Clinical trial results:
A Phase II Study of Pembrolizumab (MK-3475) as Monotherapy in Subjects with Previously Treated Locally Advanced Unresectable or Metastatic (Stage IV) Mismatched Repair Deficient or Microsatellite Instability-High Colorectal Carcinoma (KEYNOTE-164)

Summary

EudraCT number	2015-001852-32
Trial protocol	DE BE ES FR
Global end of trial date	19 February 2021

Results information

Result version number	v1 (current)
This version publication date	01 March 2022
First version publication date	01 March 2022

Trial information

Trial identification

Sponsor protocol code	MK-3475-164

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02460198
WHO universal trial number (UTN)	-
Other trial identifiers	JAPIC-CTI: 153046, Merck: KEYNOTE-164

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.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 February 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 September 2019
Global end of trial reached?	Yes
Global end of trial date	19 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Participants with previously-treated locally-advanced unresectable or metastatic mismatched repair (MMR) deficient or microsatellite instability-high (MSI-H) colorectal carcinoma (CRC) were treated with pembrolizumab (MK-3475, KEYTRUDA®) monotherapy. Cohort A participants were required to have been previously treated with standard therapies, which included fluoropyrimidine, oxaliplatin, and irinotecan. Cohort B, participants were required to have been previously treated with at least one line of systemic standard of care therapy: fluoropyrimidine + oxaliplatin or fluoropyrimidine + irinotecan +/ - anti-vascular endothelial growth factor (VEGF)/ epidermal growth factor regulator (EGFR) monoclonal antibody. The primary hypothesis is that Objective Response Rate (ORR) based on Response Evaluation Criteria in Solid Tumors v1.1 (RECIST 1.1) assessed by central imaging vendor in participants with locally advanced unresectable or metastatic MMR deficient or MSI high CRC is greater than 15%.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 August 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Israel: 8
Country: Number of subjects enrolled	Japan: 13
Country: Number of subjects enrolled	Korea, Republic of: 17
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	United States: 37
Worldwide total number of subjects	124
EEA total number of subjects	38

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)	80
From 65 to 84 years	44
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 34 clinical sites in 10 countries.

Pre-assignment

Screening details:

Participant flow as per the database cutoff date of 19FEB2021.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort A - Pembrolizumab 200 mg

Arm description:

Participants were previously treated with standard therapies, which included fluoropyrimidine, oxaliplatin, and irinotecan. Cohort A participants received pembrolizumab 200 mg intravenously (IV) on Day 1 of every 3-week cycle (Q3W) for up to approximately 52 cycles (up to approximately 3 years), which included a first course of 35 cycles and second course treatment phase of 17 cycles after experiencing PD if criteria were met for re-treatment.

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab 200 mg
Investigational medicinal product code	
Other name	KEYTRUDA® MK-3475
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV Infusion

Arm title	Cohort B - Pembrolizumab 200 mg

Arm description:

Participants were previously treated with at least one line of systemic standard of care therapy: fluoropyrimidine + oxaliplatin or fluoropyrimidine + irinotecan +/ - anti vascular endothelial growth factor (VEGF)/ epidermal growth factor regulator (EGFR) monoclonal antibody. Cohort B participants received pembrolizumab 200 mg IV on Day 1 Q3W for up to approximately 52 cycles (up to approximately 3 years), which included a first course of 35 cycles and second course treatment phase of 17 cycles after experiencing PD if criteria were met for re-treatment.

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab 200 mg
Investigational medicinal product code	
Other name	KEYTRUDA® MK-3475
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV Infusion

Number of subjects in period 1	Cohort A - Pembrolizumab 200 mg	Cohort B - Pembrolizumab 200 mg
Started	61	63
Completed	0	0
Not completed	61	63
Site Terminated By Sponsor	-	1
Consent withdrawn by subject	2	4
Adverse event, non-fatal	1	3
Death	36	28
Lost to follow-up	1	1
Transferred to extension study	15	15
Did Not Continue on Extension Study	6	11

Baseline characteristics

Reporting groups	
Reporting group title	Cohort A - Pembrolizumab 200 mg
Reporting group description:	
Participants were previously treated with standard therapies, which included fluoropyrimidine, oxaliplatin, and irinotecan. Cohort A participants received pembrolizumab 200 mg intravenously (IV) on Day 1 of every 3-week cycle (Q3W) for up to approximately 52 cycles (up to approximately 3 years), which included a first course of 35 cycles and second course treatment phase of 17 cycles after experiencing PD if criteria were met for re-treatment.	
Reporting group title	Cohort B - Pembrolizumab 200 mg
Reporting group description:	
Participants were previously treated with at least one line of systemic standard of care therapy: fluoropyrimidine + oxaliplatin or fluoropyrimidine + irinotecan +/ - anti vascular endothelial growth factor (VEGF)/ epidermal growth factor regulator (EGFR) monoclonal antibody. Cohort B participants received pembrolizumab 200 mg IV on Day 1 Q3W for up to approximately 52 cycles (up to approximately 3 years), which included a first course of 35 cycles and second course treatment phase of 17 cycles after experiencing PD if criteria were met for re-treatment.	

Reporting group values	Cohort A - Pembrolizumab 200 mg	Cohort B - Pembrolizumab 200 mg	Total
Number of subjects	61	63	124
Age categorical Units: Participants			
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)	42	38	80
From 65-84 years	19	25	44
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	54.3	57.8	
standard deviation	± 14.5	± 15.2	-
Sex: Female, Male Units: Participants			
Female	25	30	55
Male	36	33	69
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	19	14	33
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	7	7
White	42	42	84
More than one race	0	0	0

Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	3	4
Not Hispanic or Latino	59	60	119
Unknown or Not Reported	1	0	1

End points

End points reporting groups

Reporting group title	Cohort A - Pembrolizumab 200 mg

Reporting group description:

Participants were previously treated with standard therapies, which included fluoropyrimidine, oxaliplatin, and irinotecan. Cohort A participants received pembrolizumab 200 mg intravenously (IV) on Day 1 of every 3-week cycle (Q3W) for up to approximately 52 cycles (up to approximately 3 years), which included a first course of 35 cycles and second course treatment phase of 17 cycles after experiencing PD if criteria were met for re-treatment.

Reporting group title	Cohort B - Pembrolizumab 200 mg

Reporting group description:

Participants were previously treated with at least one line of systemic standard of care therapy: fluoropyrimidine + oxaliplatin or fluoropyrimidine + irinotecan +/ - anti vascular endothelial growth factor (VEGF)/ epidermal growth factor regulator (EGFR) monoclonal antibody. Cohort B participants received pembrolizumab 200 mg IV on Day 1 Q3W for up to approximately 52 cycles (up to approximately 3 years), which included a first course of 35 cycles and second course treatment phase of 17 cycles after experiencing PD if criteria were met for re-treatment.

Primary: Objective Response Rate (ORR) - Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) Assessed by Central Imaging Vendor

End point title	Objective Response Rate (ORR) - Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) Assessed by Central Imaging Vendor[1]

End point description:

Objective response rate was defined as the percentage of the participants in the analysis population who had a complete response (CR) or partial response (PR). Complete Response: disappearance of all target lesions. Partial Response: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Responses were based upon blinded central imaging vendor per RECIST 1.1. The point estimate and 95% confidence interval for the ORR, were provided using an exact binomial distribution (Clopper and Pearson method). Participants without response data were counted as nonresponders. The analysis population consisted of all participants who received at least one dose of study treatment. The data cutoff date was 09-SEPT-2019.

End point type	Primary

End point timeframe:

Up to approximately 48 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were planned for this endpoint.

End point values	Cohort A - Pembrolizumab 200 mg	Cohort B - Pembrolizumab 200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	63		
Units: Percentage of participants				
number (confidence interval 95%)	32.8 (21.3 to 46.0)	34.9 (23.3 to 48.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) per RECIST 1.1 Assessed by Central Imaging Vendor.

End point title	Disease Control Rate (DCR) per RECIST 1.1 Assessed by Central Imaging Vendor.

End point description:

Disease Control Rate was defined as the percentage of participants who achieved confirmed CR or PR or had demonstrated stable disease (SD) for at least 24 weeks prior to any evidence of progression. Complete Response: disappearance of all target lesions. Partial Response: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Stable Disease: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD), taking as reference the smallest sum diameters while on study. Progressive Disease: at least a 20% increase in the sum of diameters of target lesions and an absolute increase of at least 5 mm. or the appearance of new lesion(s). Participants in the analysis population with missing DCR were considered as disease not under control. The analysis population consisted of all participants who received at least one dose of study treatment. The data cutoff date was 19-Feb-2021.

End point type	Secondary

End point timeframe:

Up to approximately 66 months

End point values	Cohort A - Pembrolizumab 200 mg	Cohort B - Pembrolizumab 200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	63		
Units: Percentage of participants				
number (confidence interval 95%)	50.8 (37.7 to 63.9)	55.6 (42.5 to 68.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) per RECIST 1.1 Assessed by Central Imaging Vendor.

End point title	Progression-Free Survival (PFS) per RECIST 1.1 Assessed by Central Imaging Vendor.

End point description:

PFS is defined as the time from first day of study treatment to the first documented disease progression or death due to any cause, whichever occurs first. Progressive Disease: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must have also demonstrated an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions was also considered progression). PFS was summarized by Kaplan-Meier (KM) methods. The analysis population consisted of all participants who received at least one dose of study treatment. The data cutoff date was 19-FEB-2021.

End point type	Secondary

End point timeframe:

Up to approximately 66 months

End point values	Cohort A - Pembrolizumab 200 mg	Cohort B - Pembrolizumab 200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	63		
Units: Months				
median (confidence interval 95%)	2.3 (2.1 to 8.1)	4.1 (2.1 to 18.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as the time from first day of study treatment to death due to any cause. Participants without documented death at the time of analysis are censored at the date of the last follow-up. OS was summarized by Kaplan-Meier (KM) methods. The analysis population consisted of all participants who received at least one dose of study treatment. "9999" indicates OS upper limit was not reached for Cohort B. The data cutoff date was 19-FEB-2021.

End point type	Secondary

End point timeframe:

Up to approximately 66 months

End point values	Cohort A - Pembrolizumab 200 mg	Cohort B - Pembrolizumab 200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	63		
Units: Months				
median (confidence interval 95%)	31.4 (21.4 to 58)	47 (19.2 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experienced an Adverse Event (AE).

End point title	Number of Participants Who Experienced an Adverse Event (AE).

End point description:

An adverse event (AE) was defined as any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease associated with the use of a medical treatment or procedure,

regardless of whether it was considered related to the medical treatment or procedure, that occurred during the course of the study. The analysis population consisted of all participants who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Up to approximately 66 months

End point values	Cohort A - Pembrolizumab 200 mg	Cohort B - Pembrolizumab 200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	63		
Units: Participants	60	63		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Discontinued Study Treatment Due to an AE.

End point title	Number of Participants Who Discontinued Study Treatment Due to an AE.

End point description:

An adverse event (AE) was defined as any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it was considered related to the medical treatment or procedure, that occurred during the course of the study. The analysis population consisted of all participants who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Up to approximately 36 months

End point values	Cohort A - Pembrolizumab 200 mg	Cohort B - Pembrolizumab 200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	63		
Units: Participants	5	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) per RECIST 1.1 as Assessed by the Central

Imaging Vendor

End point title	Duration of Response (DOR) per RECIST 1.1 as Assessed by the Central Imaging Vendor

End point description:

For participants who demonstrated a CR or PR, duration of response was defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurred first. Complete Response: disappearance of all target lesions. Partial Response: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Responses were based upon blinded central imaging vendor per RECIST 1.1. Duration of Response was based on independent radiologist review (IRC) review using RECIST 1.1 and was summarized by Kaplan-Meier (KM) methods for censored data. Nonresponders were excluded from the analysis of DOR. The analysis population consisted of all participants who received at least one dose of study treatment and demonstrated a CR or PR. "9999" indicates median DOR and DOR upper limit for both cohorts A and B were not reached by the time of last disease assessment.

End point type	Secondary

End point timeframe:

Up to approximately 66 months

End point values	Cohort A - Pembrolizumab 200 mg	Cohort B - Pembrolizumab 200 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	22		
Units: Months				
median (full range (min-max))	9999 (6.2 to 9999)	9999 (4.4 to 9999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 66 months

Adverse event reporting additional description:

Adverse events were collected for a minimum of 30 days after the end of treatment and every 12 weeks during follow-up. The analysis population for AEs included all randomized participants who received at least one dose of study medication whereas the analysis population for deaths included all randomized participants.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Cohort A First Course

Reporting group description:

Participants were previously treated with standard therapies, which must include fluoropyrimidine, oxaliplatin, and irinotecan. Cohort A participants received pembrolizumab 200 mg intravenously (IV) on Day 1 of every 3-week cycle (Q3W) for up to approximately 35 cycles (up to approximately 2 years).

Reporting group title	Cohort A Second Course

Reporting group description:

Participants who completed first course of treatment were treated with pembrolizumab 200 mg intravenously (IV) on Day 1 of every 3-week cycle (Q3W) for up to 17 cycles (approximately 1 year) after experiencing PD if criteria were met for re-treatment.

Reporting group title	Cohort B Second Course

Reporting group description:

Participants who completed first course of treatment were treated with pembrolizumab 200 mg intravenously (IV) on Day 1 of every 3-week cycle (Q3W) for up to 17 cycles (approximately 1 year) after experiencing PD if criteria were met for re-treatment.

Reporting group title	Cohort B First Course

Reporting group description:

Participants were previously treated with at least one line of systemic standard of care therapy: fluoropyrimidine + oxaliplatin or fluoropyrimidine + irinotecan +/ - anti vascular endothelial growth factor (VEGF)/ epidermal growth factor regulator (EGFR) monoclonal antibody. Cohort B participants received pembrolizumab 200 mg IV on Day 1 Q3W for up to approximately 35 cycles (up to approximately 2 years).

Serious adverse events	Cohort A First Course	Cohort A Second Course	Cohort B Second Course
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 61 (50.82%)	1 / 6 (16.67%)	1 / 3 (33.33%)
number of deaths (all causes)	38	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to skin			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour associated fever			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Embolism			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iliac artery occlusion			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Euthanasia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
General physical health deterioration			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised oedema			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 61 (3.28%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Female genital tract fistula			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal haemorrhage			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Aspiration			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Dyspnoea			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	2 / 61 (3.28%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicide attempt			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device breakage			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood bilirubin increased			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Incisional hernia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			

alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus bradycardia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paralysis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corneal decompensation			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhegmatogenous retinal detachment			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 61 (4.92%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 61 (1.64%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocutaneous fistula			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric fistula			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal fistula			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 61 (4.92%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incarcerated umbilical hernia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumatosis intestinalis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biloma			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Erythema multiforme			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Autoimmune arthritis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flank pain			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle swelling			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal infection			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal wall abscess			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial pyelonephritis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella sepsis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 61 (3.28%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection bacterial			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Alkalosis hypochloraemic			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort B First Course		
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 63 (39.68%)		
number of deaths (all causes)	31		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Basal cell carcinoma			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to skin			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tumour associated fever				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tumour pain				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Embolism				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Iliac artery occlusion				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Euthanasia				
alternative dictionary used: MedDRA 23.1				

subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Generalised oedema				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Female genital tract fistula				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vaginal haemorrhage				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Aspiration				
alternative dictionary used: MedDRA 23.1				

subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	4 / 63 (6.35%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Suicide attempt				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Product issues				
Device breakage				
alternative dictionary used: MedDRA 23.1				

subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood bilirubin increased			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Incisional hernia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wrist fracture			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sinus bradycardia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Paralysis				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Cataract				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Corneal decompensation				
alternative dictionary used: MedDRA 23.1				

subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rhegmatogenous retinal detachment				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colitis				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	2 / 63 (3.17%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Duodenal ulcer				
alternative dictionary used: MedDRA 23.1				

subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Enteritis				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Enterocolitis				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterocutaneous fistula				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric fistula				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal fistula				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Ileus				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Incarcerated umbilical hernia				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower gastrointestinal haemorrhage				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumatosis intestinalis				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
alternative dictionary used: MedDRA 23.1				

subjects affected / exposed	3 / 63 (4.76%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Subileus				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Biloma				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystitis acute				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholelithiasis				
alternative dictionary used: MedDRA 23.1				

subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperbilirubinaemia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Erythema multiforme			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal failure			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Urinary tract obstruction			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Autoimmune arthritis			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Flank pain				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Muscle swelling				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Abdominal infection				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal wall abscess				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bacteraemia				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bacterial pyelonephritis				
alternative dictionary used: MedDRA 23.1				

subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Device related infection				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Klebsiella sepsis				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	4 / 63 (6.35%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 1			

Urinary tract infection				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	2 / 63 (3.17%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection bacterial				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	2 / 63 (3.17%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Alkalosis hypochloraemic				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dehydration				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Malnutrition				
alternative dictionary used: MedDRA 23.1				

subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Cohort A First Course	Cohort A Second Course	Cohort B Second Course
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 61 (91.80%)	5 / 6 (83.33%)	3 / 3 (100.00%)
Vascular disorders			
Hypertension			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	4 / 61 (6.56%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	4	0	0
General disorders and administration site conditions			
Asthenia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	14 / 61 (22.95%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	20	0	0
Chills			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 61 (4.92%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	4	0	0
Fatigue			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	19 / 61 (31.15%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	24	1	0
Influenza like illness			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	4 / 61 (6.56%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	5	0	0
Malaise			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	2 / 61 (3.28%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Oedema peripheral			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	11 / 61 (18.03%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	12	0	1
Pyrexia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	13 / 61 (21.31%)	2 / 6 (33.33%)	0 / 3 (0.00%)
occurrences (all)	22	5	0
Reproductive system and breast disorders			
Pelvic pain			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 61 (3.28%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	15 / 61 (24.59%)	1 / 6 (16.67%)	1 / 3 (33.33%)
occurrences (all)	20	1	1
Dysphonia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Dyspnoea			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	9 / 61 (14.75%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	10	0	0
Epistaxis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	3 / 61 (4.92%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	3	0	1
Productive cough			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	4 / 61 (6.56%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	4	0	0
Psychiatric disorders			
Depression			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 61 (3.28%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	3	1	0
Drug dependence			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Insomnia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	8 / 61 (13.11%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	8	1	0
Investigations			
Alanine aminotransferase increased			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	8 / 61 (13.11%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	11	0	0
Aspartate aminotransferase increased			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	6 / 61 (9.84%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	9	0	0
Blood alkaline phosphatase increased			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	5 / 61 (8.20%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	5	0	0
Blood bilirubin increased			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	2 / 61 (3.28%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Blood creatinine increased			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	5 / 61 (8.20%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	7	0	1
Weight decreased			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	7 / 61 (11.48%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	7	1	0
Injury, poisoning and procedural complications			
Fall			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 61 (3.28%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	2	0	1
Limb injury			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Stoma site pruritus			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Nervous system disorders			
Amnesia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Dizziness			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	4 / 61 (6.56%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	5	0	0
Dysgeusia			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Headache			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	9 / 61 (14.75%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	11	1	0
Neuropathy peripheral			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	4 / 61 (6.56%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	6	0	0
Paraesthesia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 61 (3.28%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	4	1	0
Blood and lymphatic system disorders			
Anaemia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	12 / 61 (19.67%)	2 / 6 (33.33%)	1 / 3 (33.33%)
occurrences (all)	21	4	1
Ear and labyrinth disorders			
Tinnitus			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Eye disorders			
Dry eye			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	4 / 61 (6.56%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	4	0	0
Ocular discomfort			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Gastrointestinal disorders			

Abdominal discomfort			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	4 / 61 (6.56%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	5	0	0
Abdominal distension			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	4 / 61 (6.56%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	4	0	0
Abdominal pain			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	18 / 61 (29.51%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	26	1	0
Angular cheilitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Colitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 61 (3.28%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Constipation			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	13 / 61 (21.31%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	15	1	0
Diarrhoea			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	23 / 61 (37.70%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	46	2	0
Dyspepsia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	5 / 61 (8.20%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	7	1	0
Nausea			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	22 / 61 (36.07%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	32	0	0
Proctalgia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 61 (3.28%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	3	0	1
Stomatitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 61 (4.92%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	3	0	2
Toothache			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 61 (3.28%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Vomiting			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	18 / 61 (29.51%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	37	2	0
Skin and subcutaneous tissue disorders			
Dermal cyst			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Dry skin			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	4 / 61 (6.56%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	4	0	0
Night sweats			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 61 (3.28%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Pruritus			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	11 / 61 (18.03%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	15	1	0
Rash			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	8 / 61 (13.11%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	13	0	0
Rash maculo-papular			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 61 (3.28%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Solar lentigo			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Urticaria			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 61 (3.28%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Renal and urinary disorders			
Dysuria			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	4 / 61 (6.56%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	4	0	0
Haematuria			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 61 (3.28%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	5	2	0
Urinary tract discomfort			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Endocrine disorders			
Hyperthyroidism			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	4 / 61 (6.56%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	5	1	0
Hypothyroidism			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	6 / 61 (9.84%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	6	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	15 / 61 (24.59%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	26	0	1
Back pain			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	8 / 61 (13.11%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	8	0	0
Flank pain			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 61 (4.92%)	1 / 6 (16.67%)	1 / 3 (33.33%)
occurrences (all)	9	2	1
Muscle spasms			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	4 / 61 (6.56%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	4	0	0
Myalgia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	6 / 61 (9.84%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	7	1	0
Pain in extremity			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	5 / 61 (8.20%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	6	0	2
Infections and infestations			
Conjunctivitis			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	4 / 61 (6.56%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	6	0	0
Enterocolitis infectious			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Folliculitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Gingivitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Groin abscess			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Nasopharyngitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	7 / 61 (11.48%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	9	0	1
Sinusitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	4 / 61 (6.56%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	8	0	0
Upper respiratory tract infection			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	8 / 61 (13.11%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	13	1	0
Urinary tract infection			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	4 / 61 (6.56%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	7	1	0

Wound infection			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 61 (3.28%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Metabolism and nutrition disorders			
Decreased appetite			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	14 / 61 (22.95%)	2 / 6 (33.33%)	0 / 3 (0.00%)
occurrences (all)	16	3	0
Hypoalbuminaemia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	5 / 61 (8.20%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	5	1	0
Hypocalcaemia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 61 (1.64%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Hypokalaemia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 61 (4.92%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	5	0	0
Hypomagnesaemia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 61 (3.28%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	12	1	0
Polydipsia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 61 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1

Non-serious adverse events	Cohort B First Course		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	58 / 63 (92.06%)		
Vascular disorders			

Hypertension			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	5 / 63 (7.94%)		
occurrences (all)	9		
General disorders and administration site conditions			
Asthenia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	5 / 63 (7.94%)		
occurrences (all)	6		
Chills			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	4		
Fatigue			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	24 / 63 (38.10%)		
occurrences (all)	29		
Influenza like illness			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	7 / 63 (11.11%)		
occurrences (all)	11		
Malaise			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 63 (4.76%)		
occurrences (all)	3		
Oedema peripheral			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	10 / 63 (15.87%)		
occurrences (all)	10		
Pyrexia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	11 / 63 (17.46%)		
occurrences (all)	19		
Reproductive system and breast disorders			

Pelvic pain			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	9 / 63 (14.29%)		
occurrences (all)	9		
Dysphonia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 63 (3.17%)		
occurrences (all)	2		
Dyspnoea			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	8 / 63 (12.70%)		
occurrences (all)	9		
Epistaxis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	5 / 63 (7.94%)		
occurrences (all)	5		
Oropharyngeal pain			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	4		
Productive cough			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences (all)	1		
Psychiatric disorders			
Depression			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	5 / 63 (7.94%)		
occurrences (all)	5		
Drug dependence			

alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences (all)	0		
Insomnia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	5 / 63 (7.94%)		
occurrences (all)	6		
Investigations			
Alanine aminotransferase increased			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	7 / 63 (11.11%)		
occurrences (all)	10		
Aspartate aminotransferase increased			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	5 / 63 (7.94%)		
occurrences (all)	7		
Blood alkaline phosphatase increased			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 63 (4.76%)		
occurrences (all)	3		
Blood bilirubin increased			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	4		
Blood creatinine increased			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 63 (4.76%)		
occurrences (all)	5		
Weight decreased			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			

Fall			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 63 (4.76%)		
occurrences (all)	3		
Limb injury			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences (all)	1		
Stoma site pruritus			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Amnesia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 63 (3.17%)		
occurrences (all)	2		
Dizziness			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 63 (4.76%)		
occurrences (all)	3		
Dysgeusia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences (all)	4		
Headache			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	8 / 63 (12.70%)		
occurrences (all)	16		
Neuropathy peripheral			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 63 (3.17%)		
occurrences (all)	2		
Paraesthesia			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 63 (1.59%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	11 / 63 (17.46%)		
occurrences (all)	13		
Ear and labyrinth disorders			
Tinnitus			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 63 (3.17%)		
occurrences (all)	2		
Eye disorders			
Dry eye			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 63 (3.17%)		
occurrences (all)	2		
Ocular discomfort			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal discomfort			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences (all)	1		
Abdominal distension			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 63 (4.76%)		
occurrences (all)	3		
Abdominal pain			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	14 / 63 (22.22%)		
occurrences (all)	18		
Angular cheilitis			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	1 / 63 (1.59%)			
occurrences (all)	1			
Colitis				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences (all)	0			
Constipation				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	13 / 63 (20.63%)			
occurrences (all)	14			
Diarrhoea				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	16 / 63 (25.40%)			
occurrences (all)	28			
Dyspepsia				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	9 / 63 (14.29%)			
occurrences (all)	9			
Nausea				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	17 / 63 (26.98%)			
occurrences (all)	26			
Proctalgia				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	2 / 63 (3.17%)			
occurrences (all)	3			
Stomatitis				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	3 / 63 (4.76%)			
occurrences (all)	5			
Toothache				
alternative dictionary used: MedDRA 23.1				
subjects affected / exposed	2 / 63 (3.17%)			
occurrences (all)	2			

Vomiting			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	14 / 63 (22.22%)		
occurrences (all)	18		
Skin and subcutaneous tissue disorders			
Dermal cyst			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences (all)	1		
Dry skin			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	5 / 63 (7.94%)		
occurrences (all)	8		
Night sweats			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	5 / 63 (7.94%)		
occurrences (all)	5		
Pruritus			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	8 / 63 (12.70%)		
occurrences (all)	9		
Rash			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	9 / 63 (14.29%)		
occurrences (all)	18		
Rash maculo-papular			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	5		
Solar lentigo			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences (all)	1		
Urticaria			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	2 / 63 (3.17%)		
occurrences (all)	2		
Renal and urinary disorders			
Dysuria			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences (all)	1		
Haematuria			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 63 (3.17%)		
occurrences (all)	2		
Urinary tract discomfort			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences (all)	1		
Endocrine disorders			
Hyperthyroidism			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	7 / 63 (11.11%)		
occurrences (all)	7		
Hypothyroidism			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	13 / 63 (20.63%)		
occurrences (all)	15		
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	16 / 63 (25.40%)		
occurrences (all)	19		
Back pain			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	14 / 63 (22.22%)		
occurrences (all)	18		
Flank pain			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	3 / 63 (4.76%)		
occurrences (all)	3		
Muscle spasms			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 63 (4.76%)		
occurrences (all)	3		
Myalgia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	7 / 63 (11.11%)		
occurrences (all)	7		
Pain in extremity			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	5 / 63 (7.94%)		
occurrences (all)	8		
Infections and infestations			
Conjunctivitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences (all)	0		
Enterocolitis infectious			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences (all)	0		
Folliculitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences (all)	0		
Gingivitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences (all)	0		
Groin abscess			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	0 / 63 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 63 (3.17%)		
occurrences (all)	2		
Sinusitis			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 63 (3.17%)		
occurrences (all)	2		
Upper respiratory tract infection			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	8 / 63 (12.70%)		
occurrences (all)	10		
Urinary tract infection			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	5 / 63 (7.94%)		
occurrences (all)	7		
Wound infection			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Decreased appetite			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	11 / 63 (17.46%)		
occurrences (all)	13		
Hypoalbuminaemia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences (all)	1		
Hypocalcaemia			
alternative dictionary used: MedDRA 23.1			

subjects affected / exposed	6 / 63 (9.52%)		
occurrences (all)	7		
Hypokalaemia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	14		
Hypomagnesaemia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	3 / 63 (4.76%)		
occurrences (all)	3		
Polydipsia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 August 2015	Amendment 1: The protocol was updated to reflect routine clinical practice and to allow enrollment flexibility when defining previous treatments.
27 November 2015	Amendment 2: The protocol was updated to further clarify prior treatments a subject should have received in order to be eligible for participation in the study.
06 May 2016	Amendment 3: The protocol was updated to include a second cohort of 60 subjects added to evaluate pembrolizumab 200 mg 3QW in subjects with CRC who have undergone 1 line of systemic treatment (fluoropyrimidine + oxaliplatin or fluoropyrimidine + irinotecan +/- anti-VEGF/EGFR monoclonal antibody). The first cohort was designated Cohort A, the second, Cohort B.
10 February 2017	Amendment 4: The protocol was amended to allow additional follow-up analysis to be performed. For Cohort A, the planned interim analysis was to be performed after the first 40 treated subjects have been followed up for at least 18 weeks. However, due to the rapid enrollment of the remaining subjects in Cohort A, it was decided to be conducted after all 61 subject enrolled in Cohort A had been followed up for at least 18 weeks. With this change, the group sequential approach based on the first 40 subjects as originally planned was no longer applicable.
13 February 2018	Amendment 7: The protocol was updated to add guidelines in the event of dose modification and toxicity management. Guidelines for pembrolizumab were modified to add guidelines in the event of myocarditis and updated guidelines for several other conditions.
21 January 2020	Amendment 8: The protocol was updated to allow participants access to an extension study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported