Bevacizumab v FOLFIRI ± Bevacizumab
Number of subjects included in analysis	1253
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7307
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.917
upper limit	1.18

Secondary: Disease Control Rate (DCR) (General population)

End point title	Disease Control Rate (DCR) (General population)

End point description:

DCR is defined as the percentage of patients with a documented complete response, partial response, and stable disease (CR + PR + SD) based on RECIST 1.1. The primary estimate of DCR will be based on patients with measurable disease by RECIST 1.1 at randomization

End point type	Secondary

End point timeframe:

Randomization to Date of Death or until the date of first documented objective disease progression or database cutoff date (28 Apr 2020) (Approximately 43 months)

End point values	Napabucasin + FOLFIRI ± Bevacizumab	FOLFIRI ± Bevacizumab	Intent-to-Treat Analysis Set in the General Population, Arm 1	Intent-to-Treat Analysis Set in the General Population, Arm 2
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	593	609	593	609
Units: Percentage				
number (confidence interval 95%)	69.6 (65.8 to 73.3)	69.1 (65.3 to 72.8)	69.6 (65.8 to 73.3)	69.1 (65.3 to 72.8)

Statistical analyses

Statistical analysis title	Statistical Test of Hypothesis, General population
Comparison groups	Napabucasin + FOLFIRI ± Bevacizumab v FOLFIRI ± Bevacizumab
Number of subjects included in analysis	1202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4797
Method	Cochran-Mantel-Haenszel
Parameter estimate	rate difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.9
upper limit	5.2

Secondary: Disease Control Rate (DCR) (pSTAT3(+) Subpopulation patients)

End point title	Disease Control Rate (DCR) (pSTAT3(+) Subpopulation patients)

End point description:

DCR is defined as the percentage of patients with a documented complete response, partial response, and stable disease (CR + PR + SD) based on RECIST 1.1. The primary estimate of DCR will be based on patients with measurable disease by RECIST 1.1 at randomization

End point type	Secondary

End point timeframe:

Randomization to Date of Death or until the date of first documented objective disease progression or database cutoff date (28 Apr 2020) (Approximately 43 months)

End point values	Napabucasin + FOLFIRI ± Bevacizumab	FOLFIRI ± Bevacizumab	Intent-to-Treat Analysis Set in the pSTAT3(+) , Arm 1	Intent-to-Treat Analysis Set in the pSTAT3(+) , Arm 2
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	268	266	268	266
Units: percentage of participants				
number (confidence interval 95%)	67.2 (61.2 to 72.8)	70.3 (64.4 to 75.7)	67.2 (61.2 to 72.8)	70.3 (64.4 to 75.7)

Statistical analyses

Statistical analysis title	Statistical Test of Hypothesis, pSTAT3(+)
Comparison groups	Intent-to-Treat Analysis Set in the pSTAT3(+) , Arm 1 v Intent-to-Treat Analysis Set in the pSTAT3(+) , Arm 2
Number of subjects included in analysis	534
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.783
Method	Z test
Parameter estimate	rate difference
Point estimate	-3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11
upper limit	4.7

Secondary: Objective Response Rate (ORR) (General population)

End point title	Objective Response Rate (ORR) (General population)

End point description:

ORR is defined as the proportion of patients with a documented complete response and partial response (CR + PR) based on RECIST 1.1. The primary estimate for ORR will be based on patients with measurable disease by RECIST 1.1 at randomization.

End point type	Secondary

End point timeframe:

Randomization to Date of Death or until the date of first documented objective disease progression or database cutoff date (28 Apr 2020) (Approximately 43 months)

End point values	Napabucasin + FOLFIRI ± Bevacizumab	FOLFIRI ± Bevacizumab	Intent-to-Treat Analysis Set in the General Population, Arm 1	Intent-to-Treat Analysis Set in the General Population, Arm 2
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	593	609	593	609
Units: percentage of participants				

number (confidence interval 95%)	13.8 (11.2 to 16.9)	14.6 (11.9 to 17.7)	13.8 (11.2 to 16.9)	14.6 (11.9 to 17.7)

Statistical analyses

Statistical analysis title	Statistical Test of Hypothesis, General population
Comparison groups	Napabucasin + FOLFIRI ± Bevacizumab v FOLFIRI ± Bevacizumab
Number of subjects included in analysis	1202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6776
Method	Cochran-Mantel-Haenszel
Parameter estimate	rate difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.8
upper limit	3

Secondary: Objective Response Rate (ORR) (pSTAT3(+) Subpopulation patients)

End point title	Objective Response Rate (ORR) (pSTAT3(+) Subpopulation patients)

End point description:

ORR is defined as the proportion of patients with a documented complete response and partial response (CR + PR) based on RECIST 1.1. The primary estimate for ORR will be based on patients with measurable disease by RECIST 1.1 at randomization.

End point type	Secondary

End point timeframe:

Randomization to Date of Death or until the date of first documented objective disease progression or database cutoff date (28 Apr 2020) (Approximately 43 months)

End point values	Napabucasin + FOLFIRI ± Bevacizumab	FOLFIRI ± Bevacizumab	Intent-to-Treat Analysis Set in the pSTAT3(+), Arm 1	Intent-to-Treat Analysis Set in the pSTAT3(+), Arm 2
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	268	266	268	266
Units: percentage of participants				
number (confidence interval 95%)	11.9 (8.3 to 16.4)	13.9 (10.0 to 18.7)	11.9 (8.3 to 16.4)	13.9 (10.0 to 18.7)

Statistical analyses

Statistical analysis title	Statistical Test of Hypothesis, pSTAT3(+)
Comparison groups	Intent-to-Treat Analysis Set in the pSTAT3(+) , Arm 1 v Intent-to-Treat Analysis Set in the pSTAT3(+) , Arm 2
Number of subjects included in analysis	534
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7513
Method	Z test
Parameter estimate	rate difference
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.7
upper limit	3.7

Secondary: Mean Change From Baseline for Global Health Status at Time 2 (Cycle 5 Day 1).

End point title	Mean Change From Baseline for Global Health Status at Time 2 (Cycle 5 Day 1).

End point description:

The Quality of Life (QoL) of patients will be assessed using European Organization for Research and Treatment of Cancer Quality of Life questionnaire (EORTC-QLQ-C30) (EORTC QLQ-30) while the patient remains on study treatment (FOLFIRI with or without BBI-608). EORTC QLQ-30 is used to assess the overall quality of life in cancer patients using 28 questions with a 4 point scale. (1 'Not at all' to 4'Very Much'); 2 questions use a 7-point sale (1 'Very Poor' to 7 'Excellent'). Scores are averaged and transformed to 0-100 scale; higher overall score = better quality of life.

End point type	Secondary

End point timeframe:

From baseline at Time 2 (Cycle 5 Day 1), approximately 57 days

End point values	Napabucasin + FOLFIRI ± Bevacizumab	FOLFIRI ± Bevacizumab	QoL Analysis Set in the General Population (QoL-GP), Arm 1	QoL Analysis Set in the General Population (QoL-GP), Arm 2
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	376	341	376	341
Units: score on a scale				
median (standard deviation)	-7.07 (± 21.936)	-5.45 (± 20.607)	-7.07 (± 21.936)	-5.45 (± 20.607)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline for Global Health Status at Time 4 (Cycle 9 Day 1).

End point title	Mean Change From Baseline for Global Health Status at Time 4 (Cycle 9 Day 1).

End point description:

The Quality of Life (QoL) of patients will be assessed using European Organization for Research and Treatment of Cancer Quality of Life questionnaire (EORTC-QLQ-C30) (EORTC QLQ-30) while the patient remains on study treatment (FOLFIRI with or without BBI-608). EORTC QLQ-30 is used to assess the overall quality of life in cancer patients using 28 questions with a 4 point scale. (1 'Not at all' to 4'Very Much'); 2 questions use a 7-point sale (1
Very Poor' to 7 'Excellent'). Scores are averaged and transformed to 0-100 scale; higher overall score = better quality of life.

End point type	Secondary

End point timeframe:

From baseline at time 4 (Cycle 9 Day 1), approximately 113 days

End point values	Napabucasin + FOLFIRI ± Bevacizumab	FOLFIRI ± Bevacizumab	QoL Analysis Set in the General Population (QoL-GP), Arm 1	QoL Analysis Set in the General Population (QoL-GP), Arm 2
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	370	360	370	360
Units: score on a scale				
median (standard deviation)	-7.70 (± 21.932)	-5.58 (± 21.590)	-7.70 (± 21.936)	-5.58 (± 21.590)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients With Adverse Events in the General Population

End point title	Number of Patients With Adverse Events in the General Population

End point description:

All patients who have received at least one dose of either BBI-608 or FOLFIRI will be included in the safety analysis according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 4.0. The incidence of adverse events will be summarized by type of adverse event and severity.

End point type	Secondary

End point timeframe:

All adverse event are collected from date of signed informed consent until 30 days after protocol treatment discontinuation. Outcome followed until study discontinuation up to 4 years

End point values	Napabucasin + FOLFIRI ± Bevacizumab	FOLFIRI ± Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	622	610		
Units: Participants	619	602		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse event are collected from date of signed informed consent until 30 days after protocol treatment discontinuation. Outcome followed until study discontinuation.

Adverse event reporting additional description:

All adverse event are collected from date of signed informed consent until 30 days after protocol treatment discontinuation. Outcome followed until study discontinuation up to 4 years. All cause mortality is analyzed in the ITT population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Napabucasin + FOLFIRI ± Bevacizumab
Reporting group description: -	
Reporting group title	FOLFIRI ± Bevacizumab

Reporting group description: -

Serious adverse events	Napabucasin + FOLFIRI ± Bevacizumab	FOLFIRI ± Bevacizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	234 / 622 (37.62%)	201 / 610 (32.95%)	
number of deaths (all causes)	507	499	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant Ascites			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases To Kidney			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases To Liver			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases To Lung			

subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pituitary Tumour Benign			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour Haemorrhage			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon Cancer Metastatic			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases To Heart			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases To Peritoneum			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
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 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	6 / 622 (0.96%)	3 / 610 (0.49%)	
occurrences causally related to treatment / all	3 / 6	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep Vein Thrombosis			

subjects affected / exposed	2 / 622 (0.32%)	2 / 610 (0.33%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	2 / 622 (0.32%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic Shock			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic Hypotension			
subjects affected / exposed	1 / 622 (0.16%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian Vein Thrombosis			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (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	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Tumour Excision			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (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	18 / 622 (2.89%)	16 / 610 (2.62%)	
occurrences causally related to treatment / all	5 / 18	5 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease Progression			
subjects affected / exposed	17 / 622 (2.73%)	15 / 610 (2.46%)	
occurrences causally related to treatment / all	0 / 17	0 / 15	
deaths causally related to treatment / all	0 / 12	0 / 11	
General Physical Health Deterioration			
subjects affected / exposed	5 / 622 (0.80%)	5 / 610 (0.82%)	
occurrences causally related to treatment / all	2 / 5	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 1	
Asthenia			
subjects affected / exposed	4 / 622 (0.64%)	4 / 610 (0.66%)	
occurrences causally related to treatment / all	2 / 4	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	4 / 622 (0.64%)	2 / 610 (0.33%)	
occurrences causally related to treatment / all	4 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	2 / 622 (0.32%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Mucosal Inflammation			
subjects affected / exposed	2 / 622 (0.32%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Cardiac Chest Pain			
subjects affected / exposed	2 / 622 (0.32%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			

subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 622 (0.16%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal Toxicity			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema Peripheral			
subjects affected / exposed	1 / 622 (0.16%)	2 / 610 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammation			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug Hypersensitivity			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic Reaction			
subjects affected / exposed	0 / 622 (0.00%)	2 / 610 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Pulmonary Embolism			
subjects affected / exposed	12 / 622 (1.93%)	9 / 610 (1.48%)	
occurrences causally related to treatment / all	5 / 12	3 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
subjects affected / exposed	5 / 622 (0.80%)	2 / 610 (0.33%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 622 (0.48%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	2 / 622 (0.32%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Failure			
subjects affected / exposed	2 / 622 (0.32%)	2 / 610 (0.33%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Aspiration			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial Lung Disease			
subjects affected / exposed	1 / 622 (0.16%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Infiltration			

subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Artery Thrombosis			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Oedema			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional State			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental Status Changes			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aggression			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			

subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device Dislocation			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis In Device			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood Bilirubin Increased			
subjects affected / exposed	2 / 622 (0.32%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil Count Decreased			
subjects affected / exposed	2 / 622 (0.32%)	8 / 610 (1.31%)	
occurrences causally related to treatment / all	2 / 2	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet Count Decreased			
subjects affected / exposed	2 / 622 (0.32%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate Aminotransferase Increased			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Myocardial Necrosis Marker Increased			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood Uric Acid Increased			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White Blood Cell Count Decreased			
subjects affected / exposed	0 / 622 (0.00%)	2 / 610 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	2 / 622 (0.32%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle Fracture			
subjects affected / exposed	2 / 622 (0.32%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip Fracture			
subjects affected / exposed	2 / 622 (0.32%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion Related Reaction			
subjects affected / exposed	2 / 622 (0.32%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Fracture			
subjects affected / exposed	2 / 622 (0.32%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Stoma Site Haemorrhage			
subjects affected / exposed	2 / 622 (0.32%)	3 / 610 (0.49%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral Neck Fracture			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur Fracture			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Stoma Complication			
subjects affected / exposed	1 / 622 (0.16%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar Vertebral Fracture			
subjects affected / exposed	1 / 622 (0.16%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road Traffic Accident			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma Complication			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural Haematoma			

subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	3 / 622 (0.48%)	4 / 610 (0.66%)	
occurrences causally related to treatment / all	0 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Coronary Syndrome			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Myocardial Infarction			
subjects affected / exposed	1 / 622 (0.16%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Flutter			
subjects affected / exposed	1 / 622 (0.16%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Arrest			
subjects affected / exposed	1 / 622 (0.16%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac Failure			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular Fibrillation			

subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (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 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	2 / 622 (0.32%)	3 / 610 (0.49%)	
occurrences causally related to treatment / all	1 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Altered State Of Consciousness			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Infarction			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid Haemorrhage			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior Sagittal Sinus Thrombosis			

subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient Ischaemic Attack			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Cord Compression			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Cord Disorder			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
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			
Anaemia			
subjects affected / exposed	9 / 622 (1.45%)	4 / 610 (0.66%)	
occurrences causally related to treatment / all	5 / 9	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone Marrow Failure			
subjects affected / exposed	1 / 622 (0.16%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile Neutropenia			

subjects affected / exposed	8 / 622 (1.29%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	8 / 8	11 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	4 / 622 (0.64%)	3 / 610 (0.49%)	
occurrences causally related to treatment / all	4 / 4	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	3 / 622 (0.48%)	2 / 610 (0.33%)	
occurrences causally related to treatment / all	2 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	2 / 622 (0.32%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated Intravascular Coagulation			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 622 (0.16%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytosis			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	39 / 622 (6.27%)	19 / 610 (3.11%)	
occurrences causally related to treatment / all	37 / 39	18 / 19	
deaths causally related to treatment / all	0 / 0	1 / 1	
Abdominal Pain			

subjects affected / exposed	17 / 622 (2.73%)	16 / 610 (2.62%)	
occurrences causally related to treatment / all	8 / 17	5 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal Obstruction			
subjects affected / exposed	10 / 622 (1.61%)	15 / 610 (2.46%)	
occurrences causally related to treatment / all	1 / 10	2 / 15	
deaths causally related to treatment / all	0 / 0	0 / 1	
Small Intestinal Obstruction			
subjects affected / exposed	10 / 622 (1.61%)	12 / 610 (1.97%)	
occurrences causally related to treatment / all	1 / 10	1 / 12	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vomiting			
subjects affected / exposed	10 / 622 (1.61%)	8 / 610 (1.31%)	
occurrences causally related to treatment / all	9 / 10	6 / 8	
deaths causally related to treatment / all	0 / 0	1 / 1	
Nausea			
subjects affected / exposed	9 / 622 (1.45%)	4 / 610 (0.66%)	
occurrences causally related to treatment / all	8 / 9	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	4 / 622 (0.64%)	8 / 610 (1.31%)	
occurrences causally related to treatment / all	0 / 4	1 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	3 / 622 (0.48%)	3 / 610 (0.49%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal Perforation			
subjects affected / exposed	3 / 622 (0.48%)	2 / 610 (0.33%)	
occurrences causally related to treatment / all	3 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large Intestinal Obstruction			

subjects affected / exposed	3 / 622 (0.48%)	4 / 610 (0.66%)	
occurrences causally related to treatment / all	0 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Gastrointestinal Haemorrhage			
subjects affected / exposed	3 / 622 (0.48%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Colitis			
subjects affected / exposed	2 / 622 (0.32%)	3 / 610 (0.49%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	2 / 622 (0.32%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Gastrointestinal Haemorrhage			
subjects affected / exposed	2 / 622 (0.32%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal Varices Haemorrhage			
subjects affected / exposed	2 / 622 (0.32%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	2 / 622 (0.32%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Haemorrhage			
subjects affected / exposed	2 / 622 (0.32%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Hernia Obstructive			

subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea Haemorrhagic			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal Ulcer Haemorrhage			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Disorder			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 622 (0.16%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Inflammation			
subjects affected / exposed	1 / 622 (0.16%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Perforation			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Toxicity			

subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 622 (0.16%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal Haemorrhage			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal Hernia Strangulated			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large Intestinal Stenosis			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction Gastric			
subjects affected / exposed	1 / 622 (0.16%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis Acute			

subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoperitoneum			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Distension			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis Ischaemic			
subjects affected / exposed	0 / 622 (0.00%)	2 / 610 (0.33%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal Perforation			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric Ulcer Perforation			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal Hernia			

subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large Intestine Perforation			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Mouth Ulceration			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumatosis Intestinalis			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 622 (0.00%)	2 / 610 (0.33%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toothache			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	3 / 622 (0.48%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile Duct Obstruction			

subjects affected / exposed	2 / 622 (0.32%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	2 / 622 (0.32%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis Acute			
subjects affected / exposed	2 / 622 (0.32%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 622 (0.16%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder Necrosis			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic Function Abnormal			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice Cholestatic			
subjects affected / exposed	1 / 622 (0.16%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile Duct Stenosis			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			

subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver Injury			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
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	7 / 622 (1.13%)	3 / 610 (0.49%)	
occurrences causally related to treatment / all	2 / 7	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Prerenal Failure			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 622 (0.16%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal Failure			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	1 / 622 (0.16%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			

subjects affected / exposed	0 / 622 (0.00%)	2 / 610 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydroureter			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
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	0 / 622 (0.00%)	2 / 610 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Obstruction			
subjects affected / exposed	0 / 622 (0.00%)	2 / 610 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	3 / 622 (0.48%)	4 / 610 (0.66%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular Weakness			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myopathy			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain In Extremity			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture Pain			

subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis Of Jaw			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	7 / 622 (1.13%)	10 / 610 (1.64%)	
occurrences causally related to treatment / all	4 / 7	4 / 10	
deaths causally related to treatment / all	0 / 0	0 / 2	
Urinary Tract Infection			
subjects affected / exposed	6 / 622 (0.96%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	1 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 622 (0.64%)	8 / 610 (1.31%)	
occurrences causally related to treatment / all	2 / 4	2 / 8	
deaths causally related to treatment / all	0 / 0	0 / 2	
Anal Abscess			
subjects affected / exposed	2 / 622 (0.32%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	2 / 622 (0.32%)	2 / 610 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium Difficile Colitis			
subjects affected / exposed	2 / 622 (0.32%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			

subjects affected / exposed	2 / 622 (0.32%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Infection			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Sepsis			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis Perforated			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial Sepsis			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium Difficile Infection			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic Abscess			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device Related Infection			

subjects affected / exposed	1 / 622 (0.16%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis Infectious			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes Zoster			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected Dermal Cyst			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Infection			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nosocomial Infection			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal Abscess			

subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 622 (0.16%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar Abscess			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Influenzal			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas Bronchitis			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Abscess			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal Abscess			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic Shock			
subjects affected / exposed	1 / 622 (0.16%)	4 / 610 (0.66%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 3	
Urosepsis			

subjects affected / exposed	1 / 622 (0.16%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral Infection			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Abscess			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Wall Abscess			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess Jaw			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess Rupture			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorectal Infection			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
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 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coccidioidomycosis			

subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Epididymitis			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal Sepsis			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Lower Respiratory Tract			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising Fasciitis			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ophthalmic Herpes Zoster			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic Abscess			

subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic Infection			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
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 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Pneumococcal			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoas Abscess			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Sepsis			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyelonephritis			
subjects affected / exposed	0 / 622 (0.00%)	4 / 610 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyonephrosis			
subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Streptococcal Bacteraemia			

subjects affected / exposed	0 / 622 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	15 / 622 (2.41%)	9 / 610 (1.48%)	
occurrences causally related to treatment / all	12 / 15	4 / 9	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hypokalaemia			
subjects affected / exposed	5 / 622 (0.80%)	6 / 610 (0.98%)	
occurrences causally related to treatment / all	4 / 5	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased Appetite			
subjects affected / exposed	4 / 622 (0.64%)	3 / 610 (0.49%)	
occurrences causally related to treatment / all	4 / 4	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure To Thrive			
subjects affected / exposed	1 / 622 (0.16%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	1 / 1	
Hyperglycaemia			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			

subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			
subjects affected / exposed	1 / 622 (0.16%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Napabucasin + FOLFIRI ± Bevacizumab	FOLFIRI ± Bevacizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	619 / 622 (99.52%)	602 / 610 (98.69%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	58 / 622 (9.32%)	65 / 610 (10.66%)	
occurrences (all)	114	124	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	233 / 622 (37.46%)	219 / 610 (35.90%)	
occurrences (all)	486	465	
Asthenia			
subjects affected / exposed	134 / 622 (21.54%)	116 / 610 (19.02%)	
occurrences (all)	361	291	
Pyrexia			
subjects affected / exposed	106 / 622 (17.04%)	89 / 610 (14.59%)	
occurrences (all)	163	142	
Mucosal Inflammation			
subjects affected / exposed	58 / 622 (9.32%)	89 / 610 (14.59%)	
occurrences (all)	93	205	
Oedema Peripheral			
subjects affected / exposed	44 / 622 (7.07%)	46 / 610 (7.54%)	
occurrences (all)	55	57	
Malaise			

subjects affected / exposed	42 / 622 (6.75%)	34 / 610 (5.57%)	
occurrences (all)	103	59	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	72 / 622 (11.58%)	75 / 610 (12.30%)	
occurrences (all)	87	103	
Epistaxis			
subjects affected / exposed	60 / 622 (9.65%)	79 / 610 (12.95%)	
occurrences (all)	78	107	
Dyspnoea			
subjects affected / exposed	55 / 622 (8.84%)	46 / 610 (7.54%)	
occurrences (all)	69	60	
Hiccups			
subjects affected / exposed	41 / 622 (6.59%)	29 / 610 (4.75%)	
occurrences (all)	49	46	
Oropharyngeal Pain			
subjects affected / exposed	19 / 622 (3.05%)	33 / 610 (5.41%)	
occurrences (all)	21	41	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	54 / 622 (8.68%)	84 / 610 (13.77%)	
occurrences (all)	87	100	
Investigations			
Neutrophil Count Decreased			
subjects affected / exposed	149 / 622 (23.95%)	176 / 610 (28.85%)	
occurrences (all)	440	422	
Weight Decreased			
subjects affected / exposed	106 / 622 (17.04%)	54 / 610 (8.85%)	
occurrences (all)	146	77	
White Blood Cell Count Decreased			
subjects affected / exposed	87 / 622 (13.99%)	109 / 610 (17.87%)	
occurrences (all)	325	302	
Aspartate Aminotransferase Increased			
subjects affected / exposed	75 / 622 (12.06%)	67 / 610 (10.98%)	
occurrences (all)	149	119	
Alanine Aminotransferase Increased			

subjects affected / exposed	67 / 622 (10.77%)	57 / 610 (9.34%)	
occurrences (all)	130	96	
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	59 / 622 (9.49%)	35 / 610 (5.74%)	
occurrences (all)	105	56	
Platelet Count Decreased			
subjects affected / exposed	42 / 622 (6.75%)	47 / 610 (7.70%)	
occurrences (all)	96	97	
Blood Bilirubin Increased			
subjects affected / exposed	29 / 622 (4.66%)	31 / 610 (5.08%)	
occurrences (all)	56	51	
Nervous system disorders			
Headache			
subjects affected / exposed	85 / 622 (13.67%)	73 / 610 (11.97%)	
occurrences (all)	137	104	
Dizziness			
subjects affected / exposed	59 / 622 (9.49%)	47 / 610 (7.70%)	
occurrences (all)	119	63	
Dysgeusia			
subjects affected / exposed	46 / 622 (7.40%)	59 / 610 (9.67%)	
occurrences (all)	49	69	
Neuropathy Peripheral			
subjects affected / exposed	32 / 622 (5.14%)	22 / 610 (3.61%)	
occurrences (all)	46	27	
Cholinergic Syndrome			
subjects affected / exposed	20 / 622 (3.22%)	33 / 610 (5.41%)	
occurrences (all)	21	74	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	151 / 622 (24.28%)	147 / 610 (24.10%)	
occurrences (all)	427	351	
Neutropenia			
subjects affected / exposed	151 / 622 (24.28%)	162 / 610 (26.56%)	
occurrences (all)	347	390	
Thrombocytopenia			

subjects affected / exposed	33 / 622 (5.31%)	23 / 610 (3.77%)	
occurrences (all)	65	38	
Leukopenia			
subjects affected / exposed	31 / 622 (4.98%)	42 / 610 (6.89%)	
occurrences (all)	80	130	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	522 / 622 (83.92%)	322 / 610 (52.79%)	
occurrences (all)	1940	874	
Nausea			
subjects affected / exposed	374 / 622 (60.13%)	307 / 610 (50.33%)	
occurrences (all)	1012	851	
Vomiting			
subjects affected / exposed	252 / 622 (40.51%)	177 / 610 (29.02%)	
occurrences (all)	660	395	
Abdominal Pain			
subjects affected / exposed	246 / 622 (39.55%)	146 / 610 (23.93%)	
occurrences (all)	522	218	
Constipation			
subjects affected / exposed	126 / 622 (20.26%)	173 / 610 (28.36%)	
occurrences (all)	176	280	
Stomatitis			
subjects affected / exposed	92 / 622 (14.79%)	116 / 610 (19.02%)	
occurrences (all)	195	198	
Abdominal Pain Upper			
subjects affected / exposed	63 / 622 (10.13%)	46 / 610 (7.54%)	
occurrences (all)	93	66	
Dyspepsia			
subjects affected / exposed	56 / 622 (9.00%)	39 / 610 (6.39%)	
occurrences (all)	67	64	
Abdominal Distension			
subjects affected / exposed	34 / 622 (5.47%)	31 / 610 (5.08%)	
occurrences (all)	42	36	
Proctalgia			
subjects affected / exposed	34 / 622 (5.47%)	20 / 610 (3.28%)	
occurrences (all)	40	25	

Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	133 / 622 (21.38%)	159 / 610 (26.07%)	
occurrences (all)	163	190	
Rash			
subjects affected / exposed	31 / 622 (4.98%)	41 / 610 (6.72%)	
occurrences (all)	38	44	
Palmar-Plantar Erythrodysaesthesia Syndrome			
subjects affected / exposed	30 / 622 (4.82%)	33 / 610 (5.41%)	
occurrences (all)	47	47	
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	70 / 622 (11.25%)	4 / 610 (0.66%)	
occurrences (all)	74	4	
Proteinuria			
subjects affected / exposed	54 / 622 (8.68%)	44 / 610 (7.21%)	
occurrences (all)	109	87	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	74 / 622 (11.90%)	82 / 610 (13.44%)	
occurrences (all)	93	97	
Infections and infestations			
Urinary Tract Infection			
subjects affected / exposed	68 / 622 (10.93%)	40 / 610 (6.56%)	
occurrences (all)	104	65	
Upper Respiratory Tract Infection			
subjects affected / exposed	44 / 622 (7.07%)	43 / 610 (7.05%)	
occurrences (all)	51	54	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	230 / 622 (36.98%)	187 / 610 (30.66%)	
occurrences (all)	484	375	
Hypokalaemia			
subjects affected / exposed	103 / 622 (16.56%)	55 / 610 (9.02%)	
occurrences (all)	191	98	
Dehydration			

subjects affected / exposed	47 / 622 (7.56%)	29 / 610 (4.75%)	
occurrences (all)	74	46	
Hypoalbuminaemia			
subjects affected / exposed	33 / 622 (5.31%)	29 / 610 (4.75%)	
occurrences (all)	70	63	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 July 2016	The protocol was amended to reflect requests from Regulatory Authority, update the frequency of collection of all safety blood samples
06 December 2016	The protocol was amended in response to a trial steering committee request to update the inclusion/exclusion criteria, correct errors and inconsistencies, and include clarifications.
26 June 2017	The protocol was amended to reflect requests from various Regulatory Authorities, update the inclusion/exclusion criteria, to include more updated safety data on BBI-60, correct errors and inconsistencies, and include clarifications.
16 February 2018	The protocol was amended for consistency with the most recent edition of the napabucasin Investigator's Brochure, to remove the efficacy analysis from the first interim analysis while keeping the futility analysis, to clarify sensitivity and subgroup analysis for overall survival, to remove the multiplicity adjustment for the secondary endpoints, to clarify the one-sided futility and efficacy boundaries for the interim analyses and the final analysis, to correct transcription errors, and to include other clarifications.
25 December 2018	The protocol was amended to update the study objectives, addition of a primary endpoint (overall survival) in the pSTAT3+ Subpopulation, reflect the addition of multiplicity adjustment strategy, include information on the Sponsor's blinding plan, implementation of an adaptive design allowing for futility stopping, patient population/hypothesis selection, and event count adjustment correct transcription errors, reflect the Sponsor's updated practices for AE reporting, and provide clarifications.
25 September 2019	The protocol was amended to specify the strategy of pSTAT3(+) Subpopulation, the pSTAT3(-) Subpopulation and pSTAT3(Unknown) Subpopulation, at the time of the interim analysis, preliminary data suggested cut slides were stable for up to 6 months. Other minor administrative and editorial changes were made throughout the amendment including typographical errors for consistency, clarification, and style.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported