Clinical trial results:
A Multi-Centre Randomised Clinical Trial of Biomarker-Driven Maintenance Treatment for First-Line Metastatic Colorectal Cancer (MODUL)

Summary

EudraCT number	2014-001017-61
Trial protocol	IT GB DE PT DK SK NL FR SE BE GR ES SI CY
Global end of trial date	24 March 2021

Results information

Result version number	v2
This version publication date	19 March 2022
First version publication date	12 June 2020
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	MO29112

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02291289
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com
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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	24 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 May 2019
Global end of trial reached?	Yes
Global end of trial date	24 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study is to evaluate the progression free survival (PFS) within each cohort.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 April 2015
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	Argentina: 4
Country: Number of subjects enrolled	Belgium: 25
Country: Number of subjects enrolled	Bosnia and Herzegovina: 5
Country: Number of subjects enrolled	Brazil: 41
Country: Number of subjects enrolled	Denmark: 15
Country: Number of subjects enrolled	Egypt: 5
Country: Number of subjects enrolled	France: 54
Country: Number of subjects enrolled	Germany: 94
Country: Number of subjects enrolled	Greece: 36
Country: Number of subjects enrolled	Italy: 95
Country: Number of subjects enrolled	Mexico: 17
Country: Number of subjects enrolled	Netherlands: 16
Country: Number of subjects enrolled	Poland: 21
Country: Number of subjects enrolled	Portugal: 12
Country: Number of subjects enrolled	Korea, Republic of: 25
Country: Number of subjects enrolled	Russian Federation: 8
Country: Number of subjects enrolled	Serbia: 9
Country: Number of subjects enrolled	Slovakia: 1
Country: Number of subjects enrolled	Spain: 45
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	Turkey: 27
Country: Number of subjects enrolled	United Kingdom: 62

Worldwide total number of subjects	620
EEA total number of subjects	417

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)	370
From 65 to 84 years	248
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

To be eligible for the study, patients provided a primary tumour sample for biomarker assessment. This sample from the original diagnosis was used for the biomarker assessment which determined treatment assignment during the Maintenance Treatment Phase.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1

Arm description:

All participants will receive either eight 2-week cycles of 5-fluorouracil (5-FU)/ leucovorin calcium (LV) and oxaliplatin (FOLFOX) in combination with bevacizumab, or six 2-week cycles of FOLFOX in combination with bevacizumab, followed by two 2-week cycles of 5-FU/LV with bevacizumab.

Arm type	Induction Treatment
Investigational medicinal product name	5-fluorouracil (5-FU), leucovorin calcium (LV), and Oxaliplatin (FOLFOX)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered per the Investigator's discretion in accordance with locally approved prescribing information.

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

Dosage and administration details:

1600-2400 mg/m^2 5-FU via 46-hour IV infusion in combination with 400 mg/m^2 LV via 2-hour infusion on Day 1 of every 2-week cycle until disease progression or death from any cause, whichever occurs first.

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

Dosage and administration details:

5 mg/kg bevacizumab via 15-30 minute IV infusion on Day 1 of every 2-week cycle per local prescribing information

Arm title	Cohort 2

Arm description:

All participants will receive either eight 2-week cycles of 5-fluorouracil (5-FU)/ leucovorin calcium (LV) and oxaliplatin (FOLFOX) in combination with bevacizumab, or six 2-week cycles of FOLFOX in

combination with bevacizumab, followed by two 2-week cycles of 5-FU/LV with bevacizumab.

Arm type	Induction Treatment
Investigational medicinal product name	5-fluorouracil (5-FU), leucovorin calcium (LV), and Oxaliplatin (FOLFOX)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered per the Investigator's discretion in accordance with locally approved prescribing information.

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

Dosage and administration details:

1600-2400 mg/m^2 5-FU via 46-hour IV infusion in combination with 400 mg/m^2 LV via 2-hour infusion on Day 1 of every 2-week cycle until disease progression or death from any cause, whichever occurs first.

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

Dosage and administration details:

5 mg/kg bevacizumab via 15-30 minute IV infusion on Day 1 of every 2-week cycle per local prescribing information

Arm title	Cohort 3

Arm description:

All participants will receive either eight 2-week cycles of 5-fluorouracil (5-FU)/ leucovorin calcium (LV) and oxaliplatin (FOLFOX) in combination with bevacizumab, or six 2-week cycles of FOLFOX in combination with bevacizumab, followed by two 2-week cycles of 5-FU/LV with bevacizumab.

Arm type	Induction Treatment
Investigational medicinal product name	5-fluorouracil (5-FU), leucovorin calcium (LV), and Oxaliplatin (FOLFOX)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered per the Investigator's discretion in accordance with locally approved prescribing information.

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

Dosage and administration details:

1600-2400 mg/m^2 5-FU via 46-hour IV infusion in combination with 400 mg/m^2 LV via 2-hour infusion on Day 1 of every 2-week cycle until disease progression or death from any cause, whichever occurs first.

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin

Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5 mg/kg bevacizumab via 15-30 minute IV infusion on Day 1 of every 2-week cycle per local prescribing information

Arm title	Cohort 4

Arm description:

All participants will receive either eight 2-week cycles of 5-fluorouracil (5-FU)/ leucovorin calcium (LV) and oxaliplatin (FOLFOX) in combination with bevacizumab, or six 2-week cycles of FOLFOX in combination with bevacizumab, followed by two 2-week cycles of 5-FU/LV with bevacizumab.

Arm type	Induction Treatment
Investigational medicinal product name	5-fluorouracil (5-FU), leucovorin calcium (LV), and Oxaliplatin (FOLFOX)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered per the Investigator's discretion in accordance with locally approved prescribing information.

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

Dosage and administration details:

1600-2400 mg/m^2 5-FU via 46-hour IV infusion in combination with 400 mg/m^2 LV via 2-hour infusion on Day 1 of every 2-week cycle until disease progression or death from any cause, whichever occurs first.

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

Dosage and administration details:

5 mg/kg bevacizumab via 15-30 minute IV infusion on Day 1 of every 2-week cycle per local prescribing information

Arm title	Early Progressing BRAFmut Cohort

Arm description:

BRAFmut participants experiencing early disease progression during induction treatment

Arm type	Induction Treatment
Investigational medicinal product name	5-fluorouracil (5-FU), leucovorin calcium (LV), and Oxaliplatin (FOLFOX)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered per the Investigator's discretion in accordance with locally approved prescribing information.

Investigational medicinal product name	5-FU/LV
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion

Routes of administration	Intravenous use

Dosage and administration details:

1600-2400 mg/m^2 5-FU via 46-hour IV infusion in combination with 400 mg/m^2 LV via 2-hour infusion on Day 1 of every 2-week cycle until disease progression or death from any cause, whichever occurs first.

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

Dosage and administration details:

5 mg/kg bevacizumab via 15-30 minute IV infusion on Day 1 of every 2-week cycle per local prescribing information

Number of subjects in period 1	Cohort 1	Cohort 2	Cohort 3
Started	60	445	5
Completed	58	436	5
Not completed	2	9	0
Not Dosed	2	9	-

Number of subjects in period 1	Cohort 4	Early Progressing BRAFmut Cohort
Started	99	11
Completed	98	11
Not completed	1	0
Not Dosed	1	-

Period 2

Period 2 title	Maintenance Treatment Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Cohort 1: 5-FU/LV,cetuximab,vemurafenib

Arm description:

Participants with v-raf murine sarcoma viral oncogene homolog B1 mutation positive (BRAFmut)/human epidermal growth factor receptor 2 negative (HER2-)/microsatellite stable (MSS)/rat sarcoma wild type (RASwt) will receive 1600-2400 milligrams per square meter (mg/m^2) 5-FU via 46-hour intravenous (IV) infusion in combination with 400 mg/m^2 LV via 2-hour infusion on Day 1 of every 2-week cycle with 500 mg/m^2 cetuximab via infusion on Day 1 of every 2-week cycle and 960 milligrams (mg) vemurafenib twice daily (BID) by mouth.

Arm type	Experimental

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

Dosage and administration details:

500 mg/m^2 via IV infusion on Day 1 of every 2-week cycle

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

Dosage and administration details:

1600-2400 mg/m^2 5-FU via 46-hour IV infusion in combination with 400 mg/m^2 LV via 2-hour infusion on Day 1 of every 2-week cycle until disease progression per the Investigator's assessment using modified Response Evaluation Criteria in Solid Tumors or death from any cause, whichever occurs first.

Investigational medicinal product name	Vemurafenib
Investigational medicinal product code	
Other name	RO5185426
Pharmaceutical forms	Solution for infusion, Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

960 mg vermurafenib BID by mouth

Arm title	Cohort 1 Control: 5-FU/LV or capecitabin, bevacizumab

Arm description:

Per Investigator discretion, participants will receive fluoropyrimidine (5-FU/LV or capecitabine) at a dose and schedule per the Investigator's discretion in accordance with locally approved prescribing information and 5 mg/kg bevacizumab via 1-30 minute IV on Day 1 of every 2-week cycle.

Arm type	Active comparator
Investigational medicinal product name	5-FU/LV or capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Per Investigator's discretion: 1600-2400 mg/m^2 administered via 46-hour IV infusion on Day 1 of every 2-week cycle and LV 400 mg/m^2 administered via a 2-hour infusion on Day 1 every 2 weeks or 1000 mg/m^2 twice-daily capecitabine (BID) by mouth given days 1-14 every 2 weeks. The chosen fluoropyrimidine should be administered in accordance with local prescribing information.

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

Dosage and administration details:

1600-2400 mg/m^2 5-FU via 46-hour IV infusion in combination with 400 mg/m^2 LV via 2-hour infusion on Day 1 of every 2-week cycle until disease progression per the Investigator's assessment using modified Response Evaluation Criteria in Solid Tumors or death from any cause, whichever occurs first.

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

Dosage and administration details:

5 mg/kg bevacizumab via 15-30 minute IV infusion on Day 1 of every 2-week cycle per local prescribing information

Arm title	Cohort 2: 5-FU/LV or capecitabine,bevacizumab,atezolizumab

Arm description:

Participants with BRAFwt will receive fluoropyrimidine (1600-2400 mg/m^2 5-FU via 46-hour IV infusion in combination with 400 mg/m^2 LV via 2-hour infusion on Day 1 of every 2-week cycle or 1000 mg/m^2 twice-daily capecitabine BID by mouth on Days 1-14 every 2 weeks followed by a 1-week break) with 5 milligrams per kilogram (mg/kg) bevacizumab via 15-30 minute IV infusion on Day 1 of every 2-week cycle and 800 mg atezolizumab via 60-minute IV infusion on Day 1 of every 2-week cycle.

Arm type	Experimental
Investigational medicinal product name	5-FU/LV or capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Per Investigator's discretion: 1600-2400 mg/m^2 administered via 46-hour IV infusion on Day 1 of every 2-week cycle and LV 400 mg/m^2 administered via a 2-hour infusion on Day 1 every 2 weeks or 1000 mg/m^2 twice-daily capecitabine (BID) by mouth given days 1-14 every 2 weeks. The chosen fluoropyrimidine should be administered in accordance with local prescribing information.

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

Dosage and administration details:

800 mg atezolizumab via 60-minute IV infusion on Day 1 of every 2-week cycle, or a fixed dose of 840 mg

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

Dosage and administration details:

5 mg/kg bevacizumab via 15-30 minute IV infusion on Day 1 of every 2-week cycle per local prescribing information

Arm title	Cohort 2 Control: 5-FU/LV or capecitabin, bevacizumab

Arm description:

Per Investigator discretion, participants will receive fluoropyrimidine (5-FU/LV or capecitabine) at a dose and schedule per the Investigator's discretion in accordance with locally approved prescribing information and 5 mg/kg bevacizumab via 1-30 minute IV on Day 1 of every 2-week cycle.

Arm type	Active comparator
Investigational medicinal product name	5-FU/LV or capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Per Investigator's discretion: 1600-2400 mg/m^2 administered via 46-hour IV infusion on Day 1 of every 2-week cycle and LV 400 mg/m^2 administered via a 2-hour infusion on Day 1 every 2 weeks or 1000 mg/m^2 twice-daily capecitabine (BID) by mouth given days 1-14 every 2 weeks. The chosen fluoropyrimidine should be administered in accordance with local prescribing information.

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

Dosage and administration details:

5 mg/kg bevacizumab via 15-30 minute IV infusion on Day 1 of every 2-week cycle per local prescribing information

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

Dosage and administration details:

1600-2400 mg/m^2 5-FU via 46-hour IV infusion in combination with 400 mg/m^2 LV via 2-hour infusion on Day 1 of every 2-week cycle until disease progression per the Investigator's assessment using modified Response Evaluation Criteria in Solid Tumors or death from any cause, whichever occurs first.

Arm title	Cohort 3: capecitabine,trastuzumab,pertuzumab

Arm description:

Participants with human epidermal growth factor receptor 2 positive (HER2+) will receive 1000 mg/m^2 twice-daily capecitabine BID by mouth on Days 1-14 every 2 weeks followed by a 1-week break with trastuzumab by IV infusion on Day 1 of every 3-week treatment cycle at an initial loading dose of 8 mg/kg followed by 6 mg/kg for subsequent doses, and pertuzumab by IV infusion on Day 1 of each 3-week treatment cycle at an initial fixed loading dose of 840 mg followed by 420 mg for subsequent doses.

Arm type	Experimental
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1000 mg/m^2 twice-daily capecitabine (BID) by mouth given days 1-14 every 2 weeks

Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	
Other name	RO4368451
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Initial fixed loading dose of 840 mg followed by 420 mg for subsequent doses by IV infusion on Day 1 of each 3-week treatment cycle

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	Herceptin; RO0452317
Pharmaceutical forms	Solution for infusion, Powder and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Initial loading dose of 8 mg/kg followed by 6 mg/kg for subsequent doses by IV infusion on Day 1 of every 3-week treatment cycle

Arm title	Cohort 3 Control: 5-FU/LV or capecitabin, bevacizumab

Arm description:

Per Investigator discretion, participants will receive fluoropyrimidine (5-FU/LV or capecitabine) at a dose and schedule per the Investigator's discretion in accordance with locally approved prescribing

information and 5 mg/kg bevacizumab via 1-30 minute IV on Day 1 of every 2-week cycle.

Arm type	Active comparator
Investigational medicinal product name	5-FU/LV or capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Per Investigator's discretion: 1600-2400 mg/m^2 administered via 46-hour IV infusion on Day 1 of every 2-week cycle and LV 400 mg/m^2 administered via a 2-hour infusion on Day 1 every 2 weeks or 1000 mg/m^2 twice-daily capecitabine (BID) by mouth given days 1-14 every 2 weeks. The chosen fluoropyrimidine should be administered in accordance with local prescribing information.

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

Dosage and administration details:

1600-2400 mg/m^2 5-FU via 46-hour IV infusion in combination with 400 mg/m^2 LV via 2-hour infusion on Day 1 of every 2-week cycle until disease progression per the Investigator's assessment using modified Response Evaluation Criteria in Solid Tumors or death from any cause, whichever occurs first.

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

Dosage and administration details:

5 mg/kg bevacizumab via 15-30 minute IV infusion on Day 1 of every 2-week cycle per local prescribing information

Arm title	Cohort 4: Cobimetinib,atezolizumab

Arm description:

Participants with HER2-/high microsatellite instability (MSI-H); HER2-/MSS/v-raf murine sarcoma viral oncogene homolog B1 wild type (BRAFwt); HER2-/MSS/BRAFmut/rat sarcoma mutation positive (RASmut) will receive 60 mg cobimetinib orally for 3 weeks followed by a 1-week treatment break and atezolizumab at a fixed dose of 840 mg via 60-minute IV infusion on Day 1 of every 2-week cycle.

Arm type	Experimental
Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	
Other name	RO5541267
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

800 mg atezolizumab via 60-minute IV infusion on Day 1 of every 2-week cycle, or a fixed dose of 840 mg

Investigational medicinal product name	Cobimetinib
Investigational medicinal product code	
Other name	RO5514041
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

60 mg orally once daily for 3 weeks followed by a 1-week treatment break

Arm title	Cohort 4 Control: 5-FU/LV or capecitabin, bevacizumab

Arm description:

Per Investigator discretion, participants will receive fluoropyrimidine (5-FU/LV or capecitabine) at a dose and schedule per the Investigator's discretion in accordance with locally approved prescribing information and 5 mg/kg bevacizumab via 1-30 minute IV on Day 1 of every 2-week cycle.

Arm type	Active comparator
Investigational medicinal product name	5-FU/LV or capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Per Investigator's discretion: 1600-2400 mg/m^2 administered via 46-hour IV infusion on Day 1 of every 2-week cycle and LV 400 mg/m^2 administered via a 2-hour infusion on Day 1 every 2 weeks or 1000 mg/m^2 twice-daily capecitabine (BID) by mouth given days 1-14 every 2 weeks. The chosen fluoropyrimidine should be administered in accordance with local prescribing information.

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

Dosage and administration details:

1600-2400 mg/m^2 5-FU via 46-hour IV infusion in combination with 400 mg/m^2 LV via 2-hour infusion on Day 1 of every 2-week cycle until disease progression per the Investigator's assessment using modified Response Evaluation Criteria in Solid Tumors or death from any cause, whichever occurs first.

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

Dosage and administration details:

5 mg/kg bevacizumab via 15-30 minute IV infusion on Day 1 of every 2-week cycle per local prescribing information

Number of subjects in period 2	Cohort 1: 5-FU/LV,cetuximab,vemurafenib	Cohort 1 Control: 5-FU/LV or capecitabin, bevacizumab	Cohort 2: 5-FU/LV or capecitabine,bevacizumab,atezolizumab
Started	40	20	297
Completed	16	4	45
Not completed	24	16	252
Adverse event, serious fatal	23	13	185
Consent withdrawn by subject	-	-	13
Physician decision	-	-	2
unknown	-	1	29
Adverse event, non-fatal	-	-	1
No Treatment Received	-	2	4
Multiple Reasons	-	-	4
Lost to follow-up	-	-	12

Protocol deviation	1	-	2

Number of subjects in period 2	Cohort 2 Control: 5-FU/LV or capecitabin, bevacizumab	Cohort 3: capecitabine,trastuzumab,pertuzumab	Cohort 3 Control: 5-FU/LV or capecitabin, bevacizumab
Started	148	3	2
Completed	19	1	0
Not completed	129	2	2
Adverse event, serious fatal	100	1	1
Consent withdrawn by subject	11	-	-
Physician decision	-	-	-
unknown	8	-	1
Adverse event, non-fatal	-	-	-
No Treatment Received	5	-	-
Multiple Reasons	1	-	-
Lost to follow-up	3	1	-
Protocol deviation	1	-	-

Number of subjects in period 2	Cohort 4: Cobimetinib,atezolizumab	Cohort 4 Control: 5-FU/LV or capecitabin, bevacizumab
Started	65	34
Completed	34	18
Not completed	31	16
Adverse event, serious fatal	26	11
Consent withdrawn by subject	2	3
Physician decision	-	1
unknown	-	-
Adverse event, non-fatal	-	-
No Treatment Received	1	-
Multiple Reasons	-	-
Lost to follow-up	2	1
Protocol deviation	-	-

Period 3

Period 3 title	Early Disease Progression
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Early Progressing BRAFmut Cohort

Arm description:

BRAFmut participants experiencing early disease progression during induction treatment will have the option of proceeding immediately to receive second-line treatment with 5-FU/LV, cetuximab and vemurafenib if their primary tumour is MSS, or with a fluoropyrimidine (5-FU/LV or capecitabine), bevacizumab, and atezolizumab if their primary tumour is MSI-H.

Arm type	Experimental
Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravascular use

Dosage and administration details:

500 mg/m^2 via IV infusion on Day 1 of every 2-week cycle

Investigational medicinal product name	Fluoropyrimidine (5-FU/LV or capecitabine)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Per Investigator's discretion: 1600-2400 mg/m^2 administered via 46-hour IV infusion on Day 1 of every 2-week cycle and LV 400 mg/m^2 administered via a 2-hour infusion on Day 1 every 2 weeks or 1000 mg/m^2 twice-daily capecitabine (BID) by mouth given days 1-14 every 2 weeks. The chosen fluoropyrimidine should be administered in accordance with local prescribing information.

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

Dosage and administration details:

1600-2400 mg/m^2 5-FU via 46-hour IV infusion in combination with 400 mg/m^2 LV via 2-hour infusion on Day 1 of every 2-week cycle until disease progression per the Investigator's assessment using modified Response Evaluation Criteria in Solid Tumors or death from any cause, whichever occurs first.

Investigational medicinal product name	Vemurafenib
Investigational medicinal product code	
Other name	RO5185426
Pharmaceutical forms	Solution for infusion, Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

960 mg vermurafenib BID by mouth

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

Dosage and administration details:

5 mg/kg bevacizumab via 15-30 minute IV infusion on Day 1 of every 2-week cycle per local prescribing information

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

Dosage and administration details:

800 mg atezolizumab via 60-minute IV infusion on Day 1 of every 2-week cycle, or a fixed dose of 840 mg

Number of subjects in period 3	Early Progressing BRAFmut Cohort
Started	11
Completed	1
Not completed	10
Adverse event, serious fatal	9
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1
Reporting group description:	
All participants will receive either eight 2-week cycles of 5-fluorouracil (5-FU)/ leucovorin calcium (LV) and oxaliplatin (FOLFOX) in combination with bevacizumab, or six 2-week cycles of FOLFOX in combination with bevacizumab, followed by two 2-week cycles of 5-FU/LV with bevacizumab.	
Reporting group title	Cohort 2
Reporting group description:	
All participants will receive either eight 2-week cycles of 5-fluorouracil (5-FU)/ leucovorin calcium (LV) and oxaliplatin (FOLFOX) in combination with bevacizumab, or six 2-week cycles of FOLFOX in combination with bevacizumab, followed by two 2-week cycles of 5-FU/LV with bevacizumab.	
Reporting group title	Cohort 3
Reporting group description:	
All participants will receive either eight 2-week cycles of 5-fluorouracil (5-FU)/ leucovorin calcium (LV) and oxaliplatin (FOLFOX) in combination with bevacizumab, or six 2-week cycles of FOLFOX in combination with bevacizumab, followed by two 2-week cycles of 5-FU/LV with bevacizumab.	
Reporting group title	Cohort 4
Reporting group description:	
All participants will receive either eight 2-week cycles of 5-fluorouracil (5-FU)/ leucovorin calcium (LV) and oxaliplatin (FOLFOX) in combination with bevacizumab, or six 2-week cycles of FOLFOX in combination with bevacizumab, followed by two 2-week cycles of 5-FU/LV with bevacizumab.	
Reporting group title	Early Progressing BRAFmut Cohort
Reporting group description:	
BRAFmut participants experiencing early disease progression during induction treatment	

Reporting group values	Cohort 1	Cohort 2	Cohort 3
Number of subjects	60	445	5
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)	39	254	5
From 65-84 years	21	189	0
85 years and over	0	2	0
Age Continuous Units: years			
arithmetic mean	59.2	60.6	49.6
standard deviation	± 11.0	± 12.3	± 7.4
Sex: Female, Male Units:			
Female	34	174	3
Male	26	271	2

Reporting group values	Cohort 4	Early Progressing	Total

		BRAFmut Cohort	
Number of subjects	99	11	620
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)	66	6	370
From 65-84 years	33	5	248
85 years and over	0	0	2
Age Continuous Units: years			
arithmetic mean	59.5	60.0	
standard deviation	± 10.2	± 17.8	-
Sex: Female, Male Units:			
Female	41	6	258
Male	58	5	362

End points

End points reporting groups

Reporting group title	Cohort 1
Reporting group description:	
All participants will receive either eight 2-week cycles of 5-fluorouracil (5-FU)/ leucovorin calcium (LV) and oxaliplatin (FOLFOX) in combination with bevacizumab, or six 2-week cycles of FOLFOX in combination with bevacizumab, followed by two 2-week cycles of 5-FU/LV with bevacizumab.	
Reporting group title	Cohort 2
Reporting group description:	
All participants will receive either eight 2-week cycles of 5-fluorouracil (5-FU)/ leucovorin calcium (LV) and oxaliplatin (FOLFOX) in combination with bevacizumab, or six 2-week cycles of FOLFOX in combination with bevacizumab, followed by two 2-week cycles of 5-FU/LV with bevacizumab.	
Reporting group title	Cohort 3
Reporting group description:	
All participants will receive either eight 2-week cycles of 5-fluorouracil (5-FU)/ leucovorin calcium (LV) and oxaliplatin (FOLFOX) in combination with bevacizumab, or six 2-week cycles of FOLFOX in combination with bevacizumab, followed by two 2-week cycles of 5-FU/LV with bevacizumab.	
Reporting group title	Cohort 4
Reporting group description:	
All participants will receive either eight 2-week cycles of 5-fluorouracil (5-FU)/ leucovorin calcium (LV) and oxaliplatin (FOLFOX) in combination with bevacizumab, or six 2-week cycles of FOLFOX in combination with bevacizumab, followed by two 2-week cycles of 5-FU/LV with bevacizumab.	
Reporting group title	Early Progressing BRAFmut Cohort
Reporting group description:	
BRAFmut participants experiencing early disease progression during induction treatment	
Reporting group title	Cohort 1: 5-FU/LV,cetuximab,vemurafenib
Reporting group description:	
Participants with v-raf murine sarcoma viral oncogene homolog B1 mutation positive (BRAFmut)/human epidermal growth factor receptor 2 negative (HER2-)/microsatellite stable (MSS)/rat sarcoma wild type (RASwt) will receive 1600-2400 milligrams per square meter (mg/m^2) 5-FU via 46-hour intravenous (IV) infusion in combination with 400 mg/m^2 LV via 2-hour infusion on Day 1 of every 2-week cycle with 500 mg/m^2 cetuximab via infusion on Day 1 of every 2-week cycle and 960 milligrams (mg) vemurafenib twice daily (BID) by mouth.	
Reporting group title	Cohort 1 Control: 5-FU/LV or capecitabin, bevacizumab
Reporting group description:	
Per Investigator discretion, participants will receive fluoropyrimidine (5-FU/LV or capecitabine) at a dose and schedule per the Investigator's discretion in accordance with locally approved prescribing information and 5 mg/kg bevacizumab via 1-30 minute IV on Day 1 of every 2-week cycle.	
Reporting group title	Cohort 2: 5-FU/LV or capecitabine,bevacizumab,atezolizumab
Reporting group description:	
Participants with BRAFwt will receive fluoropyrimidine (1600-2400 mg/m^2 5-FU via 46-hour IV infusion in combination with 400 mg/m^2 LV via 2-hour infusion on Day 1 of every 2-week cycle or 1000 mg/m^2 twice-daily capecitabine BID by mouth on Days 1-14 every 2 weeks followed by a 1-week break) with 5 milligrams per kilogram (mg/kg) bevacizumab via 15-30 minute IV infusion on Day 1 of every 2-week cycle and 800 mg atezolizumab via 60-minute IV infusion on Day 1 of every 2-week cycle.	
Reporting group title	Cohort 2 Control: 5-FU/LV or capecitabin, bevacizumab
Reporting group description:	
Per Investigator discretion, participants will receive fluoropyrimidine (5-FU/LV or capecitabine) at a dose and schedule per the Investigator's discretion in accordance with locally approved prescribing information and 5 mg/kg bevacizumab via 1-30 minute IV on Day 1 of every 2-week cycle.	
Reporting group title	Cohort 3: capecitabine,trastuzumab,pertuzumab
Reporting group description:	
Participants with human epidermal growth factor receptor 2 positive (HER2+) will receive 1000 mg/m^2 twice-daily capecitabine BID by mouth on Days 1-14 every 2 weeks followed by a 1-week break with trastuzumab by IV infusion on Day 1 of every 3-week treatment cycle at an initial loading dose of 8 mg/kg followed by 6 mg/kg for subsequent doses, and pertuzumab by IV infusion on Day 1 of each 3-week treatment cycle at an initial fixed loading dose of 840 mg followed by 420 mg for subsequent	

doses.

Reporting group title	Cohort 3 Control: 5-FU/LV or capecitabin, bevacizumab

Reporting group description:

Per Investigator discretion, participants will receive fluoropyrimidine (5-FU/LV or capecitabine) at a dose and schedule per the Investigator's discretion in accordance with locally approved prescribing information and 5 mg/kg bevacizumab via 1-30 minute IV on Day 1 of every 2-week cycle.

Reporting group title	Cohort 4: Cobimetinib,atezolizumab

Reporting group description:

Participants with HER2-/high microsatellite instability (MSI-H); HER2-/MSS/v-raf murine sarcoma viral oncogene homolog B1 wild type (BRAFwt); HER2-/MSS/BRAFmut/rat sarcoma mutation positive (RASmut) will receive 60 mg cobimetinib orally for 3 weeks followed by a 1-week treatment break and atezolizumab at a fixed dose of 840 mg via 60-minute IV infusion on Day 1 of every 2-week cycle.

Reporting group title	Cohort 4 Control: 5-FU/LV or capecitabin, bevacizumab

Reporting group description:

Per Investigator discretion, participants will receive fluoropyrimidine (5-FU/LV or capecitabine) at a dose and schedule per the Investigator's discretion in accordance with locally approved prescribing information and 5 mg/kg bevacizumab via 1-30 minute IV on Day 1 of every 2-week cycle.

Reporting group title	Early Progressing BRAFmut Cohort

Reporting group description:

BRAFmut participants experiencing early disease progression during induction treatment will have the option of proceeding immediately to receive second-line treatment with 5-FU/LV, cetuximab and vemurafenib if their primary tumour is MSS, or with a fluoropyrimidine (5-FU/LV or capecitabine), bevacizumab, and atezolizumab if their primary tumour is MSI-H.

Primary: Progression-Free Survival

End point title	Progression-Free Survival

End point description:

PFS is defined as the time from randomization to the first occurrence of disease progression according to RECIST v1.1, or death from any cause, whichever occurs first. Progressive disease (PD) for target lesion: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline). In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of >/=5 mm. PD for non-target lesion: Unequivocal progression of existing non-target lesions.

End point type	Primary

End point timeframe:

From randomization until disease progression or death from any cause, up to 5 years

End point values	Cohort 1: 5-FU/LV,cetuximab,vemurafenib	Cohort 1 Control: 5-FU/LV or capecitabin, bevacizumab	Cohort 2: 5-FU/LV or capecitabine,bevacizumab,atezolizumab	Cohort 2 Control: 5-FU/LV or capecitabin, bevacizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	20	297	148
Units: months				
median (confidence interval 95%)	9.99 (7.72 to 12.55)	11.60 (3.58 to 15.67)	7.13 (6.14 to 8.41)	7.36 (5.82 to 8.94)

End point values	Cohort 3: capecitabine,	Cohort 3 Control: 5-	Cohort 4: Cobimetinib,	Cohort 4 Control: 5-

	trastuzumab,pertuzumab	FU/LV or capecitabin, bevacizumab	atezolizumab	FU/LV or capecitabin, bevacizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	2	65	34
Units: months				
median (confidence interval 95%)	4.44 (3.55 to 14.69)	4.04 (4.04 to 5.39)	3.75 (3.42 to 3.91)	7.79 (3.98 to 9.46)

Statistical analyses

Statistical analysis title	Cohort 1 vs. Control
Comparison groups	Cohort 1: 5-FU/LV,cetuximab,vemurafenib v Cohort 1 Control: 5-FU/LV or capecitabin, bevacizumab
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.872
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.82

Statistical analysis title	Cohort 2 vs. Control
Comparison groups	Cohort 2: 5-FU/LV or capecitabine,bevacizumab,atezolizumab v Cohort 2 Control: 5-FU/LV or capecitabin, bevacizumab
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.666
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.18

Statistical analysis title	Cohort 4 vs. Control
Comparison groups	Cohort 4: Cobimetinib,atezolizumab v Cohort 4 Control: 5-FU/LV or capecitabin, bevacizumab

Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.128
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	2.29

Secondary: Overall Survival

End point title	Overall Survival

End point description:

OS is defined as the time from randomization into the MTP to time of death from any cause.

End point type	Secondary

End point timeframe:

From randomization until death from any cause, up to 5 years

End point values	Cohort 1: 5-FU/LV,cetuximab,vemurafenib	Early Progressing BRAFmut Cohort	Cohort 1 Control: 5-FU/LV or capecitabin, bevacizumab	Cohort 2: 5-FU/LV or capecitabine,bevacizumab,atezolizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	11	20	297
Units: months				
median (confidence interval 95%)	24.02 (16.07 to 34.00)	10.51 (4.83 to 19.78)	21.73 (7.92 to 37.19)	22.54 (20.04 to 26.87)

End point values	Cohort 2 Control: 5-FU/LV or capecitabin, bevacizumab	Cohort 3: capecitabine,trastuzumab,pertuzumab	Cohort 3 Control: 5-FU/LV or capecitabin, bevacizumab	Cohort 4: Cobimetinib,atezolizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	148	0[1]	0[2]	65
Units: months				
median (confidence interval 95%)	22.24 (18.50 to 25.13)	(to)	(to)	22.60 (14.23 to 27.40)

Notes:

[1] - Both the Median and the 95% CI were not evaluable due to the low number of participants/events.

[2] - Both the Median and the 95% CI were not evaluable due to the low number of participants/events.

End point values	Cohort 4 Control: 5-FU/LV or capecitabin, bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: months				
median (confidence interval 95%)	25.17 (15.90 to 32.59)			

Statistical analyses

Statistical analysis title	Cohort 1 (MP) vs Cohort 1 Control (MP)
Comparison groups	Cohort 1: 5-FU/LV,cetuximab,vemurafenib v Cohort 1 Control: 5-FU/LV or capecitabin, bevacizumab
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.276
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	1.32

Statistical analysis title	Cohort 4 (MP) vs. Cohort 4 (MP) Control
Comparison groups	Cohort 4: Cobimetinib,atezolizumab v Cohort 4 Control: 5-FU/LV or capecitabin, bevacizumab
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.415
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	2.14

Statistical analysis title	Cohort 2 (MP) vs Cohort 2 Control (MP)

Comparison groups	Cohort 2: 5-FU/LV or capecitabine,bevacizumab,atezolizumab v Cohort 2 Control: 5-FU/LV or capecitabin, bevacizumab
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.076
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.02

Secondary: Percentage of Participants with Adverse Events

End point title	Percentage of Participants with Adverse Events[3]

End point description:

End point type	Secondary

End point timeframe:

From baseline until end of study (up to 5 years)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results for all arms have been provided. Due to registry limitations and study complexity, the setup of the Early Progressing BRAFmut arm (which is not part of either the Induction or Maintenance phase) is generating this validation error.

End point values	Cohort 1	Cohort 1: 5-FU/LV,cetuximab,vemurafenib	Early Progressing BRAFmut Cohort	Cohort 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	60	40	11	445
Units: percentage of participants				
number (not applicable)	100	100	90.9	95.7

End point values	Cohort 1 Control: 5-FU/LV or capecitabin, bevacizumab	Cohort 3	Cohort 2: 5-FU/LV or capecitabine,bevacizumab,atezolizumab	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	5	297	98
Units: percentage of participants				
number (not applicable)	94.4	100	95.6	98.0

End point values	Cohort 2 Control: 5-FU/LV or capecitabin, bevacizumab	Cohort 3: capecitabine,trastuzumab,pertuzumab	Cohort 3 Control: 5-FU/LV or capecitabin, bevacizumab	Cohort 4: Cobimetinib,atezolizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	148	3	2	64
Units: percentage of participants				
number (not applicable)	88.1	100	100	98.4

End point values	Cohort 4 Control: 5-FU/LV or capecitabin, bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: percentage of participants				
number (not applicable)	88.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response

End point title	Overall Response

End point description:

Calculated as the number of participants with a best overall response of CR or PR according to RECIST 1.1. CR: disappearance of all target lesions. PR: At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR. OR= CR + PR.

End point type	Secondary

End point timeframe:

From randomization until disease progression, up to 5 years

End point values	Cohort 1: 5-FU/LV,cetuximab,vemurafenib	Early Progressing BRAFmut Cohort	Cohort 1 Control: 5-FU/LV or capecitabin, bevacizumab	Cohort 2: 5-FU/LV or capecitabine,bevacizumab,atezolizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	11	20	297
Units: participants	20	2	5	49

End point values	Cohort 2 Control: 5-FU/LV or capecitabin, bevacizumab	Cohort 3: capecitabine,trastuzumab,pertuzumab	Cohort 3 Control: 5-FU/LV or capecitabin, bevacizumab	Cohort 4: Cobimetinib,atezolizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	148	3	2	65
Units: participants	22	1	0	7

End point values	Cohort 4 Control: 5-FU/LV or capecitabin, bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: participants	8			

Statistical analyses

Statistical analysis title	Cohort 1 vs. Control
Comparison groups	Cohort 1: 5-FU/LV,cetuximab,vemurafenib v Cohort 1 Control: 5-FU/LV or capecitabin, bevacizumab
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.064
Method	Chi-squared

Statistical analysis title	Cohort 2 vs. Control
Comparison groups	Cohort 2: 5-FU/LV or capecitabine,bevacizumab,atezolizumab v Cohort 2 Control: 5-FU/LV or capecitabin, bevacizumab
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.658
Method	Chi-squared

Statistical analysis title	Cohort 4 (MP) vs. Cohort 4 (MP) Control
Comparison groups	Cohort 4: Cobimetinib,atezolizumab v Cohort 4 Control: 5-FU/LV or capecitabin, bevacizumab

Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.093
Method	Chi-squared

Secondary: Disease Control Rate

End point title	Disease Control Rate

End point description:

DCR is defined as the percentage of participants with CR, PR, or stable disease (SD) at 16 weeks. Per RECIST v1.1, CR is defined as disappearance of all target lesions. PR is defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. SD is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for disease progression, taking as reference the smallest sum on study. Disease progression is defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study including baseline, or the appearance of one or more new lesions.

End point type	Secondary

End point timeframe:

From randomization until disease progression, up to 5 years

End point values	Cohort 1: 5-FU/LV,cetuximab,vemurafenib	Early Progressing BRAFmut Cohort	Cohort 1 Control: 5-FU/LV or capecitabin, bevacizumab	Cohort 2: 5-FU/LV or capecitabine,bevacizumab,atezolizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	11	20	297
Units: participants	36	9	15	227

End point values	Cohort 2 Control: 5-FU/LV or capecitabin, bevacizumab	Cohort 3: capecitabine,trastuzumab,pertuzumab	Cohort 3 Control: 5-FU/LV or capecitabin, bevacizumab	Cohort 4: Cobimetinib,atezolizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	148	3	2	65
Units: participants	111	1	0	44

End point values	Cohort 4 Control: 5-FU/LV or capecitabin, bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: participants	26			

Statistical analyses

Statistical analysis title	Cohort 1 vs. Control
Comparison groups	Cohort 1: 5-FU/LV,cetuximab,vemurafenib v Cohort 1 Control: 5-FU/LV or capecitabin, bevacizumab
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.125
Method	Chi-squared

Statistical analysis title	Cohort 2 vs. Control
Comparison groups	Cohort 2: 5-FU/LV or capecitabine,bevacizumab,atezolizumab v Cohort 2 Control: 5-FU/LV or capecitabin, bevacizumab
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.739
Method	Chi-squared

Statistical analysis title	Cohort 4 vs. Control
Comparison groups	Cohort 4: Cobimetinib,atezolizumab v Cohort 4 Control: 5-FU/LV or capecitabin, bevacizumab
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.362
Method	Chi-squared

Secondary: Time to Treatment Response

End point title	Time to Treatment Response

End point description:

Calculated as the time from randomization to the first Occurrence of a documented Objective Response (CR or PR) determined according to RECIST 1.1. CR is defined as disappearance of all target lesions. PR is defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.

End point type	Secondary

End point timeframe:

From randomization until disease progression or death from any cause, up to 5 years

End point values	Cohort 1: 5-FU/LV,cetuximab,vemurafenib	Cohort 1 Control: 5-FU/LV or capecitabin, bevacizumab	Cohort 2: 5-FU/LV or capecitabine,bevacizumab,atezolizumab	Cohort 2 Control: 5-FU/LV or capecitabin, bevacizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	20	297	148
Units: months				
median (full range (min-max))	3.943 (1.18 to 29.70)	5.552 (1.38 to 8.02)	5.224 (1.22 to 26.74)	4.616 (1.25 to 19.91)

End point values	Cohort 3: capecitabine,trastuzumab,pertuzumab	Cohort 3 Control: 5-FU/LV or capecitabin, bevacizumab	Cohort 4: Cobimetinib,atezolizumab	Cohort 4 Control: 5-FU/LV or capecitabin, bevacizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	2	0[4]	0[5]
Units: months				
median (full range (min-max))	5.490 (5.490 to 5.490)	0 (0 to 0)	(to)	(to)

Notes:

[4] - Target number of patients not enrolled and the target number of PFS events could not be reached

[5] - Target number of patients not enrolled and the target number of PFS events could not be reached

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Defined as the time from the first assessment of CR or PR until disease progression or death from any cause, whichever occurs first. CR is defined as disappearance of all target lesions. PR is defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.

End point type	Secondary

End point timeframe:

From first objective response until disease progression or death from any cause, up to 5 years

End point values	Cohort 1: 5-FU/LV,cetuximab,vemurafenib	Cohort 1 Control: 5-FU/LV or capecitabin, bevacizumab	Cohort 2: 5-FU/LV or capecitabine,bevacizumab,atezolizumab	Cohort 2 Control: 5-FU/LV or capecitabin, bevacizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	20	297	148
Units: months				

median (confidence interval 95%)	11.50 (7.66 to 21.49)	8.74 (5.36 to 19.02)	9.30 (5.55 to 11.30)	7.59 (6.93 to 13.90)

End point values	Cohort 3: capecitabine,trastuzumab,pertuzumab	Cohort 3 Control: 5-FU/LV or capecitabin, bevacizumab	Cohort 4: Cobimetinib,atezolizumab	Cohort 4 Control: 5-FU/LV or capecitabin, bevacizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	2	0[6]	0[7]
Units: months				
median (confidence interval 95%)	9.205 (9.205 to 9.205)	0 (0 to 0)	(to)	(to)

Notes:

[6] - Target number of patients not enrolled and the target number of PFS events could not be reached

[7] - Target number of patients not enrolled and the target number of PFS events could not be reached

Statistical analyses

Statistical analysis title	Cohort 2 vs. Control
Comparison groups	Cohort 2: 5-FU/LV or capecitabine,bevacizumab,atezolizumab v Cohort 2 Control: 5-FU/LV or capecitabin, bevacizumab
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.495
Method	Logrank

Statistical analysis title	Cohort 1 vs. Control
Comparison groups	Cohort 1: 5-FU/LV,cetuximab,vemurafenib v Cohort 1 Control: 5-FU/LV or capecitabin, bevacizumab
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.421
Method	Logrank

Secondary: Change from Baseline in Eastern Cooperative Oncology Group Performance Status (ECOG PS)

End point title	Change from Baseline in Eastern Cooperative Oncology Group Performance Status (ECOG PS)

End point description:

End point type	Secondary

End point timeframe:

From baseline until end of study (up to 5 years)

End point values	Cohort 1: 5-FU/LV,cetuximab,vemurafenib	Cohort 1 Control: 5-FU/LV or capecitabin, bevacizumab	Cohort 2: 5-FU/LV or capecitabine,bevacizumab,atezolizumab	Cohort 2 Control: 5-FU/LV or capecitabin, bevacizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	20	297	148
Units: percentage of participants				
number (not applicable)				
Improved	10.0	5.0	10.4	5.4
Improved or stayed the same	75.0	85.0	76.7	82.5

End point values	Cohort 3: capecitabine,trastuzumab,pertuzumab	Cohort 3 Control: 5-FU/LV or capecitabin, bevacizumab	Cohort 4: Cobimetinib,atezolizumab	Cohort 4 Control: 5-FU/LV or capecitabin, bevacizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	2	0[8]	0[9]
Units: percentage of participants				
number (not applicable)				
Improved	0	0		
Improved or stayed the same	100	100		

Notes:

[8] - Target number of patients not enrolled and the target number of PFS events could not be reached

[9] - Target number of patients not enrolled and the target number of PFS events could not be reached

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From baseline until end of study (up to 5 years)	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.1
Reporting groups	
Reporting group title	Cohort 1 (MP)
Reporting group description: -	
Reporting group title	Cohort 1 (IP)
Reporting group description: -	
Reporting group title	Cohort 2 (MP)
Reporting group description: -	
Reporting group title	Cohort 2 Control (MP)
Reporting group description: -	
Reporting group title	Cohort 2 (IP)
Reporting group description: -	
Reporting group title	Cohort 1 Control (MP)
Reporting group description: -	
Reporting group title	Cohort 3 (IP)
Reporting group description: -	
Reporting group title	Cohort 3 (MP)
Reporting group description: -	
Reporting group title	Cohort 3 Control (MP)
Reporting group description: -	
Reporting group title	Cohort 4 (IP)
Reporting group description: -	
Reporting group title	Cohort 4 (MP)
Reporting group description: -	
Reporting group title	Cohort 4 Control (MP)
Reporting group description: -	
Reporting group title	Early Progressing BRAFmut Cohort
Reporting group description: -	

Serious adverse events	Cohort 1 (MP)	Cohort 1 (IP)	Cohort 2 (MP)
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 40 (37.50%)	13 / 58 (22.41%)	76 / 293 (25.94%)
number of deaths (all causes)	0	0	5
number of deaths resulting from adverse events	0	0	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			

subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Second primary malignancy			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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 perforation			
subjects affected / exposed	1 / 40 (2.50%)	0 / 58 (0.00%)	0 / 293 (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
Leiomyosarcoma			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Arterial thrombosis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Hypertension			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	3 / 293 (1.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			

subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superior vena cava syndrome			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Ureteral stent removal			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Chest pain			
subjects affected / exposed	1 / 40 (2.50%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Gait disturbance			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General physical health deterioration			
subjects affected / exposed	1 / 40 (2.50%)	0 / 58 (0.00%)	2 / 293 (0.68%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperthermia			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Implant site dehiscence			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Implant site thrombosis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Infusion site extravasation			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	6 / 293 (2.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Hypersensitivity			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	2 / 293 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal			

disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 40 (0.00%)	1 / 58 (1.72%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 40 (0.00%)	1 / 58 (1.72%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 40 (0.00%)	1 / 58 (1.72%)	0 / 293 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 40 (2.50%)	0 / 58 (0.00%)	0 / 293 (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			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Acute respiratory distress syndrome			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Organising pneumonia			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Psychiatric disorders			
Disorientation			
subjects affected / exposed	0 / 40 (0.00%)	1 / 58 (1.72%)	0 / 293 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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 lactate dehydrogenase increased			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood triglycerides increased			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipase increased			
subjects affected / exposed	1 / 40 (2.50%)	0 / 58 (0.00%)	0 / 293 (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
Neutrophil count decreased			

subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Injury, poisoning and procedural complications			
Anastomotic ulcer			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incisional hernia			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Post procedural haemorrhage			
subjects affected / exposed	1 / 40 (2.50%)	0 / 58 (0.00%)	0 / 293 (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
Rib fracture			
subjects affected / exposed	0 / 40 (0.00%)	1 / 58 (1.72%)	0 / 293 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	1 / 40 (2.50%)	0 / 58 (0.00%)	0 / 293 (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
Stoma site haemorrhage			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Tendon rupture			

subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Tibia fracture			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Tracheal haemorrhage			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
subjects affected / exposed	1 / 40 (2.50%)	0 / 58 (0.00%)	0 / 293 (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			
Atrial fibrillation			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Cardiogenic shock			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Coronary artery disease			
subjects affected / exposed	1 / 40 (2.50%)	0 / 58 (0.00%)	0 / 293 (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
Myocardial infarction			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Myocardial ischaemia			

subjects affected / exposed	1 / 40 (2.50%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Restrictive cardiomyopathy			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute coronary syndrome			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Angina pectoris			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoaesthesia			

subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral motor neuropathy			
subjects affected / exposed	0 / 40 (0.00%)	1 / 58 (1.72%)	0 / 293 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Syncope			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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			
subjects affected / exposed	1 / 40 (2.50%)	0 / 58 (0.00%)	0 / 293 (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
Febrile neutropenia			
subjects affected / exposed	0 / 40 (0.00%)	2 / 58 (3.45%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	0 / 40 (0.00%)	1 / 58 (1.72%)	0 / 293 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Chorioretinopathy			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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			
subjects affected / exposed	1 / 40 (2.50%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	3 / 293 (1.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 40 (2.50%)	0 / 58 (0.00%)	5 / 293 (1.71%)
occurrences causally related to treatment / all	1 / 1	0 / 0	3 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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 obstruction			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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			
subjects affected / exposed	1 / 40 (2.50%)	0 / 58 (0.00%)	2 / 293 (0.68%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated enterocolitis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Large intestinal stenosis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			

subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 40 (2.50%)	0 / 58 (0.00%)	2 / 293 (0.68%)
occurrences causally related to treatment / all	0 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Proctalgia			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			

subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	2 / 293 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 40 (0.00%)	1 / 58 (1.72%)	4 / 293 (1.37%)
occurrences causally related to treatment / all	0 / 0	3 / 3	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	0 / 40 (0.00%)	1 / 58 (1.72%)	0 / 293 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Hepatitis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular injury			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatorenal failure			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Hepatotoxicity			

subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Rash maculo-papular			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Urticaria			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	1 / 40 (2.50%)	0 / 58 (0.00%)	0 / 293 (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
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Back pain			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Muscular weakness			
subjects affected / exposed	1 / 40 (2.50%)	0 / 58 (0.00%)	0 / 293 (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
Osteonecrosis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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 infection			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Anal abscess			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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

Arthritis infective			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 40 (2.50%)	0 / 58 (0.00%)	0 / 293 (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
Erysipelas			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Gastroenteritis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	2 / 293 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis clostridial			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Gingivitis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Hepatic infection			

subjects affected / exposed	1 / 40 (2.50%)	0 / 58 (0.00%)	0 / 293 (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
Infection			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Labyrinthitis			
subjects affected / exposed	0 / 40 (0.00%)	1 / 58 (1.72%)	0 / 293 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine infection			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Lower respiratory tract infection			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Rectal abscess			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			

subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	2 / 293 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Staphylococcal infection			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Upper respiratory tract infection			
subjects affected / exposed	1 / 40 (2.50%)	0 / 58 (0.00%)	0 / 293 (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
Urinary tract infection			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	3 / 293 (1.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Vascular device infection			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Post procedural sepsis			

subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 40 (0.00%)	2 / 58 (3.45%)	0 / 293 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Hypoglycaemia			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Hypokalaemia			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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
Hyponatraemia			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (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

Serious adverse events	Cohort 2 Control (MP)	Cohort 2 (IP)	Cohort 1 Control (MP)
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 143 (13.99%)	59 / 436 (13.53%)	5 / 18 (27.78%)
number of deaths (all causes)	1	6	0
number of deaths resulting from adverse events	1	0	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Second primary malignancy			
subjects affected / exposed	1 / 143 (0.70%)	0 / 436 (0.00%)	0 / 18 (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
Tumour perforation			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Leiomyosarcoma			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Vascular disorders			
Arterial thrombosis			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Deep vein thrombosis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Hypertension			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hypotension			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Superior vena cava syndrome			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Thrombosis			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Surgical and medical procedures			
Ureteral stent removal			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 143 (0.70%)	0 / 436 (0.00%)	0 / 18 (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
Fatigue			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait disturbance			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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

General physical health deterioration			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Hyperthermia			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Implant site dehiscence			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Implant site thrombosis			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion site extravasation			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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			
subjects affected / exposed	0 / 143 (0.00%)	5 / 436 (1.15%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Respiratory, thoracic and mediastinal			

disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Dyspnoea			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Epistaxis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Pneumothorax			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Pulmonary embolism			
subjects affected / exposed	0 / 143 (0.00%)	2 / 436 (0.46%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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

Acute respiratory distress syndrome			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Organising pneumonia			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Psychiatric disorders			
Disorientation			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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 creatine phosphokinase increased			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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 lactate dehydrogenase increased			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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 triglycerides increased			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Lipase increased			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Neutrophil count decreased			

subjects affected / exposed	0 / 143 (0.00%)	2 / 436 (0.46%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Anastomotic ulcer			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Femur fracture			
subjects affected / exposed	1 / 143 (0.70%)	0 / 436 (0.00%)	0 / 18 (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
Incisional hernia			
subjects affected / exposed	1 / 143 (0.70%)	0 / 436 (0.00%)	0 / 18 (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
Post procedural haemorrhage			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Rib fracture			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Spinal fracture			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Stoma site haemorrhage			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			

subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	1 / 143 (0.70%)	0 / 436 (0.00%)	0 / 18 (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
Tracheal haemorrhage			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Pelvic fracture			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Coronary artery disease			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Myocardial infarction			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Myocardial ischaemia			

subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Pericardial effusion			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Restrictive cardiomyopathy			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Supraventricular tachycardia			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Acute coronary syndrome			
subjects affected / exposed	1 / 143 (0.70%)	0 / 436 (0.00%)	0 / 18 (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
Angina pectoris			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 143 (0.70%)	0 / 436 (0.00%)	0 / 18 (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
Haemorrhage intracranial			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Hypoaesthesia			

subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Peripheral motor neuropathy			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Presyncope			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Syncope			
subjects affected / exposed	1 / 143 (0.70%)	0 / 436 (0.00%)	0 / 18 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Febrile neutropenia			
subjects affected / exposed	0 / 143 (0.00%)	4 / 436 (0.92%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 143 (0.00%)	6 / 436 (1.38%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	9 / 9	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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			
Chorioretinopathy			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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			
subjects affected / exposed	1 / 143 (0.70%)	2 / 436 (0.46%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Colitis			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Constipation			
subjects affected / exposed	1 / 143 (0.70%)	3 / 436 (0.69%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	2 / 143 (1.40%)	3 / 436 (0.69%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	1 / 2	2 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			
subjects affected / exposed	1 / 143 (0.70%)	0 / 436 (0.00%)	0 / 18 (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

Gastrointestinal obstruction			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 143 (0.00%)	2 / 436 (0.46%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated enterocolitis			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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			
subjects affected / exposed	1 / 143 (0.70%)	1 / 436 (0.23%)	0 / 18 (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
Intestinal perforation			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Large intestinal obstruction			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal stenosis			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Large intestine perforation			

subjects affected / exposed	1 / 143 (0.70%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 143 (0.70%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 143 (0.00%)	2 / 436 (0.46%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proctalgia			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Rectal haemorrhage			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Stomatitis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			

subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 143 (0.00%)	4 / 436 (0.92%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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			
Cholestasis			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Hepatocellular injury			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Hepatorenal failure			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Hepatotoxicity			

subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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			
Rash			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Rash maculo-papular			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Urticaria			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 143 (0.70%)	2 / 436 (0.46%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Renal failure			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Back pain			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Muscular weakness			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Osteonecrosis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal infection			
subjects affected / exposed	1 / 143 (0.70%)	0 / 436 (0.00%)	0 / 18 (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
Abdominal wall abscess			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			
subjects affected / exposed	1 / 143 (0.70%)	0 / 436 (0.00%)	0 / 18 (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

Arthritis infective			
subjects affected / exposed	1 / 143 (0.70%)	0 / 436 (0.00%)	0 / 18 (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
Bronchitis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Gastroenteritis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis clostridial			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gingivitis			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic infection			

subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Infection			
subjects affected / exposed	1 / 143 (0.70%)	0 / 436 (0.00%)	0 / 18 (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
Labyrinthitis			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Large intestine infection			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Lower respiratory tract infection			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 143 (0.70%)	3 / 436 (0.69%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Rectal abscess			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Respiratory tract infection			

subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Sepsis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Staphylococcal infection			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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 infection			
subjects affected / exposed	0 / 143 (0.00%)	2 / 436 (0.46%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 143 (0.70%)	0 / 436 (0.00%)	0 / 18 (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 device infection			
subjects affected / exposed	1 / 143 (0.70%)	2 / 436 (0.46%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural sepsis			

subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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			
Dehydration			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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
Hyperglycaemia			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 143 (0.00%)	2 / 436 (0.46%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (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

Serious adverse events	Cohort 3 (IP)	Cohort 3 (MP)	Cohort 3 Control (MP)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Second primary malignancy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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 perforation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Leiomyosarcoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Vascular disorders			
Arterial thrombosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Deep vein thrombosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Hypertension			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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

Hypotension			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Superior vena cava syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Thrombosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Surgical and medical procedures			
Ureteral stent removal			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Chest pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Fatigue			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Gait disturbance			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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

General physical health deterioration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Hyperthermia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Implant site dehiscence			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Implant site thrombosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Infusion site extravasation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Hypersensitivity			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Respiratory, thoracic and mediastinal			

disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Dyspnoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Epistaxis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Interstitial lung disease			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Pneumothorax			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Pulmonary embolism			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Respiratory failure			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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

Acute respiratory distress syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Organising pneumonia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Psychiatric disorders			
Disorientation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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 creatine phosphokinase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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 lactate dehydrogenase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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 triglycerides increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Lipase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Neutrophil count decreased			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Injury, poisoning and procedural complications			
Anastomotic ulcer			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Femur fracture			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Incisional hernia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Post procedural haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Rib fracture			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Spinal fracture			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Stoma site haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Tendon rupture			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Tibia fracture			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Tracheal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Pelvic fracture			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Cardiogenic shock			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Coronary artery disease			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Myocardial infarction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Myocardial ischaemia			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Pericardial effusion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Restrictive cardiomyopathy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Supraventricular tachycardia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Acute coronary syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Angina pectoris			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Haemorrhage intracranial			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Hypoaesthesia			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Peripheral motor neuropathy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Presyncope			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Syncope			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Febrile neutropenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Neutropenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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			
Chorioretinopathy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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 pain upper			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Colitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Constipation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Diarrhoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Faecaloma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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 obstruction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Immune-mediated enterocolitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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 perforation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Large intestinal obstruction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Large intestinal stenosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Large intestine perforation			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Oesophagitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Proctalgia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Rectal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Stomatitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Subileus			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Vomiting			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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			
Cholestasis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Hepatic failure			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Hepatitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Hepatocellular injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Hepatorenal failure			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Hepatotoxicity			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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			
Rash			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Rash maculo-papular			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Urticaria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Nephrolithiasis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Renal failure			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Back pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Muscular weakness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Osteonecrosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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 infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Anal abscess			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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

Arthritis infective			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Diverticulitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Erysipelas			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Gastroenteritis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Gastroenteritis clostridial			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Gingivitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Hepatic infection			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Labyrinthitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Large intestine infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Lower respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Pyelonephritis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Rectal abscess			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Respiratory tract infection			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Sepsis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Septic shock			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Staphylococcal infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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 infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Vascular device infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Post procedural sepsis			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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			
Dehydration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Diabetic ketoacidosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Hyperglycaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Hypoglycaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Hypokalaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Hyponatraemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (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

Serious adverse events	Cohort 4 (IP)	Cohort 4 (MP)	Cohort 4 Control (MP)
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 98 (11.22%)	26 / 64 (40.63%)	3 / 34 (8.82%)
number of deaths (all causes)	4	4	0
number of deaths resulting from adverse events	0	2	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Second primary malignancy			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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 perforation			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Leiomyosarcoma			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Vascular disorders			
Arterial thrombosis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Deep vein thrombosis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Haemorrhage			
subjects affected / exposed	1 / 98 (1.02%)	0 / 64 (0.00%)	0 / 34 (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
Hypertension			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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

Hypotension			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Superior vena cava syndrome			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Thrombosis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Surgical and medical procedures			
Ureteral stent removal			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Chest pain			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Fatigue			
subjects affected / exposed	1 / 98 (1.02%)	0 / 64 (0.00%)	0 / 34 (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
Gait disturbance			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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

General physical health deterioration			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Hyperthermia			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Implant site dehiscence			
subjects affected / exposed	1 / 98 (1.02%)	0 / 64 (0.00%)	0 / 34 (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
Implant site thrombosis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Infusion site extravasation			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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			
subjects affected / exposed	0 / 98 (0.00%)	2 / 64 (3.13%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Hypersensitivity			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Respiratory, thoracic and mediastinal			

disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Dyspnoea			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Epistaxis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Interstitial lung disease			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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			
subjects affected / exposed	0 / 98 (0.00%)	2 / 64 (3.13%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Pulmonary embolism			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Respiratory failure			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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

Acute respiratory distress syndrome			
subjects affected / exposed	0 / 98 (0.00%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Organising pneumonia			
subjects affected / exposed	0 / 98 (0.00%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Psychiatric disorders			
Disorientation			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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 creatine phosphokinase increased			
subjects affected / exposed	0 / 98 (0.00%)	3 / 64 (4.69%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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 triglycerides increased			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Lipase increased			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Neutrophil count decreased			

subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Injury, poisoning and procedural complications			
Anastomotic ulcer			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Femur fracture			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Incisional hernia			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Post procedural haemorrhage			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Rib fracture			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Spinal fracture			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Stoma site haemorrhage			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Tendon rupture			

subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Tibia fracture			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Tracheal haemorrhage			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Pelvic fracture			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 98 (0.00%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	0 / 98 (0.00%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Myocardial infarction			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Myocardial ischaemia			

subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Pericardial effusion			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Restrictive cardiomyopathy			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Supraventricular tachycardia			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Acute coronary syndrome			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Angina pectoris			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Hypoaesthesia			

subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Peripheral motor neuropathy			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Presyncope			
subjects affected / exposed	1 / 98 (1.02%)	0 / 64 (0.00%)	0 / 34 (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
Syncope			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 98 (0.00%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 98 (1.02%)	0 / 64 (0.00%)	0 / 34 (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
Febrile neutropenia			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Neutropenia			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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			
Chorioretinopathy			
subjects affected / exposed	0 / 98 (0.00%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 98 (2.04%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Colitis			
subjects affected / exposed	0 / 98 (0.00%)	1 / 64 (1.56%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Diarrhoea			
subjects affected / exposed	0 / 98 (0.00%)	2 / 64 (3.13%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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 obstruction			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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			
subjects affected / exposed	1 / 98 (1.02%)	0 / 64 (0.00%)	0 / 34 (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
Immune-mediated enterocolitis			
subjects affected / exposed	0 / 98 (0.00%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	2 / 98 (2.04%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Large intestinal obstruction			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Large intestinal stenosis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Large intestine perforation			

subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Oesophagitis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Proctalgia			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Rectal haemorrhage			
subjects affected / exposed	1 / 98 (1.02%)	0 / 64 (0.00%)	0 / 34 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Stomatitis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Subileus			

subjects affected / exposed	0 / 98 (0.00%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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			
Cholestasis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Hepatic failure			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Hepatitis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Hepatocellular injury			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Hepatorenal failure			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Hepatotoxicity			

subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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			
Rash			
subjects affected / exposed	0 / 98 (0.00%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			
subjects affected / exposed	0 / 98 (0.00%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 98 (0.00%)	2 / 64 (3.13%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Renal failure			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Osteonecrosis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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 infection			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Anal abscess			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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

Arthritis infective			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Diverticulitis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Erysipelas			
subjects affected / exposed	0 / 98 (0.00%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Gastroenteritis clostridial			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Gingivitis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Hepatic infection			

subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Infection			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Labyrinthitis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Large intestine infection			
subjects affected / exposed	0 / 98 (0.00%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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			
subjects affected / exposed	0 / 98 (0.00%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 64 (0.00%)	0 / 34 (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
Rectal abscess			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Respiratory tract infection			

subjects affected / exposed	0 / 98 (0.00%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Septic shock			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Staphylococcal infection			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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 infection			
subjects affected / exposed	0 / 98 (0.00%)	2 / 64 (3.13%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Urosepsis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Vascular device infection			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Post procedural sepsis			

subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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			
Dehydration			
subjects affected / exposed	0 / 98 (0.00%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Hyperglycaemia			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Hypoglycaemia			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Hypokalaemia			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (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
Hyponatraemia			
subjects affected / exposed	0 / 98 (0.00%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Early Progressing BRAFmut Cohort		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 11 (27.27%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Second primary malignancy			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tumour perforation			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Leiomyosarcoma			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Arterial thrombosis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhage			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Hypotension				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Superior vena cava syndrome				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thrombosis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				
Ureteral stent removal				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Asthenia				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gait disturbance				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

General physical health deterioration			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperthermia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Implant site dehiscence			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Implant site thrombosis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infusion site extravasation			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypersensitivity			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal			

disorders				
Chronic obstructive pulmonary disease				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Interstitial lung disease				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Acute respiratory distress syndrome				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Organising pneumonia				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Disorientation				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Blood creatine phosphokinase increased				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood lactate dehydrogenase increased				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood triglycerides increased				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lipase increased				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutrophil count decreased				

subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Anastomotic ulcer				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Incisional hernia				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post procedural haemorrhage				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal fracture				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Stoma site haemorrhage				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tendon rupture				

subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tibia fracture				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tracheal haemorrhage				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pelvic fracture				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Atrial fibrillation				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiogenic shock				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery disease				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial ischaemia				

subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pericardial effusion				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Restrictive cardiomyopathy				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute coronary syndrome				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Angina pectoris				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebrovascular accident				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhage intracranial				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoaesthesia				

subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peripheral motor neuropathy				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Presyncope				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				

Vertigo			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Chorioretinopathy			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Faecaloma			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal obstruction				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrooesophageal reflux disease				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune-mediated enterocolitis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal perforation				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large intestinal obstruction				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large intestinal stenosis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large intestine perforation				

subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower gastrointestinal haemorrhage				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophagitis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Proctalgia				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Stomatitis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subileus				

subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholestasis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic failure				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatitis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatocellular injury				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatorenal failure				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatotoxicity				

subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rash maculo-papular			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urticaria			
subjects affected / exposed	0 / 11 (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			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteonecrosis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal infection			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal wall abscess			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anal abscess			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Arthritis infective				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Erysipelas				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis clostridial				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gingivitis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic infection				

subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Labyrinthitis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large intestine infection				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rectal abscess				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				

subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Staphylococcal infection			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular device infection			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Post procedural sepsis			

subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Diabetic ketoacidosis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	0 / 11 (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 1 (MP)	Cohort 1 (IP)	Cohort 2 (MP)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 40 (100.00%)	58 / 58 (100.00%)	270 / 293 (92.15%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences (all)	0	0	1
Cancer pain			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences (all)	0	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 40 (2.50%)	9 / 58 (15.52%)	49 / 293 (16.72%)
occurrences (all)	1	11	70
Hypotension			
subjects affected / exposed	4 / 40 (10.00%)	2 / 58 (3.45%)	3 / 293 (1.02%)
occurrences (all)	4	2	3
Phlebitis			
subjects affected / exposed	1 / 40 (2.50%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	2	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 40 (12.50%)	11 / 58 (18.97%)	40 / 293 (13.65%)
occurrences (all)	9	12	58
Face oedema			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences (all)	0	0	3
Fatigue			
subjects affected / exposed	9 / 40 (22.50%)	17 / 58 (29.31%)	52 / 293 (17.75%)
occurrences (all)	11	28	77
Influenza like illness			
subjects affected / exposed	2 / 40 (5.00%)	2 / 58 (3.45%)	9 / 293 (3.07%)
occurrences (all)	2	2	10
Mucosal inflammation			
subjects affected / exposed	7 / 40 (17.50%)	5 / 58 (8.62%)	20 / 293 (6.83%)
occurrences (all)	8	6	26

Oedema peripheral			
subjects affected / exposed	3 / 40 (7.50%)	3 / 58 (5.17%)	8 / 293 (2.73%)
occurrences (all)	6	3	8
Pain			
subjects affected / exposed	3 / 40 (7.50%)	0 / 58 (0.00%)	4 / 293 (1.37%)
occurrences (all)	3	0	4
Pyrexia			
subjects affected / exposed	8 / 40 (20.00%)	8 / 58 (13.79%)	32 / 293 (10.92%)
occurrences (all)	8	9	52
Catheter site pain			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	0	0	0
General physical health deterioration			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	1 / 40 (2.50%)	1 / 58 (1.72%)	5 / 293 (1.71%)
occurrences (all)	1	1	5
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	3 / 40 (7.50%)	0 / 58 (0.00%)	2 / 293 (0.68%)
occurrences (all)	3	0	2
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	2 / 293 (0.68%)
occurrences (all)	0	0	2
Cough			
subjects affected / exposed	5 / 40 (12.50%)	3 / 58 (5.17%)	30 / 293 (10.24%)
occurrences (all)	6	3	39
Dysphonia			
subjects affected / exposed	1 / 40 (2.50%)	4 / 58 (6.90%)	15 / 293 (5.12%)
occurrences (all)	1	4	18
Dyspnoea			
subjects affected / exposed	2 / 40 (5.00%)	3 / 58 (5.17%)	12 / 293 (4.10%)
occurrences (all)	2	3	12
Epistaxis			

subjects affected / exposed	4 / 40 (10.00%)	7 / 58 (12.07%)	23 / 293 (7.85%)
occurrences (all)	4	9	29
Hiccups			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	0	0	0
Nasal dryness			
subjects affected / exposed	0 / 40 (0.00%)	1 / 58 (1.72%)	2 / 293 (0.68%)
occurrences (all)	0	1	2
Nasal ulcer			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	0	0	0
Pulmonary embolism			
subjects affected / exposed	1 / 40 (2.50%)	3 / 58 (5.17%)	3 / 293 (1.02%)
occurrences (all)	2	3	3
Oropharyngeal pain			
subjects affected / exposed	1 / 40 (2.50%)	1 / 58 (1.72%)	6 / 293 (2.05%)
occurrences (all)	1	1	9
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 40 (2.50%)	4 / 58 (6.90%)	4 / 293 (1.37%)
occurrences (all)	1	4	4
Insomnia			
subjects affected / exposed	2 / 40 (5.00%)	7 / 58 (12.07%)	10 / 293 (3.41%)
occurrences (all)	2	7	10
Depression			
subjects affected / exposed	1 / 40 (2.50%)	0 / 58 (0.00%)	3 / 293 (1.02%)
occurrences (all)	1	0	3
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 40 (5.00%)	3 / 58 (5.17%)	8 / 293 (2.73%)
occurrences (all)	2	4	14
Amylase increased			
subjects affected / exposed	1 / 40 (2.50%)	0 / 58 (0.00%)	2 / 293 (0.68%)
occurrences (all)	1	0	2
Aspartate aminotransferase increased			

subjects affected / exposed	1 / 40 (2.50%)	4 / 58 (6.90%)	10 / 293 (3.41%)
occurrences (all)	1	6	13
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 40 (2.50%)	1 / 58 (1.72%)	5 / 293 (1.71%)
occurrences (all)	1	2	5
Blood bilirubin increased			
subjects affected / exposed	2 / 40 (5.00%)	1 / 58 (1.72%)	8 / 293 (2.73%)
occurrences (all)	3	1	10
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	4 / 40 (10.00%)	0 / 58 (0.00%)	4 / 293 (1.37%)
occurrences (all)	6	0	4
Ejection fraction decreased			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	0	0	0
Lipase increased			
subjects affected / exposed	3 / 40 (7.50%)	0 / 58 (0.00%)	2 / 293 (0.68%)
occurrences (all)	3	0	3
Neutrophil count decreased			
subjects affected / exposed	1 / 40 (2.50%)	10 / 58 (17.24%)	7 / 293 (2.39%)
occurrences (all)	1	12	11
Platelet count decreased			
subjects affected / exposed	1 / 40 (2.50%)	2 / 58 (3.45%)	6 / 293 (2.05%)
occurrences (all)	1	3	19
Weight decreased			
subjects affected / exposed	4 / 40 (10.00%)	3 / 58 (5.17%)	11 / 293 (3.75%)
occurrences (all)	4	3	12
Weight increased			
subjects affected / exposed	1 / 40 (2.50%)	0 / 58 (0.00%)	2 / 293 (0.68%)
occurrences (all)	1	0	3
White blood cell count decreased			
subjects affected / exposed	0 / 40 (0.00%)	1 / 58 (1.72%)	1 / 293 (0.34%)
occurrences (all)	0	1	1

Body temperature increased			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	3 / 293 (1.02%)
occurrences (all)	0	0	3
Cardiac murmur			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	0	0	0
Blood potassium decreased			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	2 / 40 (5.00%)	2 / 58 (3.45%)	10 / 293 (3.41%)
occurrences (all)	3	2	12
Lumbar vertebral fracture			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	0	0	0
Sunburn			
subjects affected / exposed	1 / 40 (2.50%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal stoma complication			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 40 (10.00%)	3 / 58 (5.17%)	6 / 293 (2.05%)
occurrences (all)	4	5	7
Dysgeusia			
subjects affected / exposed	4 / 40 (10.00%)	6 / 58 (10.34%)	8 / 293 (2.73%)
occurrences (all)	4	6	8
Headache			
subjects affected / exposed	2 / 40 (5.00%)	4 / 58 (6.90%)	24 / 293 (8.19%)
occurrences (all)	2	4	83
Neuropathy peripheral			

subjects affected / exposed	1 / 40 (2.50%)	7 / 58 (12.07%)	18 / 293 (6.14%)
occurrences (all)	1	8	21
Neurotoxicity			
subjects affected / exposed	3 / 40 (7.50%)	4 / 58 (6.90%)	2 / 293 (0.68%)
occurrences (all)	3	7	3
Paraesthesia			
subjects affected / exposed	4 / 40 (10.00%)	12 / 58 (20.69%)	18 / 293 (6.14%)
occurrences (all)	4	17	21
Peripheral motor neuropathy			
subjects affected / exposed	2 / 40 (5.00%)	1 / 58 (1.72%)	3 / 293 (1.02%)
occurrences (all)	3	2	3
Peripheral sensory neuropathy			
subjects affected / exposed	4 / 40 (10.00%)	14 / 58 (24.14%)	32 / 293 (10.92%)
occurrences (all)	5	19	38
Polyneuropathy			
subjects affected / exposed	0 / 40 (0.00%)	2 / 58 (3.45%)	6 / 293 (2.05%)
occurrences (all)	0	2	6
Restless legs syndrome			
subjects affected / exposed	0 / 40 (0.00%)	1 / 58 (1.72%)	0 / 293 (0.00%)
occurrences (all)	0	1	0
Sensory loss			
subjects affected / exposed	0 / 40 (0.00%)	1 / 58 (1.72%)	0 / 293 (0.00%)
occurrences (all)	0	1	0
Somnolence			
subjects affected / exposed	2 / 40 (5.00%)	0 / 58 (0.00%)	4 / 293 (1.37%)
occurrences (all)	2	0	5
Taste disorder			
subjects affected / exposed	0 / 40 (0.00%)	3 / 58 (5.17%)	1 / 293 (0.34%)
occurrences (all)	0	3	1
Ageusia			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 40 (17.50%)	9 / 58 (15.52%)	21 / 293 (7.17%)
occurrences (all)	10	11	27

Leukopenia			
subjects affected / exposed	1 / 40 (2.50%)	4 / 58 (6.90%)	4 / 293 (1.37%)
occurrences (all)	1	4	8
Neutropenia			
subjects affected / exposed	2 / 40 (5.00%)	15 / 58 (25.86%)	12 / 293 (4.10%)
occurrences (all)	2	19	12
Thrombocytopenia			
subjects affected / exposed	0 / 40 (0.00%)	4 / 58 (6.90%)	10 / 293 (3.41%)
occurrences (all)	0	5	12
Ear and labyrinth disorders			
Auditory meatus external erosion			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Cataract			
subjects affected / exposed	4 / 40 (10.00%)	0 / 58 (0.00%)	2 / 293 (0.68%)
occurrences (all)	5	0	3
Conjunctival haemorrhage			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	0	0	0
Lacrimation increased			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	4 / 293 (1.37%)
occurrences (all)	0	0	5
Periorbital oedema			
subjects affected / exposed	0 / 40 (0.00%)	2 / 58 (3.45%)	2 / 293 (0.68%)
occurrences (all)	0	2	2
Dry eye			
subjects affected / exposed	0 / 40 (0.00%)	1 / 58 (1.72%)	1 / 293 (0.34%)
occurrences (all)	0	1	1
Visual impairment			
subjects affected / exposed	1 / 40 (2.50%)	0 / 58 (0.00%)	2 / 293 (0.68%)
occurrences (all)	1	0	2
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	8 / 40 (20.00%)	9 / 58 (15.52%)	39 / 293 (13.31%)
occurrences (all)	10	10	44
Abdominal pain upper			

subjects affected / exposed	2 / 40 (5.00%)	7 / 58 (12.07%)	18 / 293 (6.14%)
occurrences (all)	2	8	22
Angular cheilitis			
subjects affected / exposed	1 / 40 (2.50%)	1 / 58 (1.72%)	0 / 293 (0.00%)
occurrences (all)	1	1	0
Constipation			
subjects affected / exposed	5 / 40 (12.50%)	9 / 58 (15.52%)	38 / 293 (12.97%)
occurrences (all)	6	10	48
Dental cyst			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	16 / 40 (40.00%)	26 / 58 (44.83%)	78 / 293 (26.62%)
occurrences (all)	43	35	120
Dyspepsia			
subjects affected / exposed	1 / 40 (2.50%)	3 / 58 (5.17%)	10 / 293 (3.41%)
occurrences (all)	1	4	12
Dysphagia			
subjects affected / exposed	2 / 40 (5.00%)	2 / 58 (3.45%)	1 / 293 (0.34%)
occurrences (all)	4	3	1
Gingival bleeding			
subjects affected / exposed	2 / 40 (5.00%)	0 / 58 (0.00%)	5 / 293 (1.71%)
occurrences (all)	3	0	5
Haemorrhoids			
subjects affected / exposed	1 / 40 (2.50%)	4 / 58 (6.90%)	5 / 293 (1.71%)
occurrences (all)	1	4	5
Nausea			
subjects affected / exposed	16 / 40 (40.00%)	30 / 58 (51.72%)	64 / 293 (21.84%)
occurrences (all)	23	60	134
Palatal ulcer			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	0	0	0
Rectal haemorrhage			
subjects affected / exposed	2 / 40 (5.00%)	0 / 58 (0.00%)	6 / 293 (2.05%)
occurrences (all)	2	0	6
Stomatitis			

subjects affected / exposed	5 / 40 (12.50%)	14 / 58 (24.14%)	35 / 293 (11.95%)
occurrences (all)	6	19	50
Vomiting			
subjects affected / exposed	8 / 40 (20.00%)	14 / 58 (24.14%)	39 / 293 (13.31%)
occurrences (all)	12	18	61
Toothache			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	8 / 293 (2.73%)
occurrences (all)	0	0	8
Dry mouth			
subjects affected / exposed	1 / 40 (2.50%)	1 / 58 (1.72%)	4 / 293 (1.37%)
occurrences (all)	1	1	4
Eructation			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 40 (0.00%)	1 / 58 (1.72%)	6 / 293 (2.05%)
occurrences (all)	0	1	8
Odynophagia			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences (all)	0	0	1
Cheilitis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	0	0	0
Anal haemorrhage			
subjects affected / exposed	0 / 40 (0.00%)	1 / 58 (1.72%)	4 / 293 (1.37%)
occurrences (all)	0	2	5
Flatulence			
subjects affected / exposed	0 / 40 (0.00%)	1 / 58 (1.72%)	2 / 293 (0.68%)
occurrences (all)	0	1	2
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Alopecia			

subjects affected / exposed	1 / 40 (2.50%)	6 / 58 (10.34%)	8 / 293 (2.73%)
occurrences (all)	1	6	8
Dermatitis			
subjects affected / exposed	0 / 40 (0.00%)	1 / 58 (1.72%)	3 / 293 (1.02%)
occurrences (all)	0	1	3
Dermatitis acneiform			
subjects affected / exposed	11 / 40 (27.50%)	0 / 58 (0.00%)	4 / 293 (1.37%)
occurrences (all)	13	0	4
Dermatitis contact			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	12 / 40 (30.00%)	2 / 58 (3.45%)	18 / 293 (6.14%)
occurrences (all)	16	2	21
Eczema			
subjects affected / exposed	2 / 40 (5.00%)	0 / 58 (0.00%)	2 / 293 (0.68%)
occurrences (all)	2	0	2
Erythema			
subjects affected / exposed	8 / 40 (20.00%)	0 / 58 (0.00%)	11 / 293 (3.75%)
occurrences (all)	11	0	12
Nail ridging			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	0	0	0
Onychoclasis			
subjects affected / exposed	3 / 40 (7.50%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences (all)	3	0	1
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	5 / 40 (12.50%)	3 / 58 (5.17%)	44 / 293 (15.02%)
occurrences (all)	5	4	66
Photosensitivity reaction			
subjects affected / exposed	9 / 40 (22.50%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	10	0	0
Pruritus			
subjects affected / exposed	5 / 40 (12.50%)	0 / 58 (0.00%)	20 / 293 (6.83%)
occurrences (all)	5	0	25

Rash			
subjects affected / exposed	13 / 40 (32.50%)	2 / 58 (3.45%)	24 / 293 (8.19%)
occurrences (all)	17	2	30
Rash erythematous			
subjects affected / exposed	3 / 40 (7.50%)	0 / 58 (0.00%)	2 / 293 (0.68%)
occurrences (all)	4	0	2
Rash macular			
subjects affected / exposed	2 / 40 (5.00%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	3	0	0
Skin disorder			
subjects affected / exposed	2 / 40 (5.00%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	2	0	0
Skin fissures			
subjects affected / exposed	7 / 40 (17.50%)	0 / 58 (0.00%)	2 / 293 (0.68%)
occurrences (all)	11	0	2
Skin toxicity			
subjects affected / exposed	4 / 40 (10.00%)	1 / 58 (1.72%)	4 / 293 (1.37%)
occurrences (all)	7	1	5
Decubitus ulcer			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	0	0	0
Dermal cyst			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	0	0	0
Erythema nodosum			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	0	0	0
Rash maculo-papular			
subjects affected / exposed	1 / 40 (2.50%)	0 / 58 (0.00%)	4 / 293 (1.37%)
occurrences (all)	1	0	6
Rosacea			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	4 / 293 (1.37%)
occurrences (all)	0	0	5

Acne			
subjects affected / exposed	1 / 40 (2.50%)	1 / 58 (1.72%)	0 / 293 (0.00%)
occurrences (all)	2	1	0
Blister			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences (all)	0	0	1
Hand dermatitis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences (all)	0	0	1
Skin exfoliation			
subjects affected / exposed	1 / 40 (2.50%)	0 / 58 (0.00%)	5 / 293 (1.71%)
occurrences (all)	1	0	5
Hair texture abnormal			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 40 (0.00%)	1 / 58 (1.72%)	2 / 293 (0.68%)
occurrences (all)	0	1	2
Proteinuria			
subjects affected / exposed	1 / 40 (2.50%)	0 / 58 (0.00%)	17 / 293 (5.80%)
occurrences (all)	1	0	25
Renal colic			
subjects affected / exposed	1 / 40 (2.50%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	1	0	0
Nephrolithiasis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 40 (0.00%)	1 / 58 (1.72%)	16 / 293 (5.46%)
occurrences (all)	0	1	17
Hypothyroidism			
subjects affected / exposed	0 / 40 (0.00%)	1 / 58 (1.72%)	24 / 293 (8.19%)
occurrences (all)	0	1	32
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	18 / 40 (45.00%)	3 / 58 (5.17%)	50 / 293 (17.06%)
occurrences (all)	30	6	67
Back pain			
subjects affected / exposed	5 / 40 (12.50%)	6 / 58 (10.34%)	22 / 293 (7.51%)
occurrences (all)	5	6	32
Bone pain			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	6 / 293 (2.05%)
occurrences (all)	0	0	6
Muscle spasms			
subjects affected / exposed	2 / 40 (5.00%)	1 / 58 (1.72%)	5 / 293 (1.71%)
occurrences (all)	2	1	5
Muscle tightness			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences (all)	0	0	1
Musculoskeletal chest pain			
subjects affected / exposed	2 / 40 (5.00%)	0 / 58 (0.00%)	5 / 293 (1.71%)
occurrences (all)	2	0	6
Myalgia			
subjects affected / exposed	6 / 40 (15.00%)	4 / 58 (6.90%)	15 / 293 (5.12%)
occurrences (all)	8	4	17
Pain in extremity			
subjects affected / exposed	7 / 40 (17.50%)	1 / 58 (1.72%)	13 / 293 (4.44%)
occurrences (all)	10	1	18
Osteoporosis			
subjects affected / exposed	1 / 40 (2.50%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	1	0	0
Muscular weakness			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	0	0	0
Osteoporotic fracture			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			

subjects affected / exposed	0 / 40 (0.00%)	1 / 58 (1.72%)	5 / 293 (1.71%)
occurrences (all)	0	1	5
Conjunctivitis			
subjects affected / exposed	3 / 40 (7.50%)	2 / 58 (3.45%)	5 / 293 (1.71%)
occurrences (all)	3	2	6
Eye infection			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	0	0	0
Folliculitis			
subjects affected / exposed	6 / 40 (15.00%)	0 / 58 (0.00%)	2 / 293 (0.68%)
occurrences (all)	8	0	3
Nasopharyngitis			
subjects affected / exposed	1 / 40 (2.50%)	1 / 58 (1.72%)	15 / 293 (5.12%)
occurrences (all)	1	1	21
Onychomycosis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	2 / 293 (0.68%)
occurrences (all)	0	0	4
Oral herpes			
subjects affected / exposed	1 / 40 (2.50%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	1	0	0
Paronychia			
subjects affected / exposed	5 / 40 (12.50%)	1 / 58 (1.72%)	2 / 293 (0.68%)
occurrences (all)	13	1	2
Rhinitis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	5 / 293 (1.71%)
occurrences (all)	0	0	5
Tracheitis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	3 / 40 (7.50%)	0 / 58 (0.00%)	12 / 293 (4.10%)
occurrences (all)	4	0	22
Urinary tract infection			
subjects affected / exposed	1 / 40 (2.50%)	1 / 58 (1.72%)	12 / 293 (4.10%)
occurrences (all)	1	1	13
Gastroenteritis			

subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences (all)	0	0	1
Vulvitis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	0	0	0
Device related infection			
subjects affected / exposed	2 / 40 (5.00%)	1 / 58 (1.72%)	2 / 293 (0.68%)
occurrences (all)	2	1	3
Catheter site infection			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences (all)	0	0	1
Febrile infection			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences (all)	0	0	1
Vascular device infection			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	1 / 293 (0.34%)
occurrences (all)	0	0	1
Staphylococcal infection			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	0	0	0
Anal abscess			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	2 / 293 (0.68%)
occurrences (all)	0	0	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 40 (20.00%)	7 / 58 (12.07%)	24 / 293 (8.19%)
occurrences (all)	10	8	26
Food craving			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	0 / 293 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	1 / 40 (2.50%)	0 / 58 (0.00%)	5 / 293 (1.71%)
occurrences (all)	1	0	6

Hypoalbuminaemia			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	2 / 293 (0.68%)
occurrences (all)	0	0	2
Hypocalcaemia			
subjects affected / exposed	2 / 40 (5.00%)	0 / 58 (0.00%)	5 / 293 (1.71%)
occurrences (all)	3	0	10
Hypokalaemia			
subjects affected / exposed	3 / 40 (7.50%)	7 / 58 (12.07%)	6 / 293 (2.05%)
occurrences (all)	6	8	7
Hypomagnesaemia			
subjects affected / exposed	6 / 40 (15.00%)	1 / 58 (1.72%)	4 / 293 (1.37%)
occurrences (all)	6	2	4
Hypophosphataemia			
subjects affected / exposed	2 / 40 (5.00%)	0 / 58 (0.00%)	2 / 293 (0.68%)
occurrences (all)	2	0	2
Hypercalcaemia			
subjects affected / exposed	0 / 40 (0.00%)	1 / 58 (1.72%)	1 / 293 (0.34%)
occurrences (all)	0	1	1
Hyperkalaemia			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	4 / 293 (1.37%)
occurrences (all)	0	0	5
Dehydration			
subjects affected / exposed	0 / 40 (0.00%)	0 / 58 (0.00%)	4 / 293 (1.37%)
occurrences (all)	0	0	4

Non-serious adverse events	Cohort 2 Control (MP)	Cohort 2 (IP)	Cohort 1 Control (MP)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	120 / 143 (83.92%)	417 / 436 (95.64%)	17 / 18 (94.44%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Cancer pain			
subjects affected / exposed	0 / 143 (0.00%)	3 / 436 (0.69%)	0 / 18 (0.00%)
occurrences (all)	0	3	0
Vascular disorders			

Hypertension			
subjects affected / exposed	15 / 143 (10.49%)	90 / 436 (20.64%)	1 / 18 (5.56%)
occurrences (all)	19	119	1
Hypotension			
subjects affected / exposed	1 / 143 (0.70%)	4 / 436 (0.92%)	0 / 18 (0.00%)
occurrences (all)	1	4	0
Phlebitis			
subjects affected / exposed	0 / 143 (0.00%)	5 / 436 (1.15%)	0 / 18 (0.00%)
occurrences (all)	0	5	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	12 / 143 (8.39%)	73 / 436 (16.74%)	1 / 18 (5.56%)
occurrences (all)	20	109	2
Face oedema			
subjects affected / exposed	0 / 143 (0.00%)	2 / 436 (0.46%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Fatigue			
subjects affected / exposed	23 / 143 (16.08%)	134 / 436 (30.73%)	2 / 18 (11.11%)
occurrences (all)	27	205	2
Influenza like illness			
subjects affected / exposed	3 / 143 (2.10%)	9 / 436 (2.06%)	0 / 18 (0.00%)
occurrences (all)	3	9	0
Mucosal inflammation			
subjects affected / exposed	7 / 143 (4.90%)	31 / 436 (7.11%)	2 / 18 (11.11%)
occurrences (all)	9	34	4
Oedema peripheral			
subjects affected / exposed	2 / 143 (1.40%)	6 / 436 (1.38%)	0 / 18 (0.00%)
occurrences (all)	2	6	0
Pain			
subjects affected / exposed	1 / 143 (0.70%)	4 / 436 (0.92%)	0 / 18 (0.00%)
occurrences (all)	1	4	0
Pyrexia			
subjects affected / exposed	13 / 143 (9.09%)	43 / 436 (9.86%)	1 / 18 (5.56%)
occurrences (all)	14	53	1
Catheter site pain			

subjects affected / exposed	0 / 143 (0.00%)	2 / 436 (0.46%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
General physical health deterioration			
subjects affected / exposed	0 / 143 (0.00%)	2 / 436 (0.46%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Malaise			
subjects affected / exposed	1 / 143 (0.70%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 143 (0.70%)	10 / 436 (2.29%)	0 / 18 (0.00%)
occurrences (all)	1	10	0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 143 (0.70%)	0 / 436 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Cough			
subjects affected / exposed	9 / 143 (6.29%)	31 / 436 (7.11%)	3 / 18 (16.67%)
occurrences (all)	11	33	3
Dysphonia			
subjects affected / exposed	3 / 143 (2.10%)	25 / 436 (5.73%)	1 / 18 (5.56%)
occurrences (all)	3	35	1
Dyspnoea			
subjects affected / exposed	3 / 143 (2.10%)	17 / 436 (3.90%)	2 / 18 (11.11%)
occurrences (all)	3	18	2
Epistaxis			
subjects affected / exposed	16 / 143 (11.19%)	68 / 436 (15.60%)	1 / 18 (5.56%)
occurrences (all)	20	74	1
Hiccups			
subjects affected / exposed	1 / 143 (0.70%)	12 / 436 (2.75%)	1 / 18 (5.56%)
occurrences (all)	1	17	1
Nasal dryness			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Nasal ulcer			

subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Pulmonary embolism			
subjects affected / exposed	1 / 143 (0.70%)	9 / 436 (2.06%)	1 / 18 (5.56%)
occurrences (all)	1	9	1
Oropharyngeal pain			
subjects affected / exposed	3 / 143 (2.10%)	12 / 436 (2.75%)	0 / 18 (0.00%)
occurrences (all)	4	14	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 143 (0.70%)	10 / 436 (2.29%)	1 / 18 (5.56%)
occurrences (all)	1	10	1
Insomnia			
subjects affected / exposed	3 / 143 (2.10%)	19 / 436 (4.36%)	1 / 18 (5.56%)
occurrences (all)	3	20	1
Depression			
subjects affected / exposed	5 / 143 (3.50%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences (all)	5	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 143 (4.20%)	19 / 436 (4.36%)	0 / 18 (0.00%)
occurrences (all)	9	25	0
Amylase increased			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 143 (4.20%)	16 / 436 (3.67%)	1 / 18 (5.56%)
occurrences (all)	7	19	1
Blood alkaline phosphatase increased			
subjects affected / exposed	4 / 143 (2.80%)	7 / 436 (1.61%)	0 / 18 (0.00%)
occurrences (all)	5	7	0
Blood bilirubin increased			
subjects affected / exposed	5 / 143 (3.50%)	5 / 436 (1.15%)	1 / 18 (5.56%)
occurrences (all)	6	5	1
Blood creatine phosphokinase increased			

subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	1 / 143 (0.70%)	7 / 436 (1.61%)	0 / 18 (0.00%)
occurrences (all)	4	8	0
Ejection fraction decreased			
subjects affected / exposed	1 / 143 (0.70%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Lipase increased			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Neutrophil count decreased			
subjects affected / exposed	3 / 143 (2.10%)	46 / 436 (10.55%)	0 / 18 (0.00%)
occurrences (all)	4	68	0
Platelet count decreased			
subjects affected / exposed	3 / 143 (2.10%)	23 / 436 (5.28%)	0 / 18 (0.00%)
occurrences (all)	4	35	0
Weight decreased			
subjects affected / exposed	2 / 143 (1.40%)	33 / 436 (7.57%)	2 / 18 (11.11%)
occurrences (all)	3	34	2
Weight increased			
subjects affected / exposed	1 / 143 (0.70%)	7 / 436 (1.61%)	0 / 18 (0.00%)
occurrences (all)	1	7	0
White blood cell count decreased			
subjects affected / exposed	1 / 143 (0.70%)	9 / 436 (2.06%)	0 / 18 (0.00%)
occurrences (all)	1	14	0
Body temperature increased			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			
subjects affected / exposed	1 / 143 (0.70%)	3 / 436 (0.69%)	0 / 18 (0.00%)
occurrences (all)	1	3	0
Cardiac murmur			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Blood potassium decreased			

subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 143 (0.00%)	6 / 436 (1.38%)	0 / 18 (0.00%)
occurrences (all)	0	11	0
Lumbar vertebral fracture			
subjects affected / exposed	1 / 143 (0.70%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Sunburn			
subjects affected / exposed	1 / 143 (0.70%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal stoma complication			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 143 (0.70%)	15 / 436 (3.44%)	1 / 18 (5.56%)
occurrences (all)	1	17	2
Dysgeusia			
subjects affected / exposed	3 / 143 (2.10%)	30 / 436 (6.88%)	0 / 18 (0.00%)
occurrences (all)	3	39	0
Headache			
subjects affected / exposed	5 / 143 (3.50%)	39 / 436 (8.94%)	0 / 18 (0.00%)
occurrences (all)	15	71	0
Neuropathy peripheral			
subjects affected / exposed	9 / 143 (6.29%)	68 / 436 (15.60%)	0 / 18 (0.00%)
occurrences (all)	9	96	0
Neurotoxicity			
subjects affected / exposed	2 / 143 (1.40%)	14 / 436 (3.21%)	0 / 18 (0.00%)
occurrences (all)	3	20	0
Paraesthesia			
subjects affected / exposed	10 / 143 (6.99%)	63 / 436 (14.45%)	0 / 18 (0.00%)
occurrences (all)	11	75	0
Peripheral motor neuropathy			

subjects affected / exposed	0 / 143 (0.00%)	5 / 436 (1.15%)	0 / 18 (0.00%)
occurrences (all)	0	5	0
Peripheral sensory neuropathy			
subjects affected / exposed	15 / 143 (10.49%)	153 / 436 (35.09%)	1 / 18 (5.56%)
occurrences (all)	16	233	1
Polyneuropathy			
subjects affected / exposed	1 / 143 (0.70%)	16 / 436 (3.67%)	1 / 18 (5.56%)
occurrences (all)	2	18	1
Restless legs syndrome			
subjects affected / exposed	1 / 143 (0.70%)	0 / 436 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Sensory loss			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Somnolence			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Taste disorder			
subjects affected / exposed	1 / 143 (0.70%)	9 / 436 (2.06%)	0 / 18 (0.00%)
occurrences (all)	1	9	0
Ageusia			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 143 (5.59%)	35 / 436 (8.03%)	1 / 18 (5.56%)
occurrences (all)	13	42	2
Leukopenia			
subjects affected / exposed	3 / 143 (2.10%)	24 / 436 (5.50%)	0 / 18 (0.00%)
occurrences (all)	3	32	0
Neutropenia			
subjects affected / exposed	8 / 143 (5.59%)	97 / 436 (22.25%)	1 / 18 (5.56%)
occurrences (all)	17	151	1
Thrombocytopenia			
subjects affected / exposed	4 / 143 (2.80%)	27 / 436 (6.19%)	0 / 18 (0.00%)
occurrences (all)	10	35	0

Ear and labyrinth disorders			
Auditory meatus external erosion			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Conjunctival haemorrhage			
subjects affected / exposed	1 / 143 (0.70%)	0 / 436 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Lacrimation increased			
subjects affected / exposed	5 / 143 (3.50%)	6 / 436 (1.38%)	1 / 18 (5.56%)
occurrences (all)	5	6	1
Periorbital oedema			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Dry eye			
subjects affected / exposed	2 / 143 (1.40%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences (all)	2	1	0
Visual impairment			
subjects affected / exposed	0 / 143 (0.00%)	3 / 436 (0.69%)	0 / 18 (0.00%)
occurrences (all)	0	3	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	12 / 143 (8.39%)	53 / 436 (12.16%)	1 / 18 (5.56%)
occurrences (all)	15	66	1
Abdominal pain upper			
subjects affected / exposed	11 / 143 (7.69%)	20 / 436 (4.59%)	3 / 18 (16.67%)
occurrences (all)	15	23	3
Angular cheilitis			
subjects affected / exposed	0 / 143 (0.00%)	2 / 436 (0.46%)	1 / 18 (5.56%)
occurrences (all)	0	2	1
Constipation			
subjects affected / exposed	17 / 143 (11.89%)	82 / 436 (18.81%)	0 / 18 (0.00%)
occurrences (all)	26	106	0
Dental cyst			

subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	21 / 143 (14.69%)	158 / 436 (36.24%)	4 / 18 (22.22%)
occurrences (all)	36	266	5
Dyspepsia			
subjects affected / exposed	4 / 143 (2.80%)	14 / 436 (3.21%)	1 / 18 (5.56%)
occurrences (all)	4	17	1
Dysphagia			
subjects affected / exposed	1 / 143 (0.70%)	11 / 436 (2.52%)	0 / 18 (0.00%)
occurrences (all)	1	18	0
Gingival bleeding			
subjects affected / exposed	0 / 143 (0.00%)	3 / 436 (0.69%)	0 / 18 (0.00%)
occurrences (all)	0	3	0
Haemorrhoids			
subjects affected / exposed	1 / 143 (0.70%)	11 / 436 (2.52%)	1 / 18 (5.56%)
occurrences (all)	2	12	1
Nausea			
subjects affected / exposed	27 / 143 (18.88%)	177 / 436 (40.60%)	0 / 18 (0.00%)
occurrences (all)	41	297	0
Palatal ulcer			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Rectal haemorrhage			
subjects affected / exposed	4 / 143 (2.80%)	8 / 436 (1.83%)	1 / 18 (5.56%)
occurrences (all)	6	8	1
Stomatitis			
subjects affected / exposed	11 / 143 (7.69%)	82 / 436 (18.81%)	3 / 18 (16.67%)
occurrences (all)	19	111	3
Vomiting			
subjects affected / exposed	8 / 143 (5.59%)	82 / 436 (18.81%)	1 / 18 (5.56%)
occurrences (all)	11	113	1
Toothache			
subjects affected / exposed	2 / 143 (1.40%)	8 / 436 (1.83%)	0 / 18 (0.00%)
occurrences (all)	2	8	0
Dry mouth			

subjects affected / exposed	0 / 143 (0.00%)	12 / 436 (2.75%)	0 / 18 (0.00%)
occurrences (all)	0	13	0
Eructation			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 143 (0.70%)	11 / 436 (2.52%)	0 / 18 (0.00%)
occurrences (all)	1	11	0
Odynophagia			
subjects affected / exposed	0 / 143 (0.00%)	3 / 436 (0.69%)	0 / 18 (0.00%)
occurrences (all)	0	3	0
Cheilitis			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Anal haemorrhage			
subjects affected / exposed	0 / 143 (0.00%)	5 / 436 (1.15%)	0 / 18 (0.00%)
occurrences (all)	0	5	0
Flatulence			
subjects affected / exposed	1 / 143 (0.70%)	11 / 436 (2.52%)	0 / 18 (0.00%)
occurrences (all)	1	15	0
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	0 / 143 (0.00%)	2 / 436 (0.46%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 143 (1.40%)	40 / 436 (9.17%)	2 / 18 (11.11%)
occurrences (all)	2	40	2
Dermatitis			
subjects affected / exposed	1 / 143 (0.70%)	1 / 436 (0.23%)	1 / 18 (5.56%)
occurrences (all)	1	1	1
Dermatitis acneiform			
subjects affected / exposed	0 / 143 (0.00%)	4 / 436 (0.92%)	0 / 18 (0.00%)
occurrences (all)	0	5	0
Dermatitis contact			

subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Dry skin			
subjects affected / exposed	3 / 143 (2.10%)	24 / 436 (5.50%)	3 / 18 (16.67%)
occurrences (all)	6	24	3
Eczema			
subjects affected / exposed	0 / 143 (0.00%)	2 / 436 (0.46%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Erythema			
subjects affected / exposed	2 / 143 (1.40%)	7 / 436 (1.61%)	1 / 18 (5.56%)
occurrences (all)	2	7	4
Nail ridging			
subjects affected / exposed	3 / 143 (2.10%)	0 / 436 (0.00%)	1 / 18 (5.56%)
occurrences (all)	3	0	1
Onychoclasis			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	25 / 143 (17.48%)	23 / 436 (5.28%)	4 / 18 (22.22%)
occurrences (all)	40	30	5
Photosensitivity reaction			
subjects affected / exposed	0 / 143 (0.00%)	3 / 436 (0.69%)	0 / 18 (0.00%)
occurrences (all)	0	3	0
Pruritus			
subjects affected / exposed	6 / 143 (4.20%)	8 / 436 (1.83%)	2 / 18 (11.11%)
occurrences (all)	6	9	2
Rash			
subjects affected / exposed	1 / 143 (0.70%)	15 / 436 (3.44%)	0 / 18 (0.00%)
occurrences (all)	1	16	0
Rash erythematous			
subjects affected / exposed	0 / 143 (0.00%)	4 / 436 (0.92%)	0 / 18 (0.00%)
occurrences (all)	0	4	0
Rash macular			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0

Skin disorder			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Skin fissures			
subjects affected / exposed	0 / 143 (0.00%)	3 / 436 (0.69%)	0 / 18 (0.00%)
occurrences (all)	0	3	0
Skin toxicity			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Decubitus ulcer			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Dermal cyst			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Erythema nodosum			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Rash maculo-papular			
subjects affected / exposed	0 / 143 (0.00%)	5 / 436 (1.15%)	0 / 18 (0.00%)
occurrences (all)	0	5	0
Rosacea			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	0 / 143 (0.00%)	4 / 436 (0.92%)	0 / 18 (0.00%)
occurrences (all)	0	5	0
Acne			
subjects affected / exposed	1 / 143 (0.70%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Blister			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Hand dermatitis			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0

Skin exfoliation			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Hair texture abnormal			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 143 (0.70%)	9 / 436 (2.06%)	1 / 18 (5.56%)
occurrences (all)	1	9	1
Proteinuria			
subjects affected / exposed	4 / 143 (2.80%)	17 / 436 (3.90%)	0 / 18 (0.00%)
occurrences (all)	4	19	0
Renal colic			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Nephrolithiasis			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Hypothyroidism			
subjects affected / exposed	1 / 143 (0.70%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 143 (5.59%)	14 / 436 (3.21%)	3 / 18 (16.67%)
occurrences (all)	10	16	5
Back pain			
subjects affected / exposed	9 / 143 (6.29%)	13 / 436 (2.98%)	2 / 18 (11.11%)
occurrences (all)	9	14	2
Bone pain			
subjects affected / exposed	0 / 143 (0.00%)	4 / 436 (0.92%)	1 / 18 (5.56%)
occurrences (all)	0	4	1

Muscle spasms			
subjects affected / exposed	0 / 143 (0.00%)	9 / 436 (2.06%)	0 / 18 (0.00%)
occurrences (all)	0	9	0
Muscle tightness			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Musculoskeletal chest pain			
subjects affected / exposed	2 / 143 (1.40%)	4 / 436 (0.92%)	0 / 18 (0.00%)
occurrences (all)	2	5	0
Myalgia			
subjects affected / exposed	3 / 143 (2.10%)	8 / 436 (1.83%)	1 / 18 (5.56%)
occurrences (all)	3	12	1
Pain in extremity			
subjects affected / exposed	8 / 143 (5.59%)	15 / 436 (3.44%)	0 / 18 (0.00%)
occurrences (all)	9	19	0
Osteoporosis			
subjects affected / exposed	2 / 143 (1.40%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Muscular weakness			
subjects affected / exposed	0 / 143 (0.00%)	6 / 436 (1.38%)	0 / 18 (0.00%)
occurrences (all)	0	6	0
Osteoporotic fracture			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 143 (2.10%)	3 / 436 (0.69%)	1 / 18 (5.56%)
occurrences (all)	3	3	2
Conjunctivitis			
subjects affected / exposed	2 / 143 (1.40%)	4 / 436 (0.92%)	1 / 18 (5.56%)
occurrences (all)	2	4	1
Eye infection			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Folliculitis			

subjects affected / exposed	1 / 143 (0.70%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	10 / 143 (6.99%)	15 / 436 (3.44%)	1 / 18 (5.56%)
occurrences (all)	12	17	1
Onychomycosis			
subjects affected / exposed	2 / 143 (1.40%)	2 / 436 (0.46%)	2 / 18 (11.11%)
occurrences (all)	2	2	2
Oral herpes			
subjects affected / exposed	0 / 143 (0.00%)	4 / 436 (0.92%)	1 / 18 (5.56%)
occurrences (all)	0	4	1
Paronychia			
subjects affected / exposed	1 / 143 (0.70%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	3 / 143 (2.10%)	15 / 436 (3.44%)	0 / 18 (0.00%)
occurrences (all)	3	15	0
Tracheitis			
subjects affected / exposed	1 / 143 (0.70%)	0 / 436 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Upper respiratory tract infection			
subjects affected / exposed	2 / 143 (1.40%)	12 / 436 (2.75%)	2 / 18 (11.11%)
occurrences (all)	2	13	2
Urinary tract infection			
subjects affected / exposed	4 / 143 (2.80%)	22 / 436 (5.05%)	1 / 18 (5.56%)
occurrences (all)	4	26	1
Gastroenteritis			
subjects affected / exposed	1 / 143 (0.70%)	3 / 436 (0.69%)	0 / 18 (0.00%)
occurrences (all)	1	3	0
Vulvitis			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Device related infection			
subjects affected / exposed	0 / 143 (0.00%)	4 / 436 (0.92%)	0 / 18 (0.00%)
occurrences (all)	0	4	0
Catheter site infection			

subjects affected / exposed	0 / 143 (0.00%)	2 / 436 (0.46%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Febrile infection			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Vascular device infection			
subjects affected / exposed	1 / 143 (0.70%)	2 / 436 (0.46%)	0 / 18 (0.00%)
occurrences (all)	1	2	0
Staphylococcal infection			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Anal abscess			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	1 / 143 (0.70%)	4 / 436 (0.92%)	0 / 18 (0.00%)
occurrences (all)	1	4	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	14 / 143 (9.79%)	65 / 436 (14.91%)	0 / 18 (0.00%)
occurrences (all)	15	85	0
Food craving			
subjects affected / exposed	0 / 143 (0.00%)	0 / 436 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Hyperglycaemia			
subjects affected / exposed	2 / 143 (1.40%)	22 / 436 (5.05%)	0 / 18 (0.00%)
occurrences (all)	5	29	0
Hypoalbuminaemia			
subjects affected / exposed	2 / 143 (1.40%)	9 / 436 (2.06%)	1 / 18 (5.56%)
occurrences (all)	4	9	1
Hypocalcaemia			
subjects affected / exposed	6 / 143 (4.20%)	12 / 436 (2.75%)	1 / 18 (5.56%)
occurrences (all)	10	16	1
Hypokalaemia			
subjects affected / exposed	8 / 143 (5.59%)	35 / 436 (8.03%)	1 / 18 (5.56%)
occurrences (all)	9	44	1

Hypomagnesaemia			
subjects affected / exposed	0 / 143 (0.00%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Hypophosphataemia			
subjects affected / exposed	3 / 143 (2.10%)	4 / 436 (0.92%)	0 / 18 (0.00%)
occurrences (all)	3	4	0
Hypercalcaemia			
subjects affected / exposed	1 / 143 (0.70%)	0 / 436 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Hyperkalaemia			
subjects affected / exposed	1 / 143 (0.70%)	1 / 436 (0.23%)	0 / 18 (0.00%)
occurrences (all)	2	1	0
Dehydration			
subjects affected / exposed	0 / 143 (0.00%)	5 / 436 (1.15%)	0 / 18 (0.00%)
occurrences (all)	0	5	0

Non-serious adverse events	Cohort 3 (IP)	Cohort 3 (MP)	Cohort 3 Control (MP)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	3 / 3 (100.00%)	2 / 2 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Cancer pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Hypotension			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Phlebitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0

General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Face oedema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	3 / 5 (60.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	4	1	0
Influenza like illness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Mucosal inflammation			
subjects affected / exposed	2 / 5 (40.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	2	1	0
Oedema peripheral			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Catheter site pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
General physical health deterioration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			

Hypersensitivity			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Dysphonia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Epistaxis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	2 / 2 (100.00%)
occurrences (all)	1	0	2
Hiccups			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Nasal dryness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Nasal ulcer			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Pulmonary embolism			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			

Anxiety			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Amylase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Blood bilirubin increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Blood creatinine increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Ejection fraction decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Lipase increased			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Neutrophil count decreased			
subjects affected / exposed	2 / 5 (40.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Platelet count decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Weight increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Body temperature increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Cardiac murmur			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Blood potassium decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Lumbar vertebral fracture			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Sunburn			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal stoma complication			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Dysgeusia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Neuropathy peripheral			
subjects affected / exposed	2 / 5 (40.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Neurotoxicity			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	2 / 5 (40.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Peripheral motor neuropathy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 5 (40.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	3	0	0
Polyneuropathy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0

Restless legs syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Sensory loss			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Taste disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Ageusia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Leukopenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Auditory meatus external erosion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Conjunctival haemorrhage			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Lacrimation increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Periorbital oedema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Dry eye			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Visual impairment			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Angular cheilitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences (all)	1	0	1
Dental cyst			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	2 / 5 (40.00%)	2 / 3 (66.67%)	0 / 2 (0.00%)
occurrences (all)	2	5	0
Dyspepsia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0

Dysphagia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Gingival bleeding			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Haemorrhoids			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Palatal ulcer			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Rectal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Dry mouth			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Eructation			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0

Odynophagia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Cheilitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Anal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Dermatitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Dermatitis acneiform			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Dermatitis contact			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Eczema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Erythema			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Nail ridging			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Onychoclasis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 5 (20.00%)	3 / 3 (100.00%)	0 / 2 (0.00%)
occurrences (all)	1	6	0
Photosensitivity reaction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Rash erythematous			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Rash macular			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Skin disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Skin fissures			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Skin toxicity			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0

Decubitus ulcer			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Dermal cyst			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Erythema nodosum			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Rash maculo-papular			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Rosacea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Acne			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Blister			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hand dermatitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Skin exfoliation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Hair texture abnormal			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Dysuria			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Proteinuria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Renal colic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Nephrolithiasis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hypothyroidism			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Bone pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Muscle tightness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Osteoporosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Muscular weakness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Osteoporotic fracture			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Eye infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Folliculitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Onychomycosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0

Oral herpes			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Paronychia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Tracheitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Vulvitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Device related infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Catheter site infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Febrile infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Vascular device infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0

Staphylococcal infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Anal abscess			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Food craving			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Hypomagnesaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hypophosphataemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hypercalcaemia			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Dehydration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort 4 (IP)	Cohort 4 (MP)	Cohort 4 Control (MP)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	96 / 98 (97.96%)	61 / 64 (95.31%)	29 / 34 (85.29%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Cancer pain			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	19 / 98 (19.39%)	3 / 64 (4.69%)	5 / 34 (14.71%)
occurrences (all)	27	4	7
Hypotension			
subjects affected / exposed	0 / 98 (0.00%)	3 / 64 (4.69%)	0 / 34 (0.00%)
occurrences (all)	0	3	0
Phlebitis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	15 / 98 (15.31%)	13 / 64 (20.31%)	3 / 34 (8.82%)
occurrences (all)	28	18	3
Face oedema			
subjects affected / exposed	0 / 98 (0.00%)	5 / 64 (7.81%)	0 / 34 (0.00%)
occurrences (all)	0	5	0

Fatigue			
subjects affected / exposed	34 / 98 (34.69%)	12 / 64 (18.75%)	7 / 34 (20.59%)
occurrences (all)	49	20	8
Influenza like illness			
subjects affected / exposed	2 / 98 (2.04%)	1 / 64 (1.56%)	1 / 34 (2.94%)
occurrences (all)	2	1	1
Mucosal inflammation			
subjects affected / exposed	15 / 98 (15.31%)	4 / 64 (6.25%)	1 / 34 (2.94%)
occurrences (all)	19	5	1
Oedema peripheral			
subjects affected / exposed	1 / 98 (1.02%)	6 / 64 (9.38%)	1 / 34 (2.94%)
occurrences (all)	1	8	1
Pain			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	11 / 98 (11.22%)	20 / 64 (31.25%)	3 / 34 (8.82%)
occurrences (all)	13	27	3
Catheter site pain			
subjects affected / exposed	2 / 98 (2.04%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	2	0	0
General physical health deterioration			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	1 / 98 (1.02%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences (all)	1	1	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 98 (1.02%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences (all)	1	1	0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Cough			

subjects affected / exposed	6 / 98 (6.12%)	7 / 64 (10.94%)	3 / 34 (8.82%)
occurrences (all)	6	7	3
Dysphonia			
subjects affected / exposed	4 / 98 (4.08%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences (all)	4	1	0
Dyspnoea			
subjects affected / exposed	5 / 98 (5.10%)	2 / 64 (3.13%)	1 / 34 (2.94%)
occurrences (all)	5	2	1
Epistaxis			
subjects affected / exposed	18 / 98 (18.37%)	6 / 64 (9.38%)	3 / 34 (8.82%)
occurrences (all)	19	6	4
Hiccups			
subjects affected / exposed	4 / 98 (4.08%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	4	0	0
Nasal dryness			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Nasal ulcer			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Pulmonary embolism			
subjects affected / exposed	1 / 98 (1.02%)	0 / 64 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Oropharyngeal pain			
subjects affected / exposed	1 / 98 (1.02%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences (all)	1	1	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	5 / 98 (5.10%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences (all)	5	1	0
Insomnia			
subjects affected / exposed	3 / 98 (3.06%)	3 / 64 (4.69%)	0 / 34 (0.00%)
occurrences (all)	3	3	0
Depression			
subjects affected / exposed	1 / 98 (1.02%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	1	0	0

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 98 (2.04%)	12 / 64 (18.75%)	0 / 34 (0.00%)
occurrences (all)	2	13	0
Amylase increased			
subjects affected / exposed	1 / 98 (1.02%)	4 / 64 (6.25%)	0 / 34 (0.00%)
occurrences (all)	1	4	0
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 98 (2.04%)	15 / 64 (23.44%)	0 / 34 (0.00%)
occurrences (all)	2	15	0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 98 (1.02%)	6 / 64 (9.38%)	0 / 34 (0.00%)
occurrences (all)	2	6	0
Blood bilirubin increased			
subjects affected / exposed	0 / 98 (0.00%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 98 (1.02%)	31 / 64 (48.44%)	0 / 34 (0.00%)
occurrences (all)	1	39	0
Blood creatinine increased			
subjects affected / exposed	1 / 98 (1.02%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences (all)	1	1	0
Ejection fraction decreased			
subjects affected / exposed	1 / 98 (1.02%)	5 / 64 (7.81%)	0 / 34 (0.00%)
occurrences (all)	1	6	0
Lipase increased			
subjects affected / exposed	2 / 98 (2.04%)	5 / 64 (7.81%)	0 / 34 (0.00%)
occurrences (all)	2	7	0
Neutrophil count decreased			
subjects affected / exposed	9 / 98 (9.18%)	2 / 64 (3.13%)	0 / 34 (0.00%)
occurrences (all)	15	2	0
Platelet count decreased			
subjects affected / exposed	11 / 98 (11.22%)	6 / 64 (9.38%)	1 / 34 (2.94%)
occurrences (all)	13	7	1
Weight decreased			

subjects affected / exposed	4 / 98 (4.08%)	6 / 64 (9.38%)	0 / 34 (0.00%)
occurrences (all)	4	6	0
Weight increased			
subjects affected / exposed	2 / 98 (2.04%)	3 / 64 (4.69%)	2 / 34 (5.88%)
occurrences (all)	3	7	2
White blood cell count decreased			
subjects affected / exposed	1 / 98 (1.02%)	2 / 64 (3.13%)	0 / 34 (0.00%)
occurrences (all)	1	4	0
Body temperature increased			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Cardiac murmur			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Blood potassium decreased			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	6 / 98 (6.12%)	2 / 64 (3.13%)	0 / 34 (0.00%)
occurrences (all)	11	2	0
Lumbar vertebral fracture			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Sunburn			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal stoma complication			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			

Dizziness			
subjects affected / exposed	4 / 98 (4.08%)	4 / 64 (6.25%)	1 / 34 (2.94%)
occurrences (all)	4	4	1
Dysgeusia			
subjects affected / exposed	6 / 98 (6.12%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	7	0	0
Headache			
subjects affected / exposed	14 / 98 (14.29%)	6 / 64 (9.38%)	3 / 34 (8.82%)
occurrences (all)	24	8	5
Neuropathy peripheral			
subjects affected / exposed	18 / 98 (18.37%)	1 / 64 (1.56%)	5 / 34 (14.71%)
occurrences (all)	25	2	5
Neurotoxicity			
subjects affected / exposed	8 / 98 (8.16%)	3 / 64 (4.69%)	1 / 34 (2.94%)
occurrences (all)	16	3	1
Paraesthesia			
subjects affected / exposed	14 / 98 (14.29%)	1 / 64 (1.56%)	1 / 34 (2.94%)
occurrences (all)	17	1	1
Peripheral motor neuropathy			
subjects affected / exposed	5 / 98 (5.10%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences (all)	5	1	0
Peripheral sensory neuropathy			
subjects affected / exposed	28 / 98 (28.57%)	3 / 64 (4.69%)	4 / 34 (11.76%)
occurrences (all)	42	6	4
Polyneuropathy			
subjects affected / exposed	1 / 98 (1.02%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	1	0	0
Restless legs syndrome			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Sensory loss			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0

Taste disorder			
subjects affected / exposed	1 / 98 (1.02%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	1	0	0
Ageusia			
subjects affected / exposed	3 / 98 (3.06%)	0 / 64 (0.00%)	1 / 34 (2.94%)
occurrences (all)	3	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 98 (10.20%)	8 / 64 (12.50%)	1 / 34 (2.94%)
occurrences (all)	11	10	1
Leukopenia			
subjects affected / exposed	3 / 98 (3.06%)	0 / 64 (0.00%)	1 / 34 (2.94%)
occurrences (all)	3	0	1
Neutropenia			
subjects affected / exposed	25 / 98 (25.51%)	7 / 64 (10.94%)	3 / 34 (8.82%)
occurrences (all)	40	9	4
Thrombocytopenia			
subjects affected / exposed	6 / 98 (6.12%)	4 / 64 (6.25%)	1 / 34 (2.94%)
occurrences (all)	8	4	5
Ear and labyrinth disorders			
Auditory meatus external erosion			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Cataract			
subjects affected / exposed	1 / 98 (1.02%)	3 / 64 (4.69%)	0 / 34 (0.00%)
occurrences (all)	1	3	0
Conjunctival haemorrhage			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Lacrimation increased			
subjects affected / exposed	2 / 98 (2.04%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	2	0	0
Periorbital oedema			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Dry eye			

subjects affected / exposed	1 / 98 (1.02%)	0 / 64 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Visual impairment			
subjects affected / exposed	1 / 98 (1.02%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	11 / 98 (11.22%)	12 / 64 (18.75%)	5 / 34 (14.71%)
occurrences (all)	13	15	5
Abdominal pain upper			
subjects affected / exposed	3 / 98 (3.06%)	5 / 64 (7.81%)	1 / 34 (2.94%)
occurrences (all)	3	6	1
Angular cheilitis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	20 / 98 (20.41%)	7 / 64 (10.94%)	2 / 34 (5.88%)
occurrences (all)	23	9	2
Dental cyst			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	33 / 98 (33.67%)	40 / 64 (62.50%)	8 / 34 (23.53%)
occurrences (all)	68	87	11
Dyspepsia			
subjects affected / exposed	8 / 98 (8.16%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences (all)	8	1	0
Dysphagia			
subjects affected / exposed	1 / 98 (1.02%)	1 / 64 (1.56%)	2 / 34 (5.88%)
occurrences (all)	1	1	2
Gingival bleeding			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	0 / 98 (0.00%)	2 / 64 (3.13%)	0 / 34 (0.00%)
occurrences (all)	0	2	0

Nausea			
subjects affected / exposed	43 / 98 (43.88%)	17 / 64 (26.56%)	6 / 34 (17.65%)
occurrences (all)	90	22	22
Palatal ulcer			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Rectal haemorrhage			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	16 / 98 (16.33%)	1 / 64 (1.56%)	3 / 34 (8.82%)
occurrences (all)	21	1	3
Vomiting			
subjects affected / exposed	19 / 98 (19.39%)	13 / 64 (20.31%)	3 / 34 (8.82%)
occurrences (all)	32	19	9
Toothache			
subjects affected / exposed	1 / 98 (1.02%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences (all)	1	1	0
Dry mouth			
subjects affected / exposed	1 / 98 (1.02%)	3 / 64 (4.69%)	0 / 34 (0.00%)
occurrences (all)	1	3	0
Eructation			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Odynophagia			
subjects affected / exposed	1 / 98 (1.02%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	1	0	0
Cheilitis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	1	0	0
Anal haemorrhage			
subjects affected / exposed	0 / 98 (0.00%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences (all)	0	1	0

Flatulence			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	6 / 98 (6.12%)	0 / 64 (0.00%)	1 / 34 (2.94%)
occurrences (all)	6	0	1
Dermatitis			
subjects affected / exposed	0 / 98 (0.00%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences (all)	0	2	0
Dermatitis acneiform			
subjects affected / exposed	1 / 98 (1.02%)	18 / 64 (28.13%)	2 / 34 (5.88%)
occurrences (all)	1	20	2
Dermatitis contact			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	3 / 98 (3.06%)	6 / 64 (9.38%)	1 / 34 (2.94%)
occurrences (all)	3	6	1
Eczema			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	0 / 98 (0.00%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Nail ridging			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Onychoclasis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Palmar-plantar erythrodysaesthesia syndrome			

subjects affected / exposed	3 / 98 (3.06%)	1 / 64 (1.56%)	3 / 34 (8.82%)
occurrences (all)	3	1	3
Photosensitivity reaction			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	3 / 98 (3.06%)	7 / 64 (10.94%)	1 / 34 (2.94%)
occurrences (all)	3	14	1
Rash			
subjects affected / exposed	3 / 98 (3.06%)	28 / 64 (43.75%)	0 / 34 (0.00%)
occurrences (all)	3	33	0
Rash erythematous			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Rash macular			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Skin disorder			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Skin fissures			
subjects affected / exposed	0 / 98 (0.00%)	1 / 64 (1.56%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Skin toxicity			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Decubitus ulcer			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Dermal cyst			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Erythema nodosum			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Rash maculo-papular			

subjects affected / exposed	1 / 98 (1.02%)	3 / 64 (4.69%)	0 / 34 (0.00%)
occurrences (all)	2	3	0
Rosacea			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	1 / 98 (1.02%)	3 / 64 (4.69%)	0 / 34 (0.00%)
occurrences (all)	1	5	0
Acne			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Blister			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Hand dermatitis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Skin exfoliation			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Hair texture abnormal			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	3 / 98 (3.06%)	2 / 64 (3.13%)	0 / 34 (0.00%)
occurrences (all)	4	2	0
Proteinuria			
subjects affected / exposed	1 / 98 (1.02%)	1 / 64 (1.56%)	2 / 34 (5.88%)
occurrences (all)	1	1	4
Renal colic			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Nephrolithiasis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0

Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 98 (0.00%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Hypothyroidism			
subjects affected / exposed	0 / 98 (0.00%)	3 / 64 (4.69%)	0 / 34 (0.00%)
occurrences (all)	0	3	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 98 (4.08%)	8 / 64 (12.50%)	3 / 34 (8.82%)
occurrences (all)	4	8	5
Back pain			
subjects affected / exposed	3 / 98 (3.06%)	5 / 64 (7.81%)	3 / 34 (8.82%)
occurrences (all)	3	5	3
Bone pain			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 98 (0.00%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Muscle tightness			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	5 / 98 (5.10%)	5 / 64 (7.81%)	2 / 34 (5.88%)
occurrences (all)	9	5	3
Pain in extremity			
subjects affected / exposed	3 / 98 (3.06%)	5 / 64 (7.81%)	2 / 34 (5.88%)
occurrences (all)	3	6	2
Osteoporosis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Muscular weakness			

subjects affected / exposed	1 / 98 (1.02%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences (all)	1	1	0
Osteoporotic fracture			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	0 / 98 (0.00%)	2 / 64 (3.13%)	1 / 34 (2.94%)
occurrences (all)	0	2	1
Eye infection			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Folliculitis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	3 / 98 (3.06%)	3 / 64 (4.69%)	1 / 34 (2.94%)
occurrences (all)	3	4	1
Onychomycosis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Oral herpes			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Paronychia			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	2 / 98 (2.04%)	1 / 64 (1.56%)	3 / 34 (8.82%)
occurrences (all)	2	1	3
Tracheitis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0

Upper respiratory tract infection			
subjects affected / exposed	4 / 98 (4.08%)	2 / 64 (3.13%)	3 / 34 (8.82%)
occurrences (all)	5	2	3
Urinary tract infection			
subjects affected / exposed	3 / 98 (3.06%)	7 / 64 (10.94%)	1 / 34 (2.94%)
occurrences (all)	3	10	1
Gastroenteritis			
subjects affected / exposed	1 / 98 (1.02%)	2 / 64 (3.13%)	0 / 34 (0.00%)
occurrences (all)	1	2	0
Vulvitis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Device related infection			
subjects affected / exposed	1 / 98 (1.02%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	1	0	0
Catheter site infection			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Febrile infection			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Vascular device infection			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Staphylococcal infection			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Anal abscess			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	0 / 98 (0.00%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	14 / 98 (14.29%)	11 / 64 (17.19%)	1 / 34 (2.94%)
occurrences (all)	17	12	1
Food craving			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	5 / 98 (5.10%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences (all)	7	1	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 98 (0.00%)	1 / 64 (1.56%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Hypocalcaemia			
subjects affected / exposed	1 / 98 (1.02%)	2 / 64 (3.13%)	0 / 34 (0.00%)
occurrences (all)	1	2	0
Hypokalaemia			
subjects affected / exposed	2 / 98 (2.04%)	4 / 64 (6.25%)	1 / 34 (2.94%)
occurrences (all)	2	4	1
Hypomagnesaemia			
subjects affected / exposed	1 / 98 (1.02%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	1	0	0
Hypophosphataemia			
subjects affected / exposed	2 / 98 (2.04%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	2	0	0
Hypercalcaemia			
subjects affected / exposed	0 / 98 (0.00%)	0 / 64 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Hyperkalaemia			
subjects affected / exposed	1 / 98 (1.02%)	0 / 64 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Dehydration			
subjects affected / exposed	0 / 98 (0.00%)	2 / 64 (3.13%)	0 / 34 (0.00%)
occurrences (all)	0	2	0

Non-serious adverse events	Early Progressing BRAFmut Cohort		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 11 (100.00%)		

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Cancer pain			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Phlebitis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Face oedema			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	3		
Influenza like illness			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Mucosal inflammation			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	3		
Oedema peripheral			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	3		

Pain			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Catheter site pain			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
General physical health deterioration			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Cough			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Dysphonia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Dyspnoea			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	3		
Epistaxis			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	3		
Hiccups			

subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0		
Nasal dryness subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Nasal ulcer subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0		
Pulmonary embolism subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0		
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0		
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0		
Insomnia subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 2		
Depression subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 2		
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0		
Amylase increased subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0		
Blood alkaline phosphatase increased			

subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Blood bilirubin increased				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Blood creatine phosphokinase increased				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Blood creatinine increased				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Ejection fraction decreased				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Lipase increased				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Neutrophil count decreased				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Platelet count decreased				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Weight decreased				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Weight increased				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
White blood cell count decreased				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Body temperature increased				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			

C-reactive protein increased			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Cardiac murmur			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Blood potassium decreased			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Lumbar vertebral fracture			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Sunburn			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	3		
Gastrointestinal stoma complication			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Dysgeusia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Neuropathy peripheral			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Neurotoxicity			

subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Paraesthesia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Peripheral motor neuropathy			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Polyneuropathy			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Restless legs syndrome			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Sensory loss			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Taste disorder			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Ageusia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Leukopenia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		

Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0 0 / 11 (0.00%) 0		
Ear and labyrinth disorders Auditory meatus external erosion subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Eye disorders Cataract subjects affected / exposed occurrences (all) Conjunctival haemorrhage subjects affected / exposed occurrences (all) Lacrimation increased subjects affected / exposed occurrences (all) Periorbital oedema subjects affected / exposed occurrences (all) Dry eye subjects affected / exposed occurrences (all) Visual impairment subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0 0 / 11 (0.00%) 0 0 / 11 (0.00%) 0 0 / 11 (0.00%) 0 1 / 11 (9.09%) 1 0 / 11 (0.00%) 0		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Angular cheilitis	4 / 11 (36.36%) 5 0 / 11 (0.00%) 0		

subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Constipation				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Dental cyst				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Diarrhoea				
subjects affected / exposed	5 / 11 (45.45%)			
occurrences (all)	5			
Dyspepsia				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Dysphagia				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Gingival bleeding				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Haemorrhoids				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Nausea				
subjects affected / exposed	3 / 11 (27.27%)			
occurrences (all)	4			
Palatal ulcer				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Rectal haemorrhage				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Stomatitis				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	2			
Vomiting				

subjects affected / exposed	4 / 11 (36.36%)		
occurrences (all)	5		
Toothache			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Dry mouth			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Eructation			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Odynophagia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Cheilitis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Anal haemorrhage			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Flatulence			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Dermatitis			

subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Dermatitis acneiform				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Dermatitis contact				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Dry skin				
subjects affected / exposed	3 / 11 (27.27%)			
occurrences (all)	3			
Eczema				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Erythema				
subjects affected / exposed	2 / 11 (18.18%)			
occurrences (all)	4			
Nail ridging				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Onychoclasis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Palmar-plantar erythrodysaesthesia syndrome				
subjects affected / exposed	2 / 11 (18.18%)			
occurrences (all)	2			
Photosensitivity reaction				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Pruritus				
subjects affected / exposed	3 / 11 (27.27%)			
occurrences (all)	3			
Rash				
subjects affected / exposed	4 / 11 (36.36%)			
occurrences (all)	4			

Rash erythematous				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Rash macular				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Skin disorder				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Skin fissures				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Skin toxicity				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Decubitus ulcer				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Dermal cyst				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	2			
Erythema nodosum				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Rash maculo-papular				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Rosacea				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	2			
Urticaria				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Acne				
subjects affected / exposed	3 / 11 (27.27%)			
occurrences (all)	4			

Blister			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Hand dermatitis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Skin exfoliation			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Hair texture abnormal			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Proteinuria			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Renal colic			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Nephrolithiasis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Hypothyroidism			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 11 (45.45%)		
occurrences (all)	5		

Back pain			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	4		
Bone pain			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Muscle tightness			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Musculoskeletal chest pain			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Osteoporosis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Muscular weakness			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Osteoporotic fracture			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Conjunctivitis			

subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Eye infection				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Folliculitis				
subjects affected / exposed	2 / 11 (18.18%)			
occurrences (all)	3			
Nasopharyngitis				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Onychomycosis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Oral herpes				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Paronychia				
subjects affected / exposed	2 / 11 (18.18%)			
occurrences (all)	8			
Rhinitis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Tracheitis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Upper respiratory tract infection				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Urinary tract infection				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Gastroenteritis				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Vulvitis				

subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Device related infection			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Catheter site infection			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Febrile infection			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Vascular device infection			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Staphylococcal infection			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Anal abscess			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Cystitis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Food craving			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Hyperglycaemia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Hypoalbuminaemia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		

Hypocalcaemia subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0		
Hypokalaemia subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 2		
Hypomagnesaemia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Hypophosphataemia subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0		
Hypercalcaemia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Hyperkalaemia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 2		
Dehydration subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 November 2015	Changes include the replacement of terms "MPDL3280A" and "MPDL3280A (anti-PD-L1 antibody)" with "atezolizumab" (international, non-proprietary name); revision of study eligibility criteria to allow patients with cerebellar metastases, exclude patients with progression of CNS disease between last CNS-directed therapy and study baseline prior to baseline, exclude patients requiring steroid therapy for CNS disease; revision of Cohort 2 eligibility criteria to exclude patients continuing RANKL inhibitor therapy; clarifications and updates on drug products; updates to address any safety concerns or knowledge gaps; and other minor details.
11 April 2016	Changes include increasing the Cohort 2 target sample size from 330 to 405 patients to increase statistical power for Cohort 2 analyses and accommodate rapid accrual into Cohort 2. As a result of this change, the estimated duration of the study for Cohort 2 was increased from 17 to 22 months and the estimated overall study accrual was increased from 610 to 700 patients.
24 November 2016	Changes include Cohort 2 closure due to completion of accrual; incorporation of two new cohorts (Cohort 3: capecitabine/trastuzumab/pertuzumab vs fluoropyrimidine/bevacizumab in HER2+ patients; Cohort 4: cobimetinib/atezolizumab vs fluoropyrimidine/bevacizumab in HER2-/MSI-H; HER2-/MSS/BRAFwt or HER2-/MSS/BRAFmut/RASmut patients); adaptation of cohort assignment decision tree and study length estimates to accommodate new cohorts and Cohort 2 closure; removal of co-primary endpoint "early efficacy during the Maintenance Treatment Phase" based on advisory committees' advice (PFS remains as single primary efficacy endpoint); optional stool sample collection added to address a new exploratory microbiome biomarker evaluation objective; preliminary assessments of efficacy in each cohort removed based on advisory committees' advice; maximum allowable 5-FU dosing in Cohort 1 increased to 2,400 mg/m2 based on completion of safety run-in review by the iDMC; local ablation for liver metastases now allowed during the induction treatment phase; second-line treatment for BRAFmut early progressors modified to 5-FU/vemurafenib/cetuximab for BRAFmut/MSS patients and FP/bevacizumab/atezolizumab for BRAFmut/MSI-H patients; updates to cohort-specific exclusion criteria, safety monitoring, and treatment management based on current safety data. Country specific protocols versions introduced for Spain and France due to jurisdictional requirements for safety monitoring and for Egypt and the UK where Cohorts 3 and 4 were not opened (study enrolment closed in Egypt and UK).
08 August 2018	In accordance with independent Data Monitoring Committee recommendations following review of safety data, accrual into Cohort 4 was closed.
19 December 2019	Enrolment into study was closed. Cohort 4 (now closed due to iDMC recommendations) had broad biomarker eligibility criteria and was introduced to replace Cohort 2 (previously closed due to completion of accrual). No new or modified cohorts with broad eligibility criteria suitable for addition to protocol MO29112 were identified. Without a broad eligibility cohort to replace Cohort 4, the majority of patients eligible for study entry would not be eligible for any maintenance cohort assignment upon completion of study induction treatment. For this reason, the Sponsor decided to permanently discontinue enrolment.
18 February 2020	Changes include updates to safety information and treatment management for patients receiving atezolizumab; update to responsible Medical Monitor.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
12 February 2018	Following the iDMC review of cohort 4 data a temporary recruitment halt to the whole study and a temporary halt to randomisation into cohort 4 was undertaken.	-

Notes:

Limitations and caveats

None reported