Clinical trial results:
A Multicenter, Randomized, Open-label, 3-Arm Phase 3 Study of Encorafenib + Cetuximab Plus or Minus Binimetinib vs. Irinotecan/Cetuximab or Infusional 5-Fluorouracil (5-FU)/Folinic Acid (FA)/Irinotecan (FOLFIRI)/Cetuximab with a Safety Lead-in of Encorafenib + Binimetinib + Cetuximab in Patients with BRAF V600E-mutant Metastatic Colorectal Cancer

Summary

EudraCT number	2015-005805-35
Trial protocol	GB HU BE AT NL CZ DK ES NO DE IT
Global end of trial date	10 November 2022

Results information

Result version number	v1 (current)
This version publication date	13 November 2023
First version publication date	13 November 2023

Trial information

Trial identification

Sponsor protocol code	C4221009

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02928224
WHO universal trial number (UTN)	-
Other trial identifiers	ARRAY-818-302: BEACON CRC

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 December 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 November 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Safety Lead-in-
- Assess the safety/tolerability of the combination of encorafenib + binimetinib + cetuximab in subjects with B-RAF proto-oncogene, serine/threonine kinase (BRAF) V600E-mutant (BRAFV600E) metastatic colorectal cancer (mCRC).

Randomised Phase 3-
In subjects with BRAFV600E mCRC:
- Compare the activity of encorafenib + binimetinib + cetuximab (Triplet Arm) vs. irinotecan/cetuximab or 5- fluorouracil (5-FU)/folinic acid (FA)/irinotecan (FOLFIRI)/cetuximab (Control Arm) as measured by overall survival (OS)
- Compare the activity of encorafenib + binimetinib + cetuximab (Triplet Arm) vs. irinotecan/cetuximab or FOLFIRI/cetuximab (Control Arm) as measured by Objective Response Rate (ORR) per Blinded Independent Central Review (BICR).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trials subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 October 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 7
Country: Number of subjects enrolled	Australia: 36
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belgium: 45
Country: Number of subjects enrolled	Brazil: 20
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Czechia: 10
Country: Number of subjects enrolled	Denmark: 10
Country: Number of subjects enrolled	France: 25
Country: Number of subjects enrolled	Germany: 29

Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Israel: 8
Country: Number of subjects enrolled	Italy: 85
Country: Number of subjects enrolled	Japan: 27
Country: Number of subjects enrolled	Mexico: 2
Country: Number of subjects enrolled	Netherlands: 39
Country: Number of subjects enrolled	Norway: 15
Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	Russian Federation: 27
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 41
Country: Number of subjects enrolled	Spain: 102
Country: Number of subjects enrolled	Taiwan: 17
Country: Number of subjects enrolled	Turkey: 7
Country: Number of subjects enrolled	Ukraine: 4
Country: Number of subjects enrolled	United Kingdom: 31
Country: Number of subjects enrolled	United States: 85
Worldwide total number of subjects	702
EEA total number of subjects	383

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)	450
From 65 to 84 years	252
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects were at least 18 years of age with confirmed metastatic colorectal cancer (CRC) whose disease had progressed after 1 or 2 prior regimens in the metastatic setting and whose tumor tissue was BRAF V600E-mutant as previously determined by a local assay at any time prior to screening.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Combined Safety Lead-in

Arm description:

Encorafenib + binimetinib + cetuximab. Encorafenib: Orally, once daily. Binimetinib: Orally, twice daily. Cetuximab: Standard of care.

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

Dosage and administration details:

300 milligrams (mg), once daily.

Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

400 mg/meter square initial dose (120-minute infusion), then 250 mg/meter square (60-minute infusion) thereafter, once weekly.

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

Dosage and administration details:

45 mg, twice daily

Arm title	Phase 3: Triplet Arm

Arm description:

Encorafenib + binimetinib + cetuximab. Encorafenib: Orally, once daily. Binimetinib: Orally, twice daily. Cetuximab: Standard of care.

Arm type	Experimental

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

Dosage and administration details:

Encorafenib: 300 mg, once daily.

Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

400 mg/meter square initial dose (120-minute infusion), then 250 mg/meter square (60-minute infusion) thereafter, once weekly.

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

Dosage and administration details:

45 mg, twice daily

Arm title	Phase 3: Doublet Arm

Arm description:

Encorafenib + cetuximab. Encorafenib: Orally, once daily. Cetuximab: Standard of care.

Arm type	Experimental
Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

400 mg/meter square initial dose (120-minute infusion), then 250 mg/meter square (60-minute infusion) thereafter, once weekly.

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

Dosage and administration details:

300 mg, once daily.

Arm title	Phase 3:Control Arm

Arm description:

Investigator’s choice of either irinotecan/cetuximab or FOLFIRI/cetuximab. Cetuximab: Standard of care. Irinotecan: Standard of care. Folinic Acid: Standard of care. 5-Fluorouracil: Standard of care. Following protocol amendment, eligible subjects could crossover to receive either triplet or doublet regimen.

Arm type	Active comparator

Investigational medicinal product name	Irinotecan/cetuximab or FOLFIRI/cetuximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cetuximab: Standard of care. Irinotecan: Standard of care. Folinic Acid: Standard of care. 5-Fluorouracil: Standard of care.

Number of subjects in period 1	Combined Safety Lead-in	Phase 3: Triplet Arm	Phase 3: Doublet Arm
Started	37	224	220
Crossover participants	0	0	0
Completed	0	0	0
Not completed	37	224	220
Consent withdrawn by subject	-	3	7
Death	30	209	193
Study participation terminated by sponsor	3	8	12
Unspecified	3	3	5
Lost to follow-up	1	1	3

Number of subjects in period 1	Phase 3:Control Arm
Started	221
Crossover participants	3
Completed	0
Not completed	221
Consent withdrawn by subject	20
Death	198
Study participation terminated by sponsor	3
Unspecified	-
Lost to follow-up	-

Baseline characteristics

Reporting groups	
Reporting group title	Combined Safety Lead-in
Reporting group description:	
Encorafenib + binimetinib + cetuximab. Encorafenib: Orally, once daily. Binimetinib: Orally, twice daily. Cetuximab: Standard of care.	
Reporting group title	Phase 3: Triplet Arm
Reporting group description:	
Encorafenib + binimetinib + cetuximab. Encorafenib: Orally, once daily. Binimetinib: Orally, twice daily. Cetuximab: Standard of care.	
Reporting group title	Phase 3: Doublet Arm
Reporting group description:	
Encorafenib + cetuximab. Encorafenib: Orally, once daily. Cetuximab: Standard of care.	
Reporting group title	Phase 3:Control Arm
Reporting group description:	
Investigator's choice of either irinotecan/cetuximab or FOLFIRI/cetuximab. Cetuximab: Standard of care. Irinotecan: Standard of care. Folinic Acid: Standard of care. 5-Fluorouracil: Standard of care. Following protocol amendment, eligible subjects could crossover to receive either triplet or doublet regimen.	

Reporting group values	Combined Safety Lead-in	Phase 3: Triplet Arm	Phase 3: Doublet Arm
Number of subjects	37	224	220
Age Categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	23	141	137
>=65 years	14	83	83
Age Continuous Units: years			
arithmetic mean	58.3	59.5	60.2
standard deviation	± 10.34	± 11.65	± 11.65
Sex: Female, Male Units: Subjects			
Female	22	119	106
Male	15	105	114
Race Units: Subjects			
American Indian or Alaska Native	0	0	1
Asian	7	20	25
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	2	0
White	29	195	183
More than one race	0	0	0
Unknown or Not Reported	0	7	11
Region Units: Subjects			
North America	5	30	28
Europe	25	150	145

Rest of World	7	44	47
Eastern Cooperative Oncology Group Performance Status (ECOG PS) at Baseline			
ECOG PS was used to assess the physical health of subjects, and ranges from 0 to 5 where 0: fully active, 1: restricted in physically strenuous activity, 2: ambulatory and capable of self-care but unable to work, 3: capable only of limited self-care, 4: completely disabled; cannot carry on any self-care; totally confined to bed or chair, 5: dead.			
Units: Subjects			
0-Fully active	22	116	112
1-Restircted in physically strenuous activity	15	108	104
2-Ambulatory and capable of all self-care	0	0	4
Number of Subjects According to Primary Tumor Location Units: Subjects			
Left Colon	11	79	83
Right Colon	23	126	110
Left and Right Colon	0	8	11
Unknown	3	11	16
Number of Subjects According to Removal of Primary Tumor Units: Subjects			
Completely Resected	20	133	123
Partially Resected/Unresected	17	91	97
Number of Subjects According to Number of Organs Involved Units: Subjects			
Greater than or equal to 2	16	114	117
More than 3	21	110	103
Ethnicity Units: Subjects			
Hispanic or Latino	0	14	13
Not Hispanic or Latino	37	203	195
Unknown or Not Reported	0	7	12

Reporting group values	Phase 3:Control Arm	Total	
Number of subjects	221	702	
Age Categorical Units: Subjects			
<=18 years	0	0	
Between 18 and 65 years	149	450	
>=65 years	72	252	
Age Continuous Units: years			
arithmetic mean	58.4		
standard deviation	± 12.07	-	
Sex: Female, Male Units: Subjects			
Female	127	374	
Male	94	328	

Race Units: Subjects			
American Indian or Alaska Native	0	1	
Asian	39	91	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	3	
White	172	579	
More than one race	0	0	
Unknown or Not Reported	10	28	
Region Units: Subjects			
North America	29	92	
Europe	125	445	
Rest of World	67	165	
Eastern Cooperative Oncology Group Performance Status (ECOG PS) at Baseline			
ECOG PS was used to assess the physical health of subjects, and ranges from 0 to 5 where 0: fully active, 1: restricted in physically strenuous activity, 2: ambulatory and capable of self-care but unable to work, 3: capable only of limited self-care, 4: completely disabled; cannot carry on any self-care; totally confined to bed or chair, 5: dead.			
Units: Subjects			
0-Fully active	108	358	
1-Restircted in physically strenuous activity	113	340	
2-Ambulatory and capable of all self-care	0	4	
Number of Subjects According to Primary Tumor Location Units: Subjects			
Left Colon	68	241	
Right Colon	119	378	
Left and Right Colon	22	41	
Unknown	12	42	
Number of Subjects According to Removal of Primary Tumor Units: Subjects			
Completely Resected	122	398	
Partially Resected/Unresected	99	304	
Number of Subjects According to Number of Organs Involved Units: Subjects			
Greater than or equal to 2	123	370	
More than 3	98	332	
Ethnicity Units: Subjects			
Hispanic or Latino	6	33	
Not Hispanic or Latino	202	637	
Unknown or Not Reported	13	32	

End points

End points reporting groups

Reporting group title	Combined Safety Lead-in
Reporting group description:	
Encorafenib + binimetinib + cetuximab. Encorafenib: Orally, once daily. Binimetinib: Orally, twice daily. Cetuximab: Standard of care.	
Reporting group title	Phase 3: Triplet Arm
Reporting group description:	
Encorafenib + binimetinib + cetuximab. Encorafenib: Orally, once daily. Binimetinib: Orally, twice daily. Cetuximab: Standard of care.	
Reporting group title	Phase 3: Doublet Arm
Reporting group description:	
Encorafenib + cetuximab. Encorafenib: Orally, once daily. Cetuximab: Standard of care.	
Reporting group title	Phase 3:Control Arm
Reporting group description:	
Investigator’s choice of either irinotecan/cetuximab or FOLFIRI/cetuximab. Cetuximab: Standard of care. Irinotecan: Standard of care. Folinic Acid: Standard of care. 5-Fluorouracil: Standard of care. Following protocol amendment, eligible subjects could crossover to receive either triplet or doublet regimen.	

Subject analysis set title	Pharmacokinetic Population of Encorafenib
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Encorafenib + binimetinib + cetuximab. Encorafenib + cetuximab. Investigator’s choice of either irinotecan/cetuximab or FOLFIRI/cetuximab.	

Primary: (Safety Lead-in) Number of Subjects with Adverse Events (AEs)

End point title	(Safety Lead-in) Number of Subjects with Adverse Events
End point description:	
An AE is any untoward medical occurrence in a subject or clinical study subject, temporally associated with the use of study drug, whether or not considered related to the study drug. Number of subjects reporting AEs were reported in this endpoint. The Safety Set consisted of all subjects who received at least 1 dose of study drug and had at least 1 post-treatment assessment, which may have included death. Subjects were analysed according to treatment received.	
End point type	Primary
End point timeframe:	
Duration of safety lead-in, approximately 6 months (up to 28 days per cycle)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analysed.

[2] - 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: Only descriptive data was planned to be analysed.

End point values	Combined Safety Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Subjects	37			

Statistical analyses

No statistical analyses for this end point

Primary: (Safety Lead-in) Incidence of Dose Interruptions, Dose Modifications and Discontinuations due to Adverse Events (AEs) - Interim Analysis

End point title	(Safety Lead-in) Incidence of Dose Interruptions, Dose Modifications and Discontinuations due to Adverse Events (AEs) - Interim Analysis[3][4]

End point description:

An AE is any untoward medical occurrence in a subject or clinical study subject, temporally associated with the use of study drug, whether or not considered related to the study drug. Number of subjects with dose interruptions, dose modifications and dose discontinuations due to AEs were reported in this endpoint. The Safety Set consisted of all subjects who received at least 1 dose of study drug and had at least 1 post-treatment assessment, which may have included death. Subjects were analysed according to treatment received.

End point type	Primary

End point timeframe:

Duration of safety lead-in, approximately 6 months (up to 28 days per cycle)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analysed.

[4] - 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: Only descriptive data was planned to be analysed.

End point values	Combined Safety Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Subjects	26			

Statistical analyses

No statistical analyses for this end point

Primary: (Safety Lead-in) Number of Subjects with Dose-Limiting Toxicities (DLTs)

End point title	(Safety Lead-in) Number of Subjects with Dose-Limiting Toxicities (DLTs)[5][6]

End point description:

The dose-determining set (DDS) consisted of all combined safety lead-in (CSLI) subjects from the safety set who either completed a minimum exposure requirement (received >= 75% dose intensity of the planned dose for each binimetinib, encorafenib and cetuximab) and had sufficient safety evaluations or experienced a dose-limiting toxicity (DLT).

End point type	Primary

End point timeframe:

Cycle 1 (up to 28 days)

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analysed.

[6] - 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: Only descriptive data was planned to be analysed.

End point values	Combined Safety Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Subjects	5			

Statistical analyses

No statistical analyses for this end point

Primary: (Safety Lead-in) Incidence of Dose Interruptions, Dose Modifications and Discontinuations due to Adverse Events (AEs) - Final Analysis

End point title	(Safety Lead-in) Incidence of Dose Interruptions, Dose Modifications and Discontinuations due to Adverse Events (AEs) - Final Analysis[7][8]

End point description:

An AE is any untoward medical occurrence in a subject or clinical study subject, temporally associated with the use of study drug, whether or not considered related to the study drug. Number of subjects according to incidence of dose interruptions, dose modifications and dose discontinuations due to AEs were reported in this endpoint. The Safety Set consisted of all subjects who received at least 1 dose of study drug and had at least 1 posttreatment assessment, which may have included death. Subjects were analysed according to treatment received.

End point type	Primary

End point timeframe:

From start of study treatment until 30 days post last dose of study treatment (maximum treatment exposure of 280 weeks)

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analysed.

[8] - 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: Only descriptive data was planned to be analysed.

End point values	Combined Safety Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Subjects				
Dose interruptions	30			
Dose modifications	16			
Discontinuation due to AEs	8			

Statistical analyses

No statistical analyses for this end point

Primary: (Phase 3) Overall Survival (OS) of Triplet Arm vs. Control Arm - Interim Analysis

End point title	(Phase 3) Overall Survival (OS) of Triplet Arm vs. Control Arm - Interim Analysis[9]

End point description:

OS was defined as the time from randomisation to death due to any cause. The Full Analysis Set (FAS) for the Phase 3 portion of the study consisted of all randomised Phase 3 subjects.

End point type	Primary

End point timeframe:

From randomisation to death due to any cause until 204 deaths were observed (maximum treatment exposure of 89.1 weeks for triplet arm and 52.4 weeks for control arm)

Notes:

[9] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Triplet Arm	Phase 3:Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	221		
Units: Months				
median (confidence interval 95%)	9.03 (8.02 to 11.43)	5.42 (4.76 to 6.57)		

Statistical analyses

Statistical analysis title	Triplet Arm vs. Control Arm
Comparison groups	Phase 3: Triplet Arm v Phase 3:Control Arm
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Stratified Log-rank

Primary: (Phase 3) Overall Survival (OS) of Triplet Arm vs. Control Arm - Final Analysis

End point title	(Phase 3) Overall Survival (OS) of Triplet Arm vs. Control Arm - Final Analysis[10]

End point description:

OS was defined as the time from randomisation to death due to any cause. The Full Analysis Set (FAS) for the Phase 3 portion of the study consisted of all randomised Phase 3 subjects.

End point type	Primary

End point timeframe:

From randomisation to death due to any cause (maximum treatment exposure of 277.4 weeks for triplet arm and 108 weeks for control arm)

Notes:

[10] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Triplet Arm	Phase 3:Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	221		
Units: Months				
median (confidence interval 95%)	9.82 (8.34 to 11.73)	5.88 (5.09 to 7.16)		

Statistical analyses

Statistical analysis title	Triplet vs Control Arm
Comparison groups	Phase 3: Triplet Arm v Phase 3:Control Arm
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Stratified Log-rank

Primary: (Phase 3) Objective Response Rate (ORR) by Blinded Independent Central Review (BICR) per Response Evaluation Criteria in Solid Tumors (RECIST), v1.1 of Triplet Arm vs. Control Arm

End point title	(Phase 3) Objective Response Rate (ORR) by Blinded Independent Central Review (BICR) per Response Evaluation Criteria in Solid Tumors (RECIST), v1.1 of Triplet Arm vs. Control Arm[11]

End point description:

ORR per RECIST, v1.1, was defined as the percentage of subjects achieving an overall best response of complete response (CR) or partial response (PR) divided by the total number of subjects, where CR: disappearance of all target and non-target lesions and normalisation of tumor marker level, all lymph nodes must be non-pathological in size(<10 millimeter [mm] short axis), and PR: at least 30% decrease in sum of diameters of target lesions, taking as reference the baseline sum diameters persistence of one or more non-target lesion and/or maintenance of tumor marker level above the normal limits. The Phase 3 Response Efficacy Set consisted of the first 330 subjects randomised into the Phase 3 portion of the study and any additional subjects randomised on the same day as the 330th randomised subject. Here, "Number of Subjects Analysed" signifies subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Duration of Phase 3, approximately 6 months (up to 28 days per cycle)

Notes:

[11] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Triplet Arm	Phase 3:Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	107		
Units: Percentage of subjects				
number (confidence interval 95%)	26.1 (18.2 to 35.3)	1.9 (0.2 to 6.6)		

Statistical analyses

Statistical analysis title	Triplet vs Control Arm
Comparison groups	Phase 3: Triplet Arm v Phase 3:Control Arm
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Chi-squared

Secondary: (Safety Lead-in) Objective Response Rate (ORR) by Investigator

End point title	(Safety Lead-in) Objective Response Rate (ORR) by Investigator[12]

End point description:

ORR per RECIST, v1.1, was defined as the percentage of subjects achieving an overall best response of CR or PR, where CR: disappearance of all target and non-target lesions and normalisation of tumor marker level, all lymph nodes must be non-pathological in size(<10 mm short axis), and PR: at least 30% decrease in sum of diameters of target lesions, taking as reference the baseline sum diameters persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits. The Safety Lead-in (SLI) Efficacy Set consisted of all CSLI subjects in the FAS who were identified at screening as having a BRAF V600E mutation (per local or central testing). Here, "Number of Subjects Analysed" signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From start of study treatment until 30 days post last dose of study treatment (maximum treatment exposure of 280 weeks)

Notes:

[12] - 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: Only descriptive data was planned to be analysed.

End point values	Combined Safety Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: Percentage of subjects				
number (confidence interval 95%)	52.8 (35.5 to 69.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety Lead-in) Duration of Response (DOR) by Investigator

End point title	(Safety Lead-in) Duration of Response (DOR) by

End point description:

DOR was defined as the time from first radiographic evidence of response to the earliest documented disease progression (PD) or death due to underlying disease. PD: at least a 20% increase (including an absolute increase of at least 5 mm) in the sum of diameters of target lesions, taking as reference the smallest sum on study and/or unequivocal progression of existing non-target lesions and/or appearance of 1 or more new lesions were evaluated. The SLI Efficacy Set consisted of all CSLI subjects in the FAS who were identified at screening as having a BRAF V600E mutation (per local or central testing). Here, "Number of Subjects Analysed" signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From time of response to the earliest documented PD or death due to underlying disease (maximum treatment exposure of 280 weeks)

Notes:

[13] - 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: Only descriptive data was planned to be analysed.

End point values	Combined Safety Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Months				
median (confidence interval 95%)	6.47 (4.17 to 11.07)			

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety Lead-in) Objective Response Rate (ORR) by BICR

End point title	(Safety Lead-in) Objective Response Rate (ORR) by BICR[14]

End point description:

ORR per RECIST, v1.1, was defined as the percentage of subjects achieving an overall best response of CR or PR, where CR: disappearance of all target and non-target lesions and normalisation of tumor marker level, all lymph nodes must be non-pathological in size(<10 mm short axis), and PR: at least 30% decrease in sum of diameters of target lesions, taking as reference the baseline sum diameters persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits. The SLI Efficacy Set consisted of all CSLI subjects in the FAS who were identified at screening as having a BRAF V600E mutation (per local or central testing). Here, "Number of Subjects Analysed" signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From start of study treatment until 30 days post last dose of study treatment (maximum treatment exposure of 280 weeks)

Notes:

[14] - 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: Only descriptive data was planned to be analysed.

End point values	Combined Safety Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: Percentage of subjects				
number (confidence interval 95%)	41.7 (25.5 to 59.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety Lead-in) Duration of Response (DOR) by BICR

End point title	(Safety Lead-in) Duration of Response (DOR) by BICR[15]

End point description:

DOR was defined as the time from first radiographic evidence of response to the earliest documented PD or death due to underlying disease. PD: at least a 20% increase (including an absolute increase of at least 5 mm) in the sum of diameters of target lesions, taking as reference the smallest sum on study and/or unequivocal progression of existing non-target lesions and/or appearance of 1 or more new lesions were evaluated. The SLI Efficacy Set consisted of all CSLI subjects in the FAS who were identified at screening as having a BRAF V600E mutation (per local or central testing). Here, "Number of Subjects Analysed" signifies subjects evaluable for this endpoint. 99999 indicated data could not be calculated due to insufficient subjects with events.

End point type	Secondary

End point timeframe:

From time of response to the earliest documented PD or death due to underlying disease (maximum treatment exposure of 280 weeks)

Notes:

[15] - 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: Only descriptive data was planned to be analysed.

End point values	Combined Safety Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Months				
median (confidence interval 95%)	8.15 (2.79 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety Lead-in) Time to Response by Investigator

End point title	(Safety Lead-in) Time to Response by Investigator[16]

End point description:

Time to response was defined as the time from first dose to first radiographic evidence of response. The SLI Efficacy Set consisted of all CSLI subjects in the FAS who were identified at screening as having a BRAF V600E mutation (per local or central testing). Here, "Number of Subjects Analysed" signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From first dose to first radiographic evidence of response (maximum treatment exposure of 280 weeks)

Notes:

[16] - 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: Only descriptive data was planned to be analysed.

End point values	Combined Safety Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: Months				
median (confidence interval 95%)	1.45 (1.38 to 1.64)			

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety Lead-in) Time to Response by BICR

End point title	(Safety Lead-in) Time to Response by BICR[17]

End point description:

Time to response was defined as the time from first dose to first radiographic evidence of response. The SLI Efficacy Set consisted of all CSLI subjects in the FAS who were identified at screening as having a BRAF V600E mutation (per local or central testing). Here, "Number of Subjects Analysed" signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From first dose to first radiographic evidence of response (maximum treatment exposure of 280 weeks)

Notes:

[17] - 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: Only descriptive data was planned to be analysed.

End point values	Combined Safety Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: Months				
median (confidence interval 95%)	1.45 (1.38 to 1.64)			

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety Lead-in) Progression-free Survival (PFS) by Investigator

End point title	(Safety Lead-in) Progression-free Survival (PFS) by Investigator[18]

End point description:

PFS was defined as the time from first dose to the earliest documented PD or death due to any cause. PD: at least a 20% increase (including an absolute increase of at least 5 mm) in the sum of diameters of target lesions, taking as reference the smallest sum on study and/or unequivocal progression of existing non-target lesions and/or appearance of 1 or more new lesions were evaluated. The SLI Efficacy Set consisted of all CSLI subjects in the FAS who were identified at screening as having a BRAF V600E mutation (per local or central testing). Here, "Number of Subjects Analysed" signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From first dose to the earliest documented PD or death due to any cause (maximum treatment exposure of 280 weeks)

Notes:

[18] - 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: Only descriptive data was planned to be analysed.

End point values	Combined Safety Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: Months				
median (confidence interval 95%)	8.08 (5.59 to 9.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety Lead-in) Progression-free Survival (PFS) by BICR

End point title	(Safety Lead-in) Progression-free Survival (PFS) by BICR[19]

End point description:

PFS was defined as the time from first dose to the earliest documented PD or death due to any cause. PD: at least a 20% increase (including an absolute increase of at least 5 mm) in the sum of diameters of target lesions, taking as reference the smallest sum on study and/or unequivocal progression of existing non-target lesions and/or appearance of 1 or more new lesions were evaluated. The SLI Efficacy Set consisted of all CSLI subjects in the FAS who were identified at screening as having a BRAF V600E mutation (per local or central testing). Here, "Number of Subjects Analysed" signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From first dose to the earliest documented PD or death due to any cause (maximum treatment exposure of 280 weeks)

Notes:

[19] - 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: Only descriptive data was planned to be analysed.

End point values	Combined Safety Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: Months				
median (confidence interval 95%)	5.59 (4.44 to 9.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: (Phase 3) Overall Survival (OS) in Doublet Arm vs. Control Arm

End point title	(Phase 3) Overall Survival (OS) in Doublet Arm vs. Control

End point description:

OS was defined as the time from randomisation to death due to any cause. The Full Analysis Set (FAS) for the Phase 3 portion of the study consisted of all randomised Phase 3 subjects.

End point type	Secondary

End point timeframe:

From randomisation to death due to any cause until 204 deaths were observed (maximum treatment exposure of 89.7 weeks for doublet arm and 52.4 weeks for control arm)

Notes:

[20] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Doublet Arm	Phase 3:Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	220	221		
Units: Months				
median (confidence interval 95%)	9.40 (8.11 to 11.24)	5.88 (5.09 to 7.16)		

Statistical analyses

Statistical analysis title	Doublet vs Control Arm
Comparison groups	Phase 3: Doublet Arm v Phase 3:Control Arm
Number of subjects included in analysis	441
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Stratified Log-rank

Secondary: (Phase 3) Comparison of Progression-Free Survival (PFS) in Triplet Arm

vs Control Arm per Investigator	
End point title	(Phase 3) Comparison of Progression-Free Survival (PFS) in Triplet Arm vs Control Arm per Investigator[21]

End point description:

PFS was defined as the time from first dose to the earliest documented disease progression (PD) or death due to any cause. PD: at least a 20% increase (including an absolute increase of at least 5 mm) in the sum of diameters of target lesions, taking as reference the smallest sum on study and/or unequivocal progression of existing non-target lesions and/or appearance of 1 or more new lesions were evaluated. The FAS for the Phase 3 portion of the study consisted of all randomised Phase 3 subjects.

End point type	Secondary

End point timeframe:

From first dose to the earliest documented disease progression (PD) or death due to any cause (maximum treatment exposure of 277.4 weeks for triplet arm and 108 weeks for control arm)

Notes:

[21] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Triplet Arm	Phase 3:Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	221		
Units: Months				
median (confidence interval 95%)	4.47 (4.24 to 5.36)	1.58 (1.51 to 2.07)		

Statistical analyses

Statistical analysis title	Triplet vs Control Arm
Comparison groups	Phase 3: Triplet Arm v Phase 3:Control Arm
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Stratified Log-rank

Secondary: (Phase 3) Overall Survival (OS) in Triplet Arm vs. Doublet Arm	
End point title	(Phase 3) Overall Survival (OS) in Triplet Arm vs. Doublet

End point description:

OS was defined as the time from randomisation to death due to any cause. The FAS for the Phase 3 portion of the study consisted of all randomized Phase 3 subjects.

End point type	Secondary

End point timeframe:

From randomisation to death due to any cause until 204 deaths were observed (maximum treatment exposure of 89.7 weeks for doublet arm and 89.1 weeks for triplet arm)

Notes:

[22] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Triplet Arm	Phase 3: Doublet Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	220		
Units: Months				
median (confidence interval 95%)	9.82 (8.34 to 11.73)	9.40 (8.11 to 11.24)		

Statistical analyses

Statistical analysis title	Triplet vs Doublet Arm
Comparison groups	Phase 3: Triplet Arm v Phase 3: Doublet Arm
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5958
Method	Stratified Log-rank

Secondary: (Phase 3) Comparison of Progression-Free Survival (PFS) in Triplet Arm vs Control Arm per BICR

End point title	(Phase 3) Comparison of Progression-Free Survival (PFS) in Triplet Arm vs Control Arm per BICR[23]

End point description:

PFS was defined as the time from first dose to the earliest documented disease progression (PD) or death due to any cause. PD: at least a 20% increase (including an absolute increase of at least 5 mm) in the sum of diameters of target lesions, taking as reference the smallest sum on study and/or unequivocal progression of existing non-target lesions and/or appearance of 1 or more new lesions were evaluated. The FAS for the Phase 3 portion of the study consisted of all randomised Phase 3 subjects.

End point type	Secondary

End point timeframe:

From first dose to the earliest documented disease progression (PD) or death due to any cause (maximum treatment exposure of 277.4 weeks for triplet arm and 108 weeks for control arm)

Notes:

[23] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Triplet Arm	Phase 3:Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	221		
Units: Months				
median (confidence interval 95%)	4.30 (4.14 to 5.19)	1.51 (1.45 to 1.71)		

Statistical analyses

Statistical analysis title	Triplet vs Control Arm
Comparison groups	Phase 3: Triplet Arm v Phase 3:Control Arm
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Stratified Log-rank

Secondary: (Phase 3) Comparison of Progression-Free Survival (PFS) in Doublet Arm vs Control Arm per BICR

End point title	(Phase 3) Comparison of Progression-Free Survival (PFS) in Doublet Arm vs Control Arm per BICR[24]

End point description:

PFS was defined as the time from first dose to the earliest documented PD or death due to any cause. PD: at least a 20% increase (including an absolute increase of at least 5 mm) in the sum of diameters of target lesions, taking as reference the smallest sum on study and/or unequivocal progression of existing non-target lesions and/or appearance of 1 or more new lesions were evaluated. The FAS for the Phase 3 portion of the study consisted of all randomised Phase 3 subjects.

End point type	Secondary

End point timeframe:

From first dose to the earliest documented PD or death due to any cause (maximum treatment exposure of 268 weeks for doublet arm and 108 weeks for control arm)

Notes:

[24] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Doublet Arm	Phase 3:Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	220	221		
Units: Months				
median (confidence interval 95%)	4.21 (3.71 to 5.36)	1.51 (1.45 to 1.71)		

Statistical analyses

Statistical analysis title	Doublet vs Control Arm
Comparison groups	Phase 3: Doublet Arm v Phase 3:Control Arm

Number of subjects included in analysis	441
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Stratified Log-rank

Secondary: (Phase 3) Comparison of Progression-Free Survival (PFS) in Doublet Arm vs Control Arm per Investigator

End point title	(Phase 3) Comparison of Progression-Free Survival (PFS) in Doublet Arm vs Control Arm per Investigator[25]

End point description:

PFS was defined as the time from first dose to the earliest documented PD or death due to any cause. PD: at least a 20% increase (including an absolute increase of at least 5 mm) in the sum of diameters of target lesions, taking as reference the smallest sum on study and/or unequivocal progression of existing non-target lesions and/or appearance of 1 or more new lesions were evaluated. The FAS for the Phase 3 portion of the study consisted of all randomized Phase 3 subjects.

End point type	Secondary

End point timeframe:

From first dose to the earliest documented PD or death due to any cause (maximum treatment exposure of 268 weeks for doublet arm and 108 weeks for control arm)

Notes:

[25] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Doublet Arm	Phase 3:Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	220	221		
Units: Months				
median (confidence interval 95%)	4.27 (4.04 to 5.36)	1.58 (1.51 to 2.07)		

Statistical analyses

Statistical analysis title	Doublet vs Control Arm
Comparison groups	Phase 3: Doublet Arm v Phase 3:Control Arm
Number of subjects included in analysis	441
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Stratified Log-rank

Secondary: (Phase 3) Comparison of Progression-Free Survival (PFS) in Triplet Arm vs Doublet Arm Per BICR

End point title	(Phase 3) Comparison of Progression-Free Survival (PFS) in Triplet Arm vs Doublet Arm Per BICR[26]

End point description:

PFS was defined as the time from first dose to the earliest documented PD or death due to any cause. PD: at least a 20% increase (including an absolute increase of at least 5 mm) in the sum of diameters of target lesions, taking as reference the smallest sum on study and/or unequivocal progression of existing non-target lesions and/or appearance of 1 or more new lesions were evaluated. The FAS for the Phase 3 portion of the study consisted of all randomised Phase 3 subjects.

End point type	Secondary

End point timeframe:

From first dose to the earliest documented PD or death due to any cause (maximum treatment exposure of 277.4 weeks for triplet arm and 268 weeks for doublet arm)

Notes:

[26] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Triplet Arm	Phase 3: Doublet Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	220		
Units: Months				
median (confidence interval 95%)	4.30 (4.14 to 5.19)	4.21 (3.71 to 5.36)		

Statistical analyses

Statistical analysis title	Triplet vs Doublet Arm
Comparison groups	Phase 3: Triplet Arm v Phase 3: Doublet Arm
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1004
Method	Stratified Log-rank

Secondary: (Phase 3) Comparison of Progression-free Survival (PFS) in Triplet Arm vs Doublet Arm Per Investigator

End point title	(Phase 3) Comparison of Progression-free Survival (PFS) in Triplet Arm vs Doublet Arm Per Investigator[27]

End point description:

PFS was defined as the time from first dose to the earliest documented PD or death due to any cause. PD: at least a 20% increase (including an absolute increase of at least 5 mm) in the sum of diameters of target lesions, taking as reference the smallest sum on study and/or unequivocal progression of existing non-target lesions and/or appearance of 1 or more new lesions were evaluated. The FAS for the Phase 3 portion of the study consisted of all randomised Phase 3 subjects.

End point type	Secondary

End point timeframe:

From first dose to the earliest documented PD or death due to any cause (maximum treatment exposure of 277.4 weeks for triplet arm and 268 weeks for doublet arm)

Notes:

[27] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Triplet Arm	Phase 3: Doublet Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	220		
Units: Months				
median (confidence interval 95%)	4.47 (4.24 to 5.36)	4.27 (4.04 to 5.36)		

Statistical analyses

Statistical analysis title	Triplet vs Doublet Arm
Comparison groups	Phase 3: Triplet Arm v Phase 3: Doublet Arm
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3724
Method	Stratified Log-rank

Secondary: (Phase 3) Comparison of Objective Response Rate (ORR) in Triplet Arm vs Control Arm per Investigator

End point title	(Phase 3) Comparison of Objective Response Rate (ORR) in Triplet Arm vs Control Arm per Investigator[28]

End point description:

ORR per RECIST, v1.1, was defined as the percentage of subjects achieving an overall best response of CR or PR, where CR: disappearance of all target and non-target lesions and normalisation of tumor marker level, all lymph nodes must be non-pathological in size(<10 mm short axis), and PR: at least 30% decrease in sum of diameters of target lesions, taking as reference the baseline sum diameters persistence of one or more non-target lesions and/or maintenance of tumor marker level above the normal limits. The Phase 3 Response Efficacy Set consisted of the first 330 subjects randomised into the Phase 3 portion of the study and any additional subjects randomised on the same day as the 330th randomised subject. Here, "Number of Subjects Analysed" signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Duration of Phase 3, approximately 6 months (up to 28 days per cycle)

Notes:

[28] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Triplet Arm	Phase 3:Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	107		
Units: Percentage of subjects				
number (confidence interval 95%)	26.1 (18.2 to 35.3)	3.7 (1.0 to 9.3)		

Statistical analyses

Statistical analysis title	Triplet vs Control Arm
Comparison groups	Phase 3: Triplet Arm v Phase 3:Control Arm
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Chi-squared

Secondary: (Phase 3) Comparison of Objective Response Rate (ORR) in Triplet Arm vs Doublet Arm Per BICR

End point title	(Phase 3) Comparison of Objective Response Rate (ORR) in Triplet Arm vs Doublet Arm Per BICR[29]

End point description:

ORR per RECIST, v1.1, was defined as the percentage of subjects achieving an overall best response of CR or PR, where CR: disappearance of all target and non-target lesions and normalisation of tumor marker level, all lymph nodes must be non-pathological in size(<10 mm short axis), and PR: at least 30% decrease in sum of diameters of target lesions, taking as reference the baseline sum diameters persistence of one or more non-target lesions and/or maintenance of tumor marker level above the normal limits. The Phase 3 Response Efficacy Set consisted of the first 330 subjects randomised into the Phase 3 portion of the study and any additional subjects randomised on the same day as the 330th randomised subject. Here, "Number of Subjects Analysed" signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Duration of Phase 3, approximately 6 months (up to 28 days per cycle)

Notes:

[29] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Triplet Arm	Phase 3: Doublet Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	113		
Units: Percentage of subjects				
number (confidence interval 95%)	26.1 (18.2 to 35.3)	20.4 (13.4 to 29.0)		

Statistical analyses

Statistical analysis title	Triplet vs Doublet Arm
Comparison groups	Phase 3: Triplet Arm v Phase 3: Doublet Arm

Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1928
Method	Cochran-Mantel-Haenszel

Secondary: (Phase 3) Comparison of Objective Response Rate (ORR) in Doublet Arm vs Control Arm Per BICR

End point title	(Phase 3) Comparison of Objective Response Rate (ORR) in Doublet Arm vs Control Arm Per BICR[30]

End point description:

ORR per RECIST, v1.1, was defined as the percentage of subjects achieving an overall best response of CR or PR, where CR: disappearance of all target and non-target lesions and normalisation of tumor marker level, all lymph nodes must be non-pathological in size(<10 mm short axis), and PR: at least 30% decrease in sum of diameters of target lesions, taking as reference the baseline sum diameters persistence of one or more non-target lesions and/or maintenance of tumor marker level above the normal limits. The Phase 3 Response Efficacy Set consisted of the first 330 subjects randomised into the Phase 3 portion of the study and any additional subjects randomised on the same day as the 330th randomised subject. Here, "Number of Subjects Analysed" signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Duration of Phase 3, approximately 6 months (up to 28 days per cycle)

Notes:

[30] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Doublet Arm	Phase 3:Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	107		
Units: Percentage of subjects				
number (confidence interval 95%)	20.4 (13.4 to 29.0)	1.9 (0.2 to 6.6)		

Statistical analyses

Statistical analysis title	Doublet vs Control Arm
Comparison groups	Phase 3: Doublet Arm v Phase 3:Control Arm
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Chi-squared

Secondary: (Phase 3) Comparison of Objective Response Rate (ORR) in Doublet Arm vs Control Arm Per Investigator

End point title	(Phase 3) Comparison of Objective Response Rate (ORR) in Doublet Arm vs Control Arm Per Investigator[31]

End point description:

ORR per RECIST, v1.1, was defined as the percentage of subjects achieving an overall best response of CR or PR, where CR: disappearance of all target and non-target lesions and normalisation of tumor marker level, all lymph nodes must be non-pathological in size(<10 mm short axis), and PR: at least 30% decrease in sum of diameters of target lesions, taking as reference the baseline sum diameters persistence of one or more non-target lesions and/or maintenance of tumor marker level above the normal limits. The Phase 3 Response Efficacy Set consisted of the first 330 subjects randomised into the Phase 3 portion of the study and any additional subjects randomised on the same day as the 330th randomised subject. Here, "Number of Subjects Analysed" signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Duration of Phase 3, approximately 6 months (up to 28 days per cycle)

Notes:

[31] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Doublet Arm	Phase 3:Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	107		
Units: Percentage of subjects				
number (confidence interval 95%)	15.9 (9.7 to 24.0)	3.7 (1.0 to 9.3)		

Statistical analyses

Statistical analysis title	Doublet vs Control Arm
Comparison groups	Phase 3: Doublet Arm v Phase 3:Control Arm
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Chi-squared

Secondary: (Phase 3) Comparison of Objective Response Rate (ORR) in Triplet Arm vs Doublet Arm Per Investigator

End point title	(Phase 3) Comparison of Objective Response Rate (ORR) in Triplet Arm vs Doublet Arm Per Investigator[32]

End point description:

ORR per RECIST, v1.1, was defined as the number of subjects achieving an overall best response of CR or PR, where CR: disappearance of all target and non-target lesions and normalisation of tumor marker level, all lymph nodes must be non-pathological in size(<10 mm short axis), and PR: at least 30% decrease in sum of diameters of target lesions, taking as reference the baseline sum diameters persistence of one or more non-target lesions and/or maintenance of tumor marker level above the normal limits. The Phase 3 Response Efficacy Set consisted of the first 330 subjects randomised into the Phase 3 portion of the study and any additional subjects randomised on the same day as the 330th randomised subject. Here, "Number of Subjects Analysed" signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Duration of Phase 3, approximately 6 months (up to 28 days per cycle)

Notes:

[32] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Triplet Arm	Phase 3: Doublet Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	113		
Units: Percentage of subjects				
number (confidence interval 95%)	26.1 (18.2 to 35.3)	15.9 (9.7 to 24.0)		

Statistical analyses

Statistical analysis title	Triplet vs Doublet Arm
Comparison groups	Phase 3: Triplet Arm v Phase 3: Doublet Arm
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0357
Method	Cochran-Mantel-Haenszel

Secondary: (Phase 3) Comparison of Duration of Response (DOR) in Triplet Arm vs Control Arm per Investigator

End point title	(Phase 3) Comparison of Duration of Response (DOR) in Triplet Arm vs Control Arm per Investigator[33]

End point description:

DOR was defined as the time from first radiographic evidence of response to the earliest documented PD or death due to underlying disease. PD: at least a 20% increase (including an absolute increase of at least 5 mm) in the sum of diameters of target lesions, taking as reference the smallest sum on study and/or unequivocal progression of existing non-target lesions and/or appearance of 1 or more new lesions were evaluated. The Phase 3 Response Efficacy Set consisted of the first 330 subjects randomised into the Phase 3 portion of the study and any additional subjects randomised on the same day as the 330th randomised subject. Here, "Number of Subjects Analysed" signifies subjects evaluable for this endpoint. 99999 indicated data could not be calculated due to insufficient subjects with events.

End point type	Secondary

End point timeframe:

From time of response to PD or death due to underlying disease (maximum treatment exposure of 277.4 weeks for triplet arm and 108 weeks for control arm)

Notes:

[33] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Triplet Arm	Phase 3:Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	107		
Units: Months				
median (confidence interval 95%)	4.80 (3.29 to 6.57)	5.75 (2.56 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: (Phase 3) Comparison of Duration of Response (DOR) in Triplet Arm vs Control Arm per BICR

End point title	(Phase 3) Comparison of Duration of Response (DOR) in Triplet Arm vs Control Arm per BICR[34]

End point description:

DOR was defined as the time from first radiographic evidence of response to the earliest documented PD or death due to underlying disease. PD: at least a 20% increase (including an absolute increase of at least 5 mm) in the sum of diameters of target lesions, taking as reference the smallest sum on study and/or unequivocal progression of existing non-target lesions and/or appearance of 1 or more new lesions were evaluated. The Phase 3 Response Efficacy Set consisted of the first 330 subjects randomised into the Phase 3 portion of the study and any additional subjects randomised on the same day as the 330th randomised subject. Here, "Number of Subjects Analysed" signifies subjects evaluable for this endpoint. 99999 indicated data could not be calculated due to insufficient subjects with events.

End point type	Secondary

End point timeframe:

From time of response to PD or death due to underlying disease (maximum treatment exposure of 277.4 weeks for triplet arm and 108 weeks for control arm)

Notes:

[34] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Triplet Arm	Phase 3:Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	107		
Units: Months				
median (confidence interval 95%)	4.80 (2.96 to 9.69)	99999 (2.56 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: (Phase 3) Comparison of Duration of Response (DOR) in Triplet Arm vs Doublet Arm by BICR

End point title	(Phase 3) Comparison of Duration of Response (DOR) in Triplet Arm vs Doublet Arm by BICR[35]

End point description:

DOR was defined as the time from first radiographic evidence of response to the earliest documented PD or death due to underlying disease. PD: at least a 20% increase (including an absolute increase of at least 5 mm) in the sum of diameters of target lesions, taking as reference the smallest sum on study and/or unequivocal progression of existing non-target lesions and/or appearance of 1 or more new lesions were evaluated. The Phase 3 Response Efficacy Set consisted of the first 330 subjects randomised into the Phase 3 portion of the study and any additional subjects randomised on the same day as the 330th randomised subject. Here, "Number of Subjects Analysed" signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From time of response to PD or death due to underlying disease (maximum treatment exposure of 277.4 weeks for triplet arm and 268 weeks for doublet arm)

Notes:

[35] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Triplet Arm	Phase 3: Doublet Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	113		
Units: Months				
median (confidence interval 95%)	4.80 (2.96 to 9.69)	6.06 (4.07 to 8.28)		

Statistical analyses

No statistical analyses for this end point

Secondary: (Phase 3) Comparison of Duration of Response (DOR) in Doublet Arm vs Control Arm per Investigator

End point title	(Phase 3) Comparison of Duration of Response (DOR) in Doublet Arm vs Control Arm per Investigator[36]

End point description:

DOR was defined as the time from first radiographic evidence of response to the earliest documented PD or death due to underlying disease. PD: at least a 20% increase (including an absolute increase of at least 5 mm) in the sum of diameters of target lesions, taking as reference the smallest sum on study and/or unequivocal progression of existing non-target lesions and/or appearance of 1 or more new lesions were evaluated. The Phase 3 Response Efficacy Set consisted of the first 330 subjects randomised into the Phase 3 portion of the study and any additional subjects randomised on the same day as the 330th randomised subject. Here, "Number of Subjects Analysed" signifies subjects evaluable for this endpoint. 99999 indicated data could not be calculated due to insufficient subjects with events.

End point type	Secondary

End point timeframe:

From time of response to PD or death due to underlying disease (maximum treatment exposure of 268 weeks for doublet arm and 108 weeks for control arm)

Notes:

[36] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Doublet Arm	Phase 3:Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	107		
Units: Months				
median (confidence interval 95%)	5.70 (3.65 to 6.74)	5.75 (2.56 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: (Phase 3) Comparison of Duration of Response (DOR) in Doublet Arm vs Control Arm per BICR

End point title	(Phase 3) Comparison of Duration of Response (DOR) in Doublet Arm vs Control Arm per BICR[37]

End point description:

DOR was defined as the time from first radiographic evidence of response to the earliest documented PD or death due to underlying disease. PD: at least a 20% increase (including an absolute increase of at least 5 mm) in the sum of diameters of target lesions, taking as reference the smallest sum on study and/or unequivocal progression of existing non-target lesions and/or appearance of 1 or more new lesions were evaluated. The Phase 3 Response Efficacy Set consisted of the first 330 subjects randomised into the Phase 3 portion of the study and any additional subjects randomised on the same day as the 330th randomised subject. Here, "Number of Subjects Analysed" signifies subjects evaluable for this endpoint. 99999 indicated data could not be calculated due to insufficient subjects with events.

End point type	Secondary

End point timeframe:

From time of response to PD or death due to underlying disease (maximum treatment exposure of 268 weeks for doublet arm and 108 weeks for control arm)

Notes:

[37] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Doublet Arm	Phase 3:Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	107		
Units: Months				
median (confidence interval 95%)	6.06 (4.07 to 8.28)	99999 (2.56 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: (Phase 3) Comparison of Time to Response in Triplet Arm vs Control Arm per Investigator

End point title	(Phase 3) Comparison of Time to Response in Triplet Arm vs Control Arm per Investigator[38]

End point description:

Time to response defined as the time from first dose to first radiographic evidence of response. The FAS for the Phase 3 portion of the study consisted of all randomised Phase 3 subjects. Here, "Number of Subjects Analysed" signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From first dose to first radiographic evidence of response (maximum treatment exposure of 277.4 weeks for triplet arm and 108 weeks for control arm)

Notes:

[38] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Triplet Arm	Phase 3:Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	7		
Units: Months				
median (confidence interval 95%)	1.48 (1.41 to 1.51)	2.63 (1.45 to 2.79)		

Statistical analyses

No statistical analyses for this end point

Secondary: (Phase 3) Comparison of Time to Response in Triplet Arm vs Control Arm per BICR

End point title	(Phase 3) Comparison of Time to Response in Triplet Arm vs Control Arm per BICR[39]

End point description:

Time to response defined as the time from first dose to first radiographic evidence of response. The FAS for the Phase 3 portion of the study consisted of all randomised Phase 3 subjects. Here, "Number of Subjects Analysed" signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From first dose to first radiographic evidence of response (maximum treatment exposure of 277.4 weeks for triplet arm and 108 weeks for control arm)

Notes:

[39] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Triplet Arm	Phase 3:Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	3		
Units: Months				
median (confidence interval 95%)	1.43 (1.41 to 1.51)	1.45 (1.41 to 2.63)		

Statistical analyses

No statistical analyses for this end point

Secondary: (Phase 3) Comparison of Duration of Response (DOR) in Triplet Arm vs Doublet Arm by Investigator

End point title	(Phase 3) Comparison of Duration of Response (DOR) in Triplet Arm vs Doublet Arm by Investigator[40]

End point description:

DOR was defined as the time from first radiographic evidence of response to the earliest documented PD or death due to underlying disease. PD: at least a 20% increase (including an absolute increase of at least 5 mm) in the sum of diameters of target lesions, taking as reference the smallest sum on study and/or unequivocal progression of existing non-target lesions and/or appearance of 1 or more new lesions were evaluated. The Phase 3 Response Efficacy Set consisted of the first 330 subjects randomised into the Phase 3 portion of the study and any additional subjects randomised on the same day as the 330th randomised subject. Here, "Number of Subjects Analysed" signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From time of response to PD or death due to underlying disease (maximum treatment exposure of 277.4 weeks for triplet arm and 268 weeks for doublet arm)

Notes:

[40] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Triplet Arm	Phase 3: Doublet Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	113		
Units: Months				
median (confidence interval 95%)	4.80 (3.29 to 6.57)	5.70 (3.65 to 6.74)		

Statistical analyses

No statistical analyses for this end point

Secondary: (Phase 3) Comparison of Time to Response in Doublet Arm vs Control Arm per Investigator

End point title	(Phase 3) Comparison of Time to Response in Doublet Arm vs Control Arm per Investigator[41]

End point description:

Time to response defined as the time from first dose to first radiographic evidence of response. The FAS for the Phase 3 portion of the study consisted of all randomised Phase 3 subjects. Here, "Number of Subjects Analysed" signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From first dose to first radiographic evidence of response (maximum treatment exposure of 268 weeks for doublet arm and 108 weeks for control arm)

Notes:

[41] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Doublet Arm	Phase 3:Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	7		
Units: Months				
median (confidence interval 95%)	1.48 (1.41 to 1.54)	2.63 (1.45 to 2.79)		

Statistical analyses

No statistical analyses for this end point

Secondary: (Phase 3) Comparison of Time to Response in Triplet Arm vs Doublet Arm Per BICR

End point title	(Phase 3) Comparison of Time to Response in Triplet Arm vs Doublet Arm Per BICR[42]

End point description:

Time to response defined as the time from first dose to first radiographic evidence of response. The FAS for the Phase 3 portion of the study consisted of all randomised Phase 3 subjects. Here, "Number of Subjects Analysed" signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From first dose to first radiographic evidence of response (maximum treatment exposure of 277.4 weeks for triplet arm and 268 weeks for doublet arm)

Notes:

[42] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Triplet Arm	Phase 3: Doublet Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	36		
Units: Months				
median (confidence interval 95%)	1.43 (1.41 to 1.51)	1.48 (1.41 to 1.58)		

Statistical analyses

No statistical analyses for this end point

Secondary: (Phase 3) Comparison of Time to Response in Triplet Arm vs Doublet Arm Per Investigator

End point title	(Phase 3) Comparison of Time to Response in Triplet Arm vs Doublet Arm Per Investigator[43]

End point description:

Time to response defined as the time from first dose to first radiographic evidence of response. The FAS for the Phase 3 portion of the study consisted of all randomised Phase 3 subjects. Here, "Number of Subjects Analysed" signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From first dose to first radiographic evidence of response (maximum treatment exposure of 277.4 weeks for triplet arm and 268 weeks for doublet arm)

Notes:

[43] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Triplet Arm	Phase 3: Doublet Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	31		
Units: Months				
median (confidence interval 95%)	1.48 (1.41 to 1.51)	1.48 (1.41 to 1.54)		

Statistical analyses

No statistical analyses for this end point

Secondary: (Phase 3) Comparison of Time to Response in Doublet Arm vs Control Arm per BICR

End point title	(Phase 3) Comparison of Time to Response in Doublet Arm vs Control Arm per BICR[44]

End point description:

Time to response defined as the time from first dose to first radiographic evidence of response. The FAS for the Phase 3 portion of the study consisted of all randomised Phase 3 subjects. Here, "Number of Subjects Analysed" signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From first dose to first radiographic evidence of response (maximum treatment exposure of 268 weeks for doublet arm and 108 weeks for control arm)

Notes:

[44] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Doublet Arm	Phase 3:Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	3		
Units: Months				
median (confidence interval 95%)	1.48 (1.41 to 1.58)	1.45 (1.41 to 2.63)		

Statistical analyses

No statistical analyses for this end point

Secondary: (Phase 3) Change From Baseline in the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire for Cancer Subjects (QLQ-C30) Triplet Arm vs Control Arm, Doublet Arm vs Control, and Triplet vs Doublet

End point title	(Phase 3) Change From Baseline in the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire for Cancer Subjects (QLQ-C30) Triplet Arm vs Control Arm, Doublet Arm vs Control, and Triplet vs Doublet[45]

End point description:

The EORTC QLQ-C30 questionnaire consisted of 30 questions generating 5 functional scores (physical, role, cognitive, emotional,& social); a global health (GH) status/global quality of life scale score; 3 symptom scale scores (fatigue, pain, & nausea & vomiting); & 6 standalone one-item scores that capture additional symptoms (dyspnea, appetite loss, sleep disturbance, constipation, & diarrhea) & perceived financial burden. All items were graded by severity experienced during previous week & used 4-point-scale (1: not at all, 2: a little, 3: quite a bit, 4: very much). The scores were converted to health-related quality of life (HRQoL) scale ranging from 0-100. Higher scores indicating higher response levels (i.e., higher functioning, higher symptom severity). The FAS for Phase 3 portion of study consisted of all randomised Phase 3 subjects. Here, 'n'=subjects evaluable for the specified timepoints. 99999 indicated data could not be calculated due to insufficient subjects with events.

End point type	Secondary

End point timeframe:

Baseline, Cycle(C)1 Day(D)1 , C2 D1, C3 D1, C4 D1, C5 D1, C6 D1, C7 D1, C8 D1, C9 D1, C10 D1, C11 D1, C12 D1, C13 D1, C14 D1, C15 D1, C16 D1, C17 D1, C18 D1, C19 D1, C20 D1, C21 D1, C22 D1, C23 D1, End of Treatment, 30 Day Follow Up(each cycle of 28 days)

Notes:

[45] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Triplet Arm	Phase 3: Doublet Arm	Phase 3:Control Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	224	220	221	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Change at Cycle 1 Day 1, n= 138, 120, 133	-2.4 (± 13.44)	-4.3 (± 16.27)	-3.4 (± 15.60)	
Change at Cycle 2 Day 1, n= 181,123, 180	-1.6 (± 19.06)	3.8 (± 18.46)	-1.9 (± 22.45)	
Change at Cycle 3 Day 1, n= 148, 51, 142	0.7 (± 18.86)	3.5 (± 19.96)	-0.2 (± 24.07)	
Change at Cycle 4 Day 1, n= 119, 37, 105	0.2 (± 15.63)	4.2 (± 22.17)	1.4 (± 21.65)	
Change at Cycle 5 Day 1, n= 99, 26, 81	-1.1 (± 18.66)	4.3 (± 22.09)	-2.2 (± 22.06)	

Change at Cycle 6 Day 1, n= 68, 13, 60	-4.0 (± 16.76)	5.6 (± 23.25)	-4.5 (± 19.43)	
Change at Cycle 7 Day 1, n= 47, 10, 50	-2.5 (± 16.01)	4.3 (± 21.77)	1.7 (± 12.30)	
Change at Cycle 8 Day 1, n= 39, 7, 40	-2.6 (± 14.83)	4.2 (± 16.98)	0.0 (± 27.64)	
Change at Cycle 9 Day 1, n= 33, 7, 31	-5.8 (± 17.74)	-5.6 (± 16.44)	-4.8 (± 12.60)	
Change at Cycle 10 Day 1, n= 23, 4, 24	-3.3 (± 17.90)	-2.8 (± 16.97)	2.1 (± 20.83)	
Change at Cycle 11 Day 1, n= 16, 1, 19	-5.2 (± 20.38)	3.9 (± 15.31)	33.3 (± 99999)	
Change at Cycle 12 Day 1, n= 14, 2, 18	0.0 (± 22.41)	-4.6 (± 13.77)	4.2 (± 53.03)	
Change at Cycle 13 Day 1, n= 9, 1, 13	0.0 (± 20.41)	-3.2 (± 14.25)	0.0 (± 99999)	
Change at Cycle 14 Day 1, n= 7, 0, 7	-1.2 (± 24.26)	-6.0 (± 15.00)	99999 (± 99999)	
Change at Cycle 15 Day 1, n= 7, 0, 6	3.6 (± 33.63)	2.8 (± 8.61)	99999 (± 99999)	
Change at Cycle 16 Day 1, n= 5, 0, 3	-16.7 (± 42.08)	-5.6 (± 9.62)	99999 (± 99999)	
Change at Cycle 17 Day 1, n= 3, 0, 3	-27.8 (± 20.97)	-2.8 (± 12.73)	99999 (± 99999)	
Change at Cycle 18 Day 1, n= 1, 0, 3	-16.7 (± 99999)	-8.3 (± 8.33)	99999 (± 99999)	
Change at Cycle 19 Day 1, n= 1, 0, 2	0.0 (± 99999)	-8.3 (± 11.79)	99999 (± 99999)	
Change at Cycle 20 Day 1, n= 1, 0, 1	-25 (± 99999)	-8 (± 99999)	99999 (± 99999)	
Change at Cycle 21 Day 1, n= 1, 0, 1	0.0 (± 99999)	-16.7 (± 99999)	99999 (± 99999)	
Change at Cycle 22 Day 1, n= 0, 0, 1	99999 (± 99999)	-16.7 (± 99999)	99999 (± 99999)	
Change at Cycle 23 Day 1, n= 0, 0, 1	99999 (± 99999)	0.0 (± 99999)	99999 (± 99999)	
Change at End of Treatment, n= 74, 79, 72	-14.1 (± 22.66)	-13.1 (± 21.61)	-15.5 (± 27.04)	
Change at 30 Day Follow Up, n= 24, 21, 16	-17.4 (± 22.51)	-10.4 (± 15.96)	-24.6 (± 24.08)	
Baseline, n= 209, 200, 201	62.8 (± 22.18)	60.7 (± 21.33)	62.8 (± 21.82)	

Statistical analyses

No statistical analyses for this end point

Secondary: (Phase 3) Change From Baseline in the Functional Assessment of Cancer Therapy-Colon Cancer (FACT-C) in Triplet Arm vs Control Arm, Doublet Arm vs Control, and Triplet vs Doublet

End point title	(Phase 3) Change From Baseline in the Functional Assessment of Cancer Therapy-Colon Cancer (FACT-C) in Triplet Arm vs Control Arm, Doublet Arm vs Control, and Triplet vs Doublet[46]

End point description:

FACT-C=Functional Assessment of Chronic Illness Therapy (FACIT) ,which assessed HRQoL of cancer subjects & subjects with other chronic illnesses. It consists of total 36 items (27 items of general version of FACT-C and disease-specific subscale containing 9 CRC-specific items), summarised to 5 subscales: physical well-being (7 items),functional well-being (7 items), social/family well-being (7 items);all 3 subscales range:0-28, emotional well-being (6 items)range:0-24, colorectal cancer subscale (9 items) range:0-36; higher subscale score=better QoL. All single-item measures range:0='Not at all' to 4='Very much'. Table summarises functional well-being subscale, individual questions are linearly scaled & combined to form functional well-being subscale score (range 0-28). High score represents better QoL.FAS for Phase 3 portion=all randomised Phase 3 subjects. Here, 'n'=subjects evaluable for specified timepoints. 99999=data could not be calculated due to insufficient subjects.

End point type	Secondary

End point timeframe:

Baseline,Cycle (C)1 Day (D)1, C2 D1, C3 D1, C4 D1, C5 D1, C6 D1, C7 D1, C8 D1, C9 D1, C10 D1, C11 D1, C12 D1, C13 D1, C14 D1, C15 D1, C16 D1, C17 D1, C18 D1, C19 D1, C20 D1, C21 D1, C22 D1, C23 D1, End of Treatment, 30 Day Follow Up(each cycle of 28 days)

Notes:

[46] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Triplet Arm	Phase 3: Doublet Arm	Phase 3:Control Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	224	220	221	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Change at Cycle 1 Day 1, n= 142, 117, 130	-0.2 (± 3.36)	-0.9 (± 4.06)	-1.4 (± 3.32)	
Change at Cycle 2 Day 1, n= 183, 123, 176	-0.3 (± 4.28)	-0.6 (± 5.08)	-0.9 (± 4.48)	
Change at Cycle 3 Day 1, n= 148, 50, 137	-0.2 (± 5.15)	-0.2 (± 5.23)	-0.7 (± 5.03)	
Change at Cycle 4 Day 1, n= 119, 37, 105	0.4 (± 4.53)	-0.1 (± 4.66)	-1.8 (± 6.48)	
Change at Cycle 5 Day 1, n= 100, 26, 81	0.7 (± 6.4)	-0.2 (± 4.5)	-1.6 (± 4.58)	
Change at Cycle 6 Day 1, n= 68, 13, 58	0.7 (± 6.05)	0.6 (± 4.56)	-1.9 (± 5.3)	
Change at Cycle 7 Day 1, n= 47, 10, 49	0.5 (± 5.85)	-0.1 (± 4.70)	-0.5 (± 5.41)	
Change at Cycle 8 Day 1, n= 40, 8, 39	0.9 (± 6.35)	0.2 (± 4.24)	-2.1 (± 4.97)	
Change at Cycle 9 Day 1, n= 32, 7, 30	-1.9 (± 4.32)	-0.8 (± 3.74)	-2.6 (± 2.30)	
Change at Cycle 10 Day 1, n= 22, 4, 24	-1.7 (± 4.76)	-1.3 (± 3.59)	0.5 (± 4.36)	
Change at Cycle 11 Day 1, n= 17, 2, 19	-1.5 (± 4.47)	-0.5 (± 4.65)	-4.5 (± 7.78)	
Change at Cycle 12 Day 1, n= 14, 2, 18	-1.5 (± 4.93)	-1.1 (± 4.61)	-4.5 (± 9.19)	
Change at Cycle 13 Day 1, n= 9, 1, 13	-2.0 (± 6.76)	-3.2 (± 5.34)	-8.0 (± 99999)	
Change at Cycle 14 Day 1, n= 7, 0, 7	-2.4 (± 5.22)	-4.0 (± 5.74)	99999 (± 99999)	
Change at Cycle 15 Day 1, n= 7, 0, 6	-2.3 (± 6.85)	-1.5 (± 4.72)	99999 (± 99999)	
Change at Cycle 16 Day 1, n= 5, 0, 3	-4.2 (± 4.02)	-0.7 (± 0.58)	99999 (± 99999)	
Change at Cycle 17 Day 1, n= 3, 0, 3	-6.7 (± 5.51)	-0.7 (± 4.51)	99999 (± 99999)	
Change at Cycle 18 Day 1, n= 1, 0, 3	-5.0 (± 99999)	-3.0 (± 4.36)	99999 (± 99999)	
Change at Cycle 19 Day 1, n= 1, 0, 2	-7.0 (± 99999)	-6.0 (± 0.00)	99999 (± 99999)	
Change at Cycle 20 Day 1, n= 1, 0, 1	-6.0 (± 99999)	-5.0 (± 99999)	99999 (± 99999)	
Change at Cycle 21 Day 1, n= 1, 0, 1	-9.0 (± 99999)	-5.0 (± 99999)	99999 (± 99999)	
Change at Cycle 22 Day 1, n= 0, 0, 1	99999 (± 99999)	-12.0 (± 99999)	99999 (± 99999)	
Change at Cycle 23 Day 1, n= 0, 0, 1	99999 (± 99999)	-9.0 (± 99999)	99999 (± 99999)	
Change at End of Treatment, n= 74, 79, 73	-2.4 (± 4.84)	-2.2 (± 5.14)	-3.1 (± 6.06)	
Change at 30 Day Follow Up, n= 24, 21, 16	-3.5 (± 6.44)	-0.8 (± 5.42)	-4.2 (± 6.41)	
Baseline, n= 211, 200, 199	16.3 (± 6.22)	16.2 (± 5.9)	16.8 (± 6.07)	

Statistical analyses

No statistical analyses for this end point

Secondary: (Phase 3) Change From Baseline in the EuroQol-5D-5L Visual Analog Scale (EQ-5D-5L VAS) in Triplet Arm vs Control Arm, Doublet Arm vs Control, and Triplet vs Doublet

End point title	(Phase 3) Change From Baseline in the EuroQol-5D-5L Visual Analog Scale (EQ-5D-5L VAS) in Triplet Arm vs Control Arm, Doublet Arm vs Control, and Triplet vs Doublet[47]

End point description:

The EQ-5D-5L contains 1 item for each of 5 dimensions of health-related QoL (i.e., mobility, self-care, usual activities, pain or discomfort and anxiety or depression). Response options for each item varied from having no problems to moderate problems or extreme problems. The EQ-5D-5L (v4.0) is a standardised measure of health utility that provides a single index value for one's health status. The EQ-5D-5L is frequently used for economic evaluations of health care and has been recognised as a valid and reliable instrument for this purpose. The EQ visual analog scale (VAS) is a score that is directly reported by the subject and ranges from 0 to 100 (higher is better quality health). The FAS for the Phase 3 portion of the study consisted of all randomised Phase 3 subjects. Here, 'n' signifies subjects evaluable for the specified timepoints. 99999 indicated data could not be calculated due to insufficient subjects.

End point type	Secondary

End point timeframe:

Baseline,Cycle (C)1 Day (D)1, C2 D1, C3 D1, C4 D1, C5 D1, C6 D1, C7 D1, C8 D1, C9 D1, C10 D1, C11 D1, C12 D1, C13 D1, C14 D1, C15 D1, C16 D1, C17 D1, C18 D1, C19 D1, C20 D1, C21 D1, C22 D1, C23 D1, End of Treatment, 30 Day Follow Up(each cycle of 28 days)

Notes:

[47] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Triplet Arm	Phase 3: Doublet Arm	Phase 3:Control Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	224	220	221	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Change at Cycle 1 Day 1, n= 141, 120, 135	0.8 (± 10.89)	-0.9 (± 14.09)	-2.1 (± 15.02)	
Change at Cycle 2 Day 1, n= 183, 124, 181	1.4 (± 14.74)	1.9 (± 14.81)	-2.4 (± 17.20)	
Change at Cycle 3 Day 1, n= 150, 52, 141	3.0 (± 13.94)	4.2 (± 17.32)	-1.4 (± 17.40)	
Change at Cycle 4 Day 1, n= 118, 37, 105	4.0 (± 13.06)	5.6 (± 14.87)	-0.4 (± 15.14)	
Change at Cycle 5 Day 1, n= 99, 26, 80	3.3 (± 14.66)	5.1 (± 15.11)	2.5 (± 11.17)	
Change at Cycle 6 Day 1, n= 66, 13, 58	1.3 (± 13.33)	2.9 (± 16.84)	-3.6 (± 13.26)	
Change at Cycle 7 Day 1, n= 46, 10, 47	1.4 (± 13.64)	3.6 (± 16.71)	2.4 (± 7.44)	
Change at Cycle 8 Day 1, n= 39, 8, 39	4.1 (± 10.77)	2.0 (± 16.11)	-2.8 (± 12.95)	
Change at Cycle 9 Day 1, n= 33, 7, 30	0.3 (± 15.16)	-4.0 (± 12.99)	-8.1 (± 8.80)	
Change at Cycle 10 Day 1, n= 23, 4, 23	0.2 (± 13.34)	-8.1 (± 13.68)	-1.8 (± 2.36)	

Change at Cycle 11 Day 1, n= 17, 2, 18	0.2 (± 13.87)	-0.1 (± 10.15)	4.0 (± 8.49)	
Change at Cycle 12 Day 1, n= 13, 2, 17	-4.0 (± 20.11)	-0.6 (± 11.67)	1.5 (± 12.02)	
Change at Cycle 13 Day 1, n= 9, 1, 12	-3.0 (± 17.17)	-4.1 (± 14.41)	-2.0 (± 99999)	
Change at Cycle 14 Day 1, n= 7, 0, 7	-4.0 (± 18.06)	-0.4 (± 13.99)	99999 (± 99999)	
Change at Cycle 15 Day 1, n= 7, 0, 6	-3.4 (± 14.67)	4.2 (± 7.36)	99999 (± 99999)	
Change at Cycle 16 Day 1, n= 5, 0, 3	-10.4 (± 24.87)	3.3 (± 2.89)	99999 (± 99999)	
Change at Cycle 17 Day 1, n= 3, 0, 3	-18.3 (± 20.21)	1.7 (± 5.77)	99999 (± 99999)	
Change at Cycle 18 Day 1, n= 1, 0, 3	7.0 (± 99999)	-3.3 (± 2.89)	99999 (± 99999)	
Change at Cycle 19 Day 1, n= 1, 0, 2	8.0 (± 99999)	-5.5 (± 13.44)	99999 (± 99999)	
Change at Cycle 20 Day 1, n= 1, 0, 1	8.0 (± 99999)	2.0 (± 99999)	99999 (± 99999)	
Change at Cycle 21 Day 1, n= 1, 0, 1	8.0 (± 99999)	-5.0 (± 99999)	99999 (± 99999)	
Change at Cycle 22 Day 1, n= 0, 0, 1	99999 (± 99999)	-5.0 (± 99999)	99999 (± 99999)	
Change at Cycle 23 Day 1, n= 0, 0, 1	99999 (± 99999)	-5.0 (± 99999)	99999 (± 99999)	
Change at End of Treatment, n= 75, 80, 72	-8.5 (± 17.40)	-8.0 (± 18.99)	-12.7 (± 21.34)	
Change at 30 Day Follow Up, n= 24, 21, 16	-11.1 (± 20.23)	-5.9 (± 20.18)	-11.0 (± 17.51)	
Baseline, n= 210, 199, 203	69.0 (± 19.03)	66.5 (± 19.51)	68.3 (± 19.71)	

Statistical analyses

No statistical analyses for this end point

Secondary: (Phase 3) Change From Baseline in the Subject Global Impression of Change (PGIC) in Triplet Arm vs Control Arm, Doublet Arm vs Control, and Triplet vs Doublet

End point title	(Phase 3) Change From Baseline in the Subject Global Impression of Change (PGIC) in Triplet Arm vs Control Arm, Doublet Arm vs Control, and Triplet vs Doublet[48]

End point description:

The PGIC is a measure of subject's perceptions of change in their symptoms over time that can be used as an anchoring method to determine the minimal clinically important difference for other subject reported outcome (PROs). For this assessment, subjects answered the following question: "Since starting treatment, my colorectal cancer symptoms are: (1) very much improved, (2) much improved, (3) minimally improved, (4) no change, (5) minimally worse, (6) much worse or (7) very much worse." The FAS for the Phase 3 portion of the study consisted of all randomised Phase 3 subjects. Here, 'n' signifies subjects evaluable for the specified timepoints. 99999 indicated data could not be calculated due to insufficient subjects.

End point type	Secondary

End point timeframe:

Baseline,Cycle (C)1 Day (D)1, C2 D1, C3 D1, C4 D1, C5 D1, C6 D1, C7 D1, C8 D1, C9 D1, C10 D1, C11 D1, C12 D1, C13 D1, C14 D1, C15 D1, C16 D1, C17 D1, C18 D1, C19 D1, C20 D1, C21 D1, C22 D1, C23 D1, End of Treatment, 30 Day Follow Up(each cycle of 28 days)

Notes:

[48] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Triplet Arm	Phase 3: Doublet Arm	Phase 3:Control Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	224	220	221	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Change at Cycle 1 Day 1, n= 91, 83, 92	-0.1 (± 0.93)	0.1 (± 1.21)	0.0 (± 0.90)	
Change at Cycle 2 Day 1, n= 127, 90, 130	-0.7 (± 1.44)	-0.8 (± 1.60)	-0.3 (± 1.52)	
Change at Cycle 3 Day 1, n= 101, 37, 105	-0.9 (± 1.44)	-1.2 (± 1.53)	-0.5 (± 1.56)	
Change at Cycle 4 Day 1, n= 80, 28, 79	-0.9 (± 1.49)	-1.1 (± 1.68)	-0.5 (± 1.35)	
Change at Cycle 5 Day 1, n= 66, 19, 59	-0.9 (± 1.61)	-1.1 (± 1.69)	-0.7 (± 1.41)	
Change at Cycle 6 Day 1, n= 45, 9, 40	-0.8 (± 1.31)	-1.2 (± 1.70)	-0.8 (± 1.39)	
Change at Cycle 7 Day 1, n= 30, 7, 36	-1.1 (± 1.44)	-1.0 (± 1.61)	-1.1 (± 1.07)	
Change at Cycle 8 Day 1, n= 23, 5, 27	-1.2 (± 1.56)	-1.1 (± 1.58)	-1.0 (± 0.71)	
Change at Cycle 9 Day 1, n= 21, 5, 21	-0.8 (± 1.26)	-0.9 (± 1.37)	-1.0 (± 0.71)	
Change at Cycle 10 Day 1, n= 15, 3, 17	-0.5 (± 1.51)	-0.6 (± 1.28)	-0.3 (± 0.58)	
Change at Cycle 11 Day 1, n= 13, 2, 13	-0.9 (± 1.38)	-1.1 (± 1.38)	0.0 (± 0.00)	
Change at Cycle 12 Day 1, n= 11, 2, 12	-0.9 (± 1.45)	-0.8 (± 1.36)	-0.5 (± 0.71)	
Change at Cycle 13 Day 1, n= 8, 1, 10	-1.3 (± 1.39)	-0.9 (± 1.52)	-1.0 (± 99999)	
Change at Cycle 14 Day 1, n= 7, 0, 6	-1.1 (± 1.46)	-1.5 (± 1.05)	99999 (± 99999)	
Change at Cycle 15 Day 1, n= 6, 0, 5	-1.2 (± 1.47)	-1.6 (± 0.89)	99999 (± 99999)	
Change at Cycle 16 Day 1, n= 4, 0, 3	-2.0 (± 0.82)	-0.7 (± 1.53)	99999 (± 99999)	
Change at Cycle 17 Day 1, n= 3, 0, 3	-1.3 (± 1.53)	-1.0 (± 1.00)	99999 (± 99999)	
Change at Cycle 18 Day 1, n= 1, 0, 3	-2.0 (± 99999)	-1.0 (± 1.00)	99999 (± 99999)	
Change at Cycle 19 Day 1, n= 1, 0, 2	-3.0 (± 99999)	-0.5 (± 2.12)	99999 (± 99999)	
Change at Cycle 20 Day 1, n= 1, 0, 1	-3.0 (± 99999)	-2.0 (± 99999)	99999 (± 99999)	
Change at Cycle 21 Day 1, n= 1, 0, 1	-3.0 (± 99999)	-2.0 (± 99999)	99999 (± 99999)	
Change at Cycle 22 Day 1, n= 0, 0, 1	99999 (± 99999)	-2.0 (± 99999)	99999 (± 99999)	
Change at Cycle 23 Day 1, n= 0, 0, 1	99999 (± 99999)	-2.0 (± 99999)	99999 (± 99999)	
Change at End of Treatment, n= 52, 63, 54	0.3 (± 1.85)	0.1 (± 1.82)	0.4 (± 1.58)	
Change at 30 Day Follow Up, n= 18, 19, 10	-0.1 (± 2.08)	0.5 (± 1.43)	0.7 (± 1.34)	
Baseline, n= 153, 149, 152	3.8 (± 1.30)	3.8 (± 1.30)	3.9 (± 1.28)	

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety Lead-in) Evaluation of the Area Under the Concentration-Time Curve From Zero to the Last Measurable Time Point (AUClast) for Cetuximab

End point title	(Safety Lead-in) Evaluation of the Area Under the Concentration-Time Curve From Zero to the Last Measurable Time Point (AUClast) for Cetuximab[49]

End point description:

The pharmacokinetics (PK) set included all subjects in the safety set who had at least 1 postdose blood collection for PK with associated bioanalytical results. Subjects were analysed according to the actual treatment and dose received.

End point type	Secondary

End point timeframe:

Predose and 1, 2, 4 and 6 hours post-dose on Day 1 of Cycles 1 and 2 (each cycle of 28 days)

Notes:

[49] - 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: Only descriptive data was planned to be analysed.

End point values	Combined Safety Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Nanogram/milliliter *hour				
geometric mean (geometric coefficient of variation)				
Cycle 1; n=34	841000 (± 22.2)			
Cycle 2; n=32	970000 (± 20.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety Lead-in) Evaluation of the Area Under the Concentration-Time Curve From Zero to the Last Measurable Time Point (AUClast) for Encorafenib

End point title	(Safety Lead-in) Evaluation of the Area Under the Concentration-Time Curve From Zero to the Last Measurable Time Point (AUClast) for Encorafenib[50]

End point description:

The pharmacokinetics (PK) set included all subjects in the safety set who had at least 1 postdose blood collection for PK with associated bioanalytical results. Subjects were analysed according to the actual treatment and dose received. All subjects reported under 'Number of Subjects Analysed' contributed data to the table but may not have evaluable data for every row. Here, "Number Analysed (n)" signifies subjects evaluable for specified rows.

End point type	Secondary

End point timeframe:

Predose and 1, 2, 4 and 6 hours post-dose on Day 1 of Cycles 1 and 2 (each cycle of 28 days)

Notes:

[50] - 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: Only descriptive data was planned to be analysed.

End point values	Combined Safety Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Nanogram/milliliter *hour				
geometric mean (geometric coefficient of variation)				
Cycle 1; n=34	11300 (± 61.5)			
Cycle 2; n=29	6660 (± 61.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety Lead-in) Evaluation of the Area Under the Concentration-Time Curve From Zero to the Last Measurable Time Point (AUClast) for Metabolite of Binimetinib (AR00426032)

End point title	(Safety Lead-in) Evaluation of the Area Under the Concentration-Time Curve From Zero to the Last Measurable Time Point (AUClast) for Metabolite of Binimetinib (AR00426032)[51]

End point description:

The pharmacokinetics (PK) set included all subjects in the safety set who had at least 1 postdose blood collection for PK with associated bioanalytical results. Subjects were analysed according to the actual treatment and dose received. All subjects reported under 'Number of Subjects Analysed' contributed data to the table but may not have evaluable data for every row. Here, "Number Analysed (n)" signifies subjects evaluable for specified rows.

End point type	Secondary

End point timeframe:

Predose and 1, 2, 4 and 6 hours post-dose on Day 1 of Cycles 1 and 2 (each cycle of 28 days)

Notes:

[51] - 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: Only descriptive data was planned to be analysed.

End point values	Combined Safety Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Nanogram/milliliter *hour				
geometric mean (geometric coefficient of variation)				
Cycle 1; n=35	206 (± 46.7)			
Cycle 2; n=26	70.0 (± 95.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety Lead-in) Evaluation of the Area Under the Concentration-Time

Curve From Zero to the Last Measurable Time Point (AUClast) for Binimetinib

End point title	(Safety Lead-in) Evaluation of the Area Under the Concentration-Time Curve From Zero to the Last Measurable Time Point (AUClast) for Binimetinib[52]

End point description:

The pharmacokinetics (PK) set included all subjects in the safety set who had at least 1 postdose blood collection for PK with associated bioanalytical results. Subjects were analysed according to the actual treatment and dose received. All subjects reported under 'Number of Subjects Analysed' contributed data to the table but may not have evaluable data for every row. Here, "Number Analysed (n)" signifies subjects evaluable for specified rows.

End point type	Secondary

End point timeframe:

Predose and 1, 2, 4 and 6 hours post-dose on Day 1 of Cycles 1 and 2 (each cycle of 28 days)

Notes:

[52] - 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: Only descriptive data was planned to be analysed.

End point values	Combined Safety Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Nanogram/milliliter *hour				
geometric mean (geometric coefficient of variation)				
Cycle 1, n=34	1960 (± 43.6)			
Cycle 2, n=29	1540 (± 44.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety Lead-in) Evaluation of the Maximum Concentration (Cmax) for Encorafenib

End point title	(Safety Lead-in) Evaluation of the Maximum Concentration (Cmax) for Encorafenib[53]

End point description:

The pharmacokinetics (PK) set included all subjects in the safety set who had at least 1 postdose blood collection for PK with associated bioanalytical results. Subjects were analysed according to the actual treatment and dose received. All subjects reported under 'Number of Subjects Analysed' contributed data to the table but may not have evaluable data for every row. Here, "Number Analysed (n)" signifies subjects evaluable for specified rows.

End point type	Secondary

End point timeframe:

Predose and 1, 2, 4 and 6 hours post-dose on Day 1 of Cycles 1 and 2 (each cycle of 28 days)

Notes:

[53] - 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: Only descriptive data was planned to be analysed.

End point values	Combined Safety Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Nanogram/milliliter				
geometric mean (geometric coefficient of variation)				
Cycle 1; n=34	3360 (± 65.1)			
Cycle 2; n=29	2490 (± 75.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety Lead-in) Evaluation of the Maximum Concentration (Cmax) for Binimetinib

End point title	(Safety Lead-in) Evaluation of the Maximum Concentration (Cmax) for Binimetinib[54]

End point description:

The pharmacokinetics (PK) set included all subjects in the safety set who had at least 1 postdose blood collection for PK with associated bioanalytical results. Subjects were analysed according to the actual treatment and dose received. All subjects reported under 'Number of Subjects Analysed' contributed data to the table but may not have evaluable data for every row. Here, "Number Analysed (n)" signifies subjects evaluable for specified rows.

End point type	Secondary

End point timeframe:

Predose and 1, 2, 4 and 6 hours post-dose on Day 1 of Cycles 1 and 2 (each cycle of 28 days)

Notes:

[54] - 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: Only descriptive data was planned to be analysed.

End point values	Combined Safety Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Nanogram/milliliter				
geometric mean (geometric coefficient of variation)				
Cycle 1; n=35	654 (± 50.8)			
Cycle 2; n=26	524 (± 70.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety Lead-in) Evaluation of the Maximum Concentration (Cmax) for Cetuximab

End point title	(Safety Lead-in) Evaluation of the Maximum Concentration (Cmax) for Cetuximab[55]

End point description:

The pharmacokinetics (PK) set included all subjects in the safety set who had at least 1 postdose blood collection for PK with associated bioanalytical results. Subjects were analysed according to the actual treatment and dose received. All subjects reported under 'Number of Subjects Analysed' contributed data to the table but may not have evaluable data for every row. Here, "Number Analysed (n)" signifies subjects evaluable for specified rows.

End point type	Secondary

End point timeframe:

Predose and 1, 2, 4 and 6 hours post-dose on Day 1 of Cycles 1 and 2 (each cycle of 28 days)

Notes:

[55] - 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: Only descriptive data was planned to be analysed.

End point values	Combined Safety Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Nanogram/milliliter				
geometric mean (geometric coefficient of variation)				
Cycle 1; n=34	195000 (± 22.2)			
Cycle 2; n=32	199000 (± 26.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety Lead-in) Evaluation of the Time of Maximum Observed Concentration (Tmax) for Cetuximab

End point title	(Safety Lead-in) Evaluation of the Time of Maximum Observed Concentration (Tmax) for Cetuximab[56]

End point description:

The pharmacokinetics (PK) set included all subjects in the safety set who had at least 1 postdose blood collection for PK with associated bioanalytical results. Subjects were analysed according to the actual treatment and dose received. All subjects reported under 'Number of Subjects Analysed' contributed data to the table but may not have evaluable data for every row. Here, "Number Analysed (n)" signifies subjects evaluable for specified rows.

End point type	Secondary

End point timeframe:

Predose and 1, 2, 4 and 6 hours post-dose on Day 1 of Cycles 1 and 2 (each cycle of 28 days)

Notes:

[56] - 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: Only descriptive data was planned to be analysed.

End point values	Combined Safety Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Hours				
median (full range (min-max))				
Cycle 1; n=34	3.77 (1.83 to 6.05)			
Cycle 2; n=32	3.05 (1.00 to 6.17)			

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety Lead-in) Evaluation of the Time of Maximum Observed Concentration (Tmax) for Encorafenib

End point title	(Safety Lead-in) Evaluation of the Time of Maximum Observed Concentration (Tmax) for Encorafenib[57]

End point description:

The pharmacokinetics (PK) set included all subjects in the safety set who had at least 1 postdose blood collection for PK with associated bioanalytical results. Subjects were analysed according to the actual treatment and dose received. All subjects reported under 'Number of Subjects Analysed' contributed data to the table but may not have evaluable data for every row. Here, "Number Analysed (n)" signifies subjects evaluable for specified rows.

End point type	Secondary

End point timeframe:

Predose and 1, 2, 4 and 6 hours post-dose on Day 1 of Cycles 1 and 2 (each cycle of 28 days)

Notes:

[57] - 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: Only descriptive data was planned to be analysed.

End point values	Combined Safety Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Hours				
median (full range (min-max))				
Cycle 1; n=34	2.00 (0.883 to 6.25)			
Cycle 2; n=29	2.00 (0.950 to 5.73)			

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety Lead-in) Evaluation of the Maximum Concentration (Cmax) for Metabolite of Binimetinib (AR00426032)

End point title	(Safety Lead-in) Evaluation of the Maximum Concentration (Cmax) for Metabolite of Binimetinib (AR00426032)[58]

End point description:

The pharmacokinetics (PK) set included all subjects in the safety set who had at least 1 postdose blood collection for PK with associated bioanalytical results. Subjects were analysed according to the actual treatment and dose received. All subjects reported under 'Number of Subjects Analysed' contributed data to the table but may not have evaluable data for every row. Here, "Number Analysed (n)" signifies subjects evaluable for specified rows.

End point type	Secondary

End point timeframe:

Predose and 1, 2, 4 and 6 hours post-dose on Day 1 of Cycles 1 and 2 (each cycle of 28 days)

Notes:

[58] - 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: Only descriptive data was planned to be analysed.

End point values	Combined Safety Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Nanogram/milliliter				
geometric mean (geometric coefficient of variation)				
Cycle 1; n=35	59.9 (± 50.8)			
Cycle 2; n=26	20.5 (± 119)			

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety Lead-in) Evaluation of the Steady-State Concentration Measured Just Before the Next Dose of Study Drug (Ctrough) for Binimetinib

End point title	(Safety Lead-in) Evaluation of the Steady-State Concentration Measured Just Before the Next Dose of Study Drug (Ctrough) for Binimetinib[59]

End point description:

The pharmacokinetics (PK) set included all subjects in the safety set who had at least 1 postdose blood collection for PK with associated bioanalytical results. Subjects were analysed according to the actual treatment and dose received.

End point type	Secondary

End point timeframe:

Predose and 1, 2, 4 and 6 hours post-dose on Day 1 of Cycles 1 and 2 (each cycle of 28 days)

Notes:

[59] - 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: Only descriptive data was planned to be analysed.

End point values	Combined Safety Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Nanogram/milliliter				
geometric mean (geometric coefficient of variation)	55.3 (± 61.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety Lead-in) Evaluation of the Steady-State Concentration Measured Just Before the Next Dose of Study Drug (Ctrough) for Encorafenib

End point title	(Safety Lead-in) Evaluation of the Steady-State Concentration Measured Just Before the Next Dose of Study Drug (Ctrough) for Encorafenib[60]

End point description:

The pharmacokinetics (PK) set included all subjects in the safety set who had at least 1 postdose blood collection for PK with associated bioanalytical results. Subjects were analysed according to the actual treatment and dose received.

End point type	Secondary

End point timeframe:

Predose and 1, 2, 4 and 6 hours post-dose on Day 1 of Cycles 1 and 2 (each cycle of 28 days)

Notes:

[60] - 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: Only descriptive data was planned to be analysed.

End point values	Combined Safety Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Nanogram/milliliter				
geometric mean (geometric coefficient of variation)	18.9 (± 191)			

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety Lead-in) Evaluation of the Time of Maximum Observed Concentration (Tmax) for Metabolite of Binimetinib (AR00426032)

End point title	(Safety Lead-in) Evaluation of the Time of Maximum Observed Concentration (Tmax) for Metabolite of Binimetinib (AR00426032)[61]

End point description:

The pharmacokinetics (PK) set included all subjects in the safety set who had at least 1 postdose blood collection for PK with associated bioanalytical results. Subjects were analysed according to the actual treatment and dose received. All subjects reported under 'Number of Subjects Analysed' contributed data to the table but may not have evaluable data for every row. Here, "Number Analysed

(n)" signifies subjects evaluable for specified rows.

End point type	Secondary

End point timeframe:

Predose and 1, 2, 4 and 6 hours post-dose on Day 1 of Cycles 1 and 2 (each cycle of 28 days)

Notes:

[61] - 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: Only descriptive data was planned to be analysed.

End point values	Combined Safety Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Hours				
median (full range (min-max))				
Cycle 1; n=35	2.00 (0.833 to 5.78)			
Cycle 2; n=26	1.58 (0.933 to 6.52)			

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety Lead-in) Evaluation of the Time of Maximum Observed Concentration (Tmax) for Binimetinib

End point title	(Safety Lead-in) Evaluation of the Time of Maximum Observed Concentration (Tmax) for Binimetinib[62]

End point description:

The pharmacokinetics (PK) set included all subjects in the safety set who had at least 1 postdose blood collection for PK with associated bioanalytical results. Subjects were analysed according to the actual treatment and dose received. All subjects reported under 'Number of Subjects Analysed' contributed data to the table but may not have evaluable data for every row. Here, "Number Analysed (n)" signifies subjects evaluable for specified rows.

End point type	Secondary

End point timeframe:

Predose and 1, 2, 4 and 6 hours post-dose on Day 1 of Cycles 1 and 2 (each cycle of 28 days)

Notes:

[62] - 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: Only descriptive data was planned to be analysed.

End point values	Combined Safety Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Hours				
median (full range (min-max))				
Cycle 1; n=35	1.98 (0.883 to 5.67)			
Cycle 2; n=26	1.04 (0.900 to 4.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: (Phase 3) Evaluation of the Model-Based Oral Clearance (CL/F) for Encorafenib

End point title	(Phase 3) Evaluation of the Model-Based Oral Clearance (CL/F) for Encorafenib

End point description:

The reported cross-arm CL/F value is a fixed-effect parameter determined from a population PK analysis. The analysis included pooled data from subjects enrolled in multiple studies including those who were not enrolled in this study. The NCTID include: NCT01719380, NCT01543698, and NCT01436656. An additional study ARRAY-162-105 is not required to register. The analysis set included all subjects in the PK set with measurable plasma concentrations of the test drug plus concentrations from subjects from 4 additional clinical studies. Subjects were analysed according to the actual treatment and dose received.

End point type	Secondary

End point timeframe:

2 and 6 hours post-dose on Day 1 of Cycle 1, Predose and 2 hours post-dose on Day 1 of Cycle 2 (each cycle of 28 days)

End point values	Pharmacokinetic Population of Encorafenib			
Subject group type	Subject analysis set			
Number of subjects analysed	394			
Units: Liter/hour				
geometric mean (confidence interval 95%)	16.4 (14.9 to 17.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety Lead-in) Evaluation of the Steady-State Concentration Measured Just Before the Next Dose of Study Drug (Ctrough) for a Metabolite of Binimetinib

End point title	(Safety Lead-in) Evaluation of the Steady-State Concentration Measured Just Before the Next Dose of Study Drug (Ctrough) for a Metabolite of Binimetinib[63]

End point description:

The pharmacokinetics (PK) set included all subjects in the safety set who had at least 1 postdose blood collection for PK with associated bioanalytical results. Subjects were analysed according to the actual treatment and dose received.

End point type	Secondary

End point timeframe:

Predose and 1, 2, 4 and 6 hours post-dose on Day 1 of Cycles 1 and 2 (each cycle of 28 days)

Notes:

[63] - 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: Only descriptive data was planned to be analysed.

End point values	Combined Safety Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Nanogram/milliliter				
geometric mean (geometric coefficient of variation)	3.41 (± 68.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: (Phase 3) Evaluation of the Model-Based Oral Clearance (CL/F) for Binimetinib

End point title	(Phase 3) Evaluation of the Model-Based Oral Clearance (CL/F) for Binimetinib

End point description:

The reported cross-arm CL/F value is a fixed-effect parameter determined from a population PK analysis. The analysis included pooled data from subjects enrolled in multiple studies including those who were not enrolled in this study. The NCTID include: NCT01719380, NCT01543698, and NCT01436656. An additional study ARRAY-162-105 is not required to register. The analysis set included all subjects in the PK set with measurable plasma concentrations of the test drug plus concentrations from subjects from 4 additional clinical studies. Subjects were analysed according to the actual treatment and dose received. Here, "Number of Subjects Analysed" signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

2 and 6 hours post-dose on Day 1 of Cycle 1, Predose and 2 hours post-dose on Day 1 of Cycle 2 (each cycle of 28 days)

End point values	Pharmacokinetic Population of Encorafenib			
Subject group type	Subject analysis set			
Number of subjects analysed	181			
Units: Liter/hour				
geometric mean (confidence interval 95%)	19.0 (17.7 to 20.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: (Safety Lead-in) Evaluation of the Steady-State Concentration Measured Just Before the Next Dose of Study Drug (Ctrough) for Cetuximab

End point title	(Safety Lead-in) Evaluation of the Steady-State Concentration Measured Just Before the Next Dose of Study Drug (Ctrough) for Cetuximab[64]

End point description:

The pharmacokinetics (PK) set included all subjects in the safety set who had at least 1 postdose blood collection for PK with associated bioanalytical results. Subjects were analysed according to the actual treatment and dose received.

End point type	Secondary

End point timeframe:

Predose and 1, 2, 4 and 6 hours post-dose on Day 1 of Cycles 1 and 2 (each cycle of 28 days)

Notes:

[64] - 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: Only descriptive data was planned to be analysed.

End point values	Combined Safety Lead-in			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Nanogram/milliliter				
geometric mean (geometric coefficient of variation)	55400 (± 54.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: (Phase 3) Evaluation of the Model-Based Clearance (CL) for Cetuximab

End point title	(Phase 3) Evaluation of the Model-Based Clearance (CL) for Cetuximab

End point description:

The reported cross-arm CL/F value is a fixed-effect parameter determined from a population PK analysis. The analysis included pooled data from subjects enrolled in multiple studies including those who were not enrolled in this study. The NCTID include: NCT01719380, NCT01543698, and NCT01436656. An additional study ARRAY-162-105 is not required to register. The analysis set included all subjects in the PK set with measurable plasma concentrations of the test drug plus concentrations from subjects from 4 additional clinical studies. Subjects were analysed according to the actual treatment and dose received. Here, "Number of Subjects Analysed" signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

2 and 6 hours post-dose on Day 1 of Cycle 1, Predose and 2 hours post-dose on Day 1 of Cycle 2 (each cycle of 28 days)

End point values	Pharmacokinetic Population of Encorafenib			
Subject group type	Subject analysis set			
Number of subjects analysed	261			
Units: Liter/hour				
geometric mean (confidence interval 95%)	0.0154 (0.0114 to 0.0225)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Number of Subjects With Clinically Notable Shifts in Hematology and Coagulation Laboratory Parameters

End point title	Phase 3: Number of Subjects With Clinically Notable Shifts in Hematology and Coagulation Laboratory Parameters[65]

End point description:

Clinically notable shifts was defined as worsening by at least 2 grades or to more than or equal to (>=) Grade 3 based on Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 where Grade 1: mild, Grade 2: moderate, Grade 3: severe, Grade 4: life threatening and Grade 5: death. The safety set consisted of all subjects who received at least 1 dose of study drug and had at least 1 post-treatment assessment, which may have included death. Subjects were analysed according to treatment received. Here, "Number of Subjects Analysed" signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From start of study treatment until 30 days post last dose of study treatment (for triplet arm: maximum treatment exposure of 277.4 weeks; for doublet arm: maximum treatment exposure of 268 weeks; for Control arm: maximum treatment exposure of 108 weeks)

Notes:

[65] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Triplet Arm	Phase 3: Doublet Arm	Phase 3:Control Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	222	216	193	
Units: Subjects				
Activated Partial Thromboplastin Time - Hyper	9	9	4	
Hemoglobin - Hyper	0	0	0	
Hemoglobin - Hypo	97	30	17	
Leukocytes - Hyper	0	0	0	
Leukocytes - Hypo	2	9	51	
Lymphocytes - Hyper	12	3	4	
Lymphocytes - Hypo	25	47	57	
Neutrophils - Hypo	4	8	65	
Platelets - Hypo	1	5	4	
Prothrombin Intl. Normalised Ratio - Hyper	3	2	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Number of Subjects With Clinically Notable Shifts in Serum Chemistry Laboratory Parameters

End point title	Phase 3: Number of Subjects With Clinically Notable Shifts in Serum Chemistry Laboratory Parameters[66]

End point description:

Clinically notable shifts was defined as worsening by at least 2 grades or to >= Grade 3 based on CTCAE version 4.03 where Grade 1: mild, Grade 2: moderate, Grade 3: severe, Grade 4: life threatening and Grade 5: death. The safety set consisted of all subjects who received at least 1 dose of study drug and had at least 1 post-treatment assessment, which may have included death. Subjects were analysed according to treatment received. Here, "Number of Subjects Analysed" signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From start of study treatment until 30 days post last dose of study treatment (for triplet arm: maximum treatment exposure of 277.4 weeks; for doublet arm: maximum treatment exposure of 268 weeks; for Control arm: maximum treatment exposure of 108 weeks)

Notes:

[66] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Triplet Arm	Phase 3: Doublet Arm	Phase 3:Control Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	222	216	193	
Units: Subjects				
Alanine Aminotransferase - Hyper	11	7	10	
Albumin - Hypo	50	16	17	
Alkaline Phosphatase - Hyper	13	12	18	
Aspartate Aminotransferase - Hyper	11	7	9	
Bilirubin - Hyper	11	13	12	
Calcium - Hyper	1	0	0	
Calcium - Hypo	15	8	7	
Creatine Kinase - Hyper	18	1	3	
Creatinine - Hyper	45	11	6	
Glucose - Hyper	8	16	4	
Glucose - Hypo	4	0	1	
Magnesium - Hyper	0	1	2	
Magnesium - Hypo	11	4	9	
Potassium - Hyper	14	10	5	
Potassium - Hypo	5	7	9	
Sodium - Hyper	1	1	2	
Sodium - Hypo	10	4	5	
Troponin I - Hyper	0	0	0	

Urate - Hyper	4	2	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Number of Subjects With Clinically Notable Shifts in Urinalysis Laboratory Parameters

End point title	Phase 3: Number of Subjects With Clinically Notable Shifts in Urinalysis Laboratory Parameters[67]

End point description:

Clinically notable shifts was defined as worsening by at least 2 grades or to >= Grade 3 based on CTCAE version 4.03 where Grade 1: mild, Grade 2: moderate, Grade 3: severe, Grade 4: life threatening and Grade 5: death. The safety set consisted of all subjects who received at least 1 dose of study drug and had at least 1 post-treatment assessment, which may have included death. Subjects were analysed according to treatment received. Here, "Number of Subjects Analysed" signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From start of study treatment until 30 days post last dose of study treatment (for triplet arm: maximum treatment exposure of 277.4 weeks; for doublet arm: maximum treatment exposure of 268 weeks; for Control arm: maximum treatment exposure of 108 weeks)

Notes:

[67] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Triplet Arm	Phase 3: Doublet Arm	Phase 3:Control Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	222	216	193	
Units: Subjects	8	8	5	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Number of Subjects With Newly Occurring Clinically Notable Vital Sign Abnormalities

End point title	Phase 3: Number of Subjects With Newly Occurring Clinically Notable Vital Sign Abnormalities[68]

End point description:

Newly occurring clinically notable changes was defined as subjects not meeting the criterion at baseline and meeting criterion post-baseline. The criterion included: low/high systolic blood pressure (SBP): <= 90 millimeters of mercury(mmHg) with decrease from baseline of >= 20mmHg or >= 160mmHg with increase from baseline of >= 20mmHg, low/high diastolic blood pressure (DBP): <= 50mmHg with decrease from baseline of >= 15mmHg or >= 100mmHg with increase from baseline of >= 15mmHg, low/high pulse: <= 50 beats/min with decrease from baseline of >= 15 beats/min or >= 120 beats/min with increase from baseline of >= 15 beats/min, low/high temperature: <= 36 degree Celsius (deg C)

or >= 37.5 deg C. Safety set consisted of all subjects who received at least 1 dose of study drug and had at least 1 post-treatment assessment, which may have included death. Subjects were analysed according to treatment received. Here, "Number of Subjects Analysed" signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From start of study treatment until 30 days post last dose of study treatment (for triplet arm: maximum treatment exposure of 277.4 weeks; for doublet arm: maximum treatment exposure of 268 weeks; for Control arm: maximum treatment exposure of 108 weeks)

Notes:

[68] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Triplet Arm	Phase 3: Doublet Arm	Phase 3:Control Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	222	216	193	
Units: Subjects				
Diastolic Blood Pressure - High	8	6	7	
Diastolic Blood Pressure - Low	21	27	5	
Pulse Rate - High	23	14	20	
Pulse Rate - Low	3	4	3	
Systolic Blood Pressure - High	19	13	5	
Systolic Blood Pressure - Low	37	28	10	
Temperature - High	33	23	25	
Temperature - Low	93	84	55	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Number of Subjects With Newly Occurring Clinically Notable Electrocardiogram (ECG) Values

End point title	Phase 3: Number of Subjects With Newly Occurring Clinically Notable Electrocardiogram (ECG) Values[69]

End point description:

Newly occurring clinically notable changes was defined as subjects not meeting the criterion at baseline and meeting criterion post-baseline. The criterion included: heart rate- decrease from baseline > 25% and to a value < 50 and increase from baseline > 25% and to a value > 100. QT interval- new > 450 (millisecond) msec, new > 480 msec, new > 500 msec, increase from baseline > 30 msec and increase from baseline > 60 msec. QTcF- new > 450 msec, new > 480 msec, new > 500 msec, increase from baseline > 30 msec and increase from baseline > 60 msec. The safety set consisted of all subjects who received at least 1 dose of study drug and had at least 1 post-treatment assessment, which may have included death. Subjects were analysed according to treatment received. Here, "Number of Subjects Analysed" signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From start of study treatment until 30 days post last dose of study treatment (for triplet arm: maximum treatment exposure of 277.4 weeks; for doublet arm: maximum treatment exposure of 268 weeks; for Control arm: maximum treatment exposure of 108 weeks)

Notes:

[69] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Triplet Arm	Phase 3: Doublet Arm	Phase 3:Control Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	222	216	193	
Units: Subjects				
Heart Rate-Decrease from baseline > 25% & to < 50	1	4	0	
Heart Rate-Increase from baseline > 25% & to > 100	27	24	28	
QT Interval - New > 450 millisecond (msec)	17	30	7	
QT Interval - New > 480 msec	4	7	2	
QT Interval - New > 500 msec	3	5	0	
QT Interval - increase from baseline > 30 msec	97	99	32	
QT Interval - increase from baseline > 60 msec	22	21	10	
QTcF - New > 450 msec	39	51	23	
QTcF - New > 480 msec	9	18	5	
QTcF - New > 500 msec	1	6	2	
QTcF - increase from baseline > 30 msec	59	75	24	
QTcF - increase from baseline > 60 msec	12	20	5	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Number of Subjects With Shift From Baseline to Worst Change from Baseline in Visual Acuity Logarithm of the Minimum Angle of Resolution (LogMAR) Score

End point title	Phase 3: Number of Subjects With Shift From Baseline to Worst Change from Baseline in Visual Acuity Logarithm of the Minimum Angle of Resolution (LogMAR) Score[70]

End point description:

Visual acuity was measured using the Snellen visual acuity conversion chart. This was determined by establishing the smallest optotypes that could be identified correctly by the subject at a given observation distance. Snellen visual acuity was reported as a Snellen fraction (m/M) in which the numerator (m) indicated the test distance and the denominator (M) indicated the distance at which the gap of the equivalent Landolt ring subtends 1 minute of arc. The LogMAR score was calculated as –log(m/M). The maximum increase in score of <= 0, 0 to < 0.1, 0.1 to < 0.2, 0.2 to < 0.3 and >=0.3 relative to baseline in LogMAR were reported in this endpoint. The safety set consisted of all subjects who received at least 1 dose of study drug and had at least 1 post-treatment assessment, which may have included death. Subjects were analysed according to treatment received.Here, "Number of Subjects Analysed" signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From start of study treatment until 30 days post last dose of study treatment (for triplet arm: maximum treatment exposure of 277.4 weeks; for doublet arm: maximum treatment exposure of 268 weeks; for

Control arm: maximum treatment exposure of 108 weeks)

Notes:

[70] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Triplet Arm	Phase 3: Doublet Arm	Phase 3:Control Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	222	216	193	
Units: Subjects				
Baseline <=0 to >0-<0.1 post-baseline	33	8	0	
Baseline <=0 to 0.1-<0.2 post-baseline	15	3	0	
Baseline <=0 to 0.2-<0.3 post-baseline	4	0	0	
Baseline <=0 to >=0.3 post-baseline	6	1	0	
Baseline <=0 to missing score post-baseline	9	86	129	
Baseline >0-<0.1 to <=0 post-baseline	17	6	0	
Baseline >0-<0.1 to 0.1-<0.2 post-baseline	7	2	0	
Baseline >0-<0.1 to 0.2-<0.3 post-baseline	4	1	0	
Baseline >0-<0.1 to >=0.3 post-baseline	3	0	0	
Baseline >0-<0.1 to missing score post-baseline	3	25	30	
Baseline 0.1-<0.2 to <=0 post-baseline	5	1	0	
Baseline 0.1-<0.2 to >0-<0.1 post-baseline	1	0	0	
Baseline 0.2-<0.3 to <=0 post-baseline	1	0	0	
Baseline 0.2-<0.3 to >0-<0.1 post-baseline	3	0	0	
Baseline 0.2-<0.3 to 0.1-<0.2 post-baseline	3	1	0	
Baseline 0.2-<0.3 to missing score post-baseline	1	4	5	
Baseline >=0.3 to <=0 post-baseline	9	2	0	
Baseline >=0.3 to >0-<0.1 post-baseline	4	0	0	
Baseline >=0.3 to 0.1-<0.2 post-baseline	1	1	0	
Baseline >=0.3 to 0.2-<0.3 post-baseline	2	0	0	
Baseline >=0.3 to missing score post-baseline	1	19	13	
Baseline 0.1-<0.2 to 0.2-<0.3 post-baseline	0	3	0	
Baseline 0.1-<0.2 to missing score post-baseline	0	9	7	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Number of Subjects With Shifts in Left Ventricular Ejection Fraction (LVEF) From Baseline to Maximum Grade On-treatment

End point title	Phase 3: Number of Subjects With Shifts in Left Ventricular Ejection Fraction (LVEF) From Baseline to Maximum Grade On-treatment[71]

End point description:

Left ventricular ejection fraction (LVEF) abnormalities were defined according to CTCAE version 4.03 where Grade 0: Non-missing value below Grade 2, Grade 2: LVEF between 40% and 50% or absolute change from baseline between -10% and < -20%, Grade 3: LVEF between 20% and 39% or absolute change from baseline <= -20%, Grade 4: LVEF lower than 20%. Categories with at least 1 non-zero data values showing any shift in Grade from baseline to 1 day after dose 1 (post-baseline) were reported. Subjects whose grade category was unchanged (e.g. Grade 0 to Grade 0) were not reported. The safety set consisted of all subjects who received at least 1 dose of study drug and had at least 1 post-treatment assessment, which may have included death. Subjects were analysed according to treatment received. Here, "Number of Subjects Analysed" signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From start of study treatment until 30 days post last dose of study treatment (maximum treatment exposure of 280 weeks)

Notes:

[71] - 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: Only descriptive data was planned to be analysed.

End point values	Phase 3: Triplet Arm	Phase 3: Doublet Arm	Phase 3:Control Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	222	216	193	
Units: Subjects				
Baseline Grade 0 to Grade 2 post baseline	27	0	0	
Baseline Grade 0 to Grade 3 post baseline	1	1	0	
Baseline Grade 0 to missing grade	17	205	186	
Baseline Grade 2 to missing grade	0	3	2	
Baseline missing grade to Grade 0 post baseline	1	0	0	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Site of Metastases

End point title	Site of Metastases

End point description:

Number of subjects with different sites of metastases were reported in this outcome measure. One subject may have more than one site of metastases. For CSLI: all subjects who received at least 1 dose of study drug and had at least 1 post treatment assessment, which may include death. For the randomised Phase 3 portion of the study: consisted of all randomised subjects.

End point type	Other pre-specified

End point timeframe:

At baseline

End point values	Combined Safety Lead-in	Phase 3: Triplet Arm	Phase 3: Doublet Arm	Phase 3:Control Arm
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	37	224	220	221
Units: Sites				
Liver	24	145	134	128
Lung	10	86	83	86
Lymph Node	17	86	82	88
Peritoneum/Omentum	17	77	97	93

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs = from initiation of study drug through 30 days after last dose of study drug. CSLI: maximum treatment exposure (MTE) of 280 weeks; Phase 3-Triplet: MTE of 277.4 Weeks; Phase 3- Doublet: MTE of 268 Weeks; Phase 3- Control: MTE of 108 Weeks

Adverse event reporting additional description:

An AE is defined as the appearance of (or worsening of any pre-existing) undesirable signs,symptoms, or medical conditions that occur after subject's signed informed consent has been obtained. The safety set consisted of all subjects who received at least 1 dose of study drug & had at least 1 post-treatment assessment,which may have included death.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Combined Safety Lead-in

Reporting group description:

Encorafenib + binimetinib + cetuximab. Encorafenib: Orally, once daily. Binimetinib: Orally, twice daily. Cetuximab: Standard of care.

Reporting group title	Phase 3: Triplet Arm

Reporting group description:

Encorafenib + binimetinib + cetuximab. Encorafenib: Orally, once daily. Binimetinib: Orally, twice daily. Cetuximab: Standard of care.

Reporting group title	Phase 3: Doublet Arm

Reporting group description:

Encorafenib + cetuximab. Encorafenib: Orally, once daily. Cetuximab: Standard of care.

Reporting group title	Phase 3:Control Arm

Reporting group description:

Investigator’s choice of either irinotecan/cetuximab or FOLFIRI/cetuximab. Cetuximab: Standard of care. Irinotecan: Standard of care. Folinic Acid: Standard of care. 5-Fluorouracil: Standard of care. Following protocol amendment, eligible participants could crossover to receive either triplet or doublet regimen.

Serious adverse events	Combined Safety Lead-in	Phase 3: Triplet Arm	Phase 3: Doublet Arm
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 37 (59.46%)	118 / 222 (53.15%)	91 / 216 (42.13%)
number of deaths (all causes)	5	31	38
number of deaths resulting from adverse events	0	11	8
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	5 / 216 (2.31%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			

subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	3 / 216 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Transitional cell carcinoma			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Tumour associated fever			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumor haemorrhage			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	1 / 37 (2.70%)	0 / 222 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Peripheral artery stenosis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jugular vein thrombosis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	0 / 216 (0.00%)
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 / 37 (0.00%)	0 / 222 (0.00%)	0 / 216 (0.00%)
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 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
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			
Analgesic therapy			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	0 / 216 (0.00%)
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 / 37 (0.00%)	1 / 222 (0.45%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Catheter site thrombosis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	0 / 216 (0.00%)
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 / 37 (2.70%)	0 / 222 (0.00%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pyrexia			
subjects affected / exposed	2 / 37 (5.41%)	5 / 222 (2.25%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	0 / 3	3 / 7	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Non-cardiac chest pain			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
General physical health deterioration			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perforation			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	0 / 216 (0.00%)
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 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug hypersensitivity			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast			

disorders			
Female genital tract fistula			
subjects affected / exposed	0 / 37 (0.00%)	2 / 222 (0.90%)	0 / 216 (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
Pelvic pain			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
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, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspiration			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Interstitial lung disease			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Dyspnoea			
subjects affected / exposed	0 / 37 (0.00%)	2 / 222 (0.90%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pleural effusion			
subjects affected / exposed	2 / 37 (5.41%)	0 / 222 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 37 (2.70%)	8 / 222 (3.60%)	3 / 216 (1.39%)
occurrences causally related to treatment / all	1 / 1	2 / 8	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumomediastinum			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic pain			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 37 (0.00%)	2 / 222 (0.90%)	0 / 216 (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
Confusional state			
subjects affected / exposed	1 / 37 (2.70%)	0 / 222 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device occlusion			
subjects affected / exposed	1 / 37 (2.70%)	1 / 222 (0.45%)	0 / 216 (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

Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Alanine aminotransferase increased			
subjects affected / exposed	1 / 37 (2.70%)	0 / 222 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 37 (5.41%)	0 / 222 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
International normalised ratio increased			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Body temperature increased			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Rib fracture			

subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiation inflammation			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	0 / 216 (0.00%)
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 related reaction			
subjects affected / exposed	3 / 37 (8.11%)	1 / 222 (0.45%)	3 / 216 (1.39%)
occurrences causally related to treatment / all	4 / 4	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anastomotic ulcer			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anastomotic haemorrhage			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Toxicity to various agents			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Cardiac disorders			
Cardio-respiratory arrest			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac arrest			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Atrial fibrillation			

subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	3 / 216 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Cardiac failure			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
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 myocardial infarction			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus tachycardia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Pericarditis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	0 / 216 (0.00%)
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 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			

subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Ischaemic stroke			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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 encephalopathy			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Cognitive disorder			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haematoma			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Lethargy			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Spinal cord compression			

subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 37 (2.70%)	1 / 222 (0.45%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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 / 37 (2.70%)	6 / 222 (2.70%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 1	5 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	0 / 216 (0.00%)
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 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 37 (2.70%)	10 / 222 (4.50%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	1 / 1	9 / 10	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vomiting			
subjects affected / exposed	2 / 37 (5.41%)	6 / 222 (2.70%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	0 / 2	3 / 6	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal perforation			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Ileus			
subjects affected / exposed	0 / 37 (0.00%)	5 / 222 (2.25%)	4 / 216 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 8	2 / 6
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Subileus			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 37 (0.00%)	2 / 222 (0.90%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Large intestine perforation			
subjects affected / exposed	1 / 37 (2.70%)	3 / 222 (1.35%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	0 / 1	1 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 1
Intestinal obstruction			
subjects affected / exposed	0 / 37 (0.00%)	11 / 222 (4.95%)	12 / 216 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 12	0 / 13
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 2
Abdominal pain			
subjects affected / exposed	0 / 37 (0.00%)	7 / 222 (3.15%)	5 / 216 (2.31%)
occurrences causally related to treatment / all	0 / 0	0 / 8	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			

subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal obstruction			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Gastritis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Haematemesis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 37 (0.00%)	6 / 222 (2.70%)	4 / 216 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 6	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 37 (2.70%)	2 / 222 (0.90%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	4 / 216 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			

subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
intestinal perforation			
subjects affected / exposed	0 / 37 (0.00%)	2 / 222 (0.90%)	0 / 216 (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
Ascites			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal haemorrhage			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal hernia			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Pancreatitis relapsing			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Rectal stenosis			

subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Melaena			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proctalgia			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	0 / 216 (0.00%)
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 ulcer			
subjects affected / exposed	1 / 37 (2.70%)	2 / 222 (0.90%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired gastric emptying			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal distension			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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 intestinal ulcer hemorrhage			
subjects affected / exposed	1 / 37 (2.70%)	0 / 222 (0.00%)	0 / 216 (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
Haemorrhoids			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Anal fistula			

subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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 pain upper			
subjects affected / exposed	1 / 37 (2.70%)	1 / 222 (0.45%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal hemorrhage			
subjects affected / exposed	0 / 37 (0.00%)	2 / 222 (0.90%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Esophageal ulcer hemorrhage			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	0 / 216 (0.00%)
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	1 / 37 (2.70%)	7 / 222 (3.15%)	3 / 216 (1.39%)
occurrences causally related to treatment / all	0 / 1	7 / 8	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mallory-Weiss syndrome			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Malabsorption			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proctitis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal hemorrhage			

subjects affected / exposed	1 / 37 (2.70%)	4 / 222 (1.80%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal perforation			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Upper gastrointestinal hemorrhage			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Large intestinal haemorrhage			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Gastrointestinal ulcer haemorrhage			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Gastrointestinal obstruction			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal perforation			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Oesophageal ulcer haemorrhage			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	0 / 216 (0.00%)
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			
Hepatic failure			

subjects affected / exposed	0 / 37 (0.00%)	3 / 222 (1.35%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0
Jaundice			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 37 (0.00%)	2 / 222 (0.90%)	0 / 216 (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
Hepatic function abnormal			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct obstruction			
subjects affected / exposed	0 / 37 (0.00%)	2 / 222 (0.90%)	3 / 216 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct stenosis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Biliary dilatation			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis acute			

subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 37 (0.00%)	2 / 222 (0.90%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Pruritus generalised			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 37 (2.70%)	8 / 222 (3.60%)	4 / 216 (1.85%)
occurrences causally related to treatment / all	0 / 1	5 / 8	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephritis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Hydronephrosis			
subjects affected / exposed	1 / 37 (2.70%)	2 / 222 (0.90%)	0 / 216 (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
Haematuria			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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 failure			
subjects affected / exposed	2 / 37 (5.41%)	2 / 222 (0.90%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			

subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prerenal failure			
subjects affected / exposed	0 / 37 (0.00%)	2 / 222 (0.90%)	0 / 216 (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
Renal colic			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	1 / 37 (2.70%)	4 / 222 (1.80%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Chondrocalcinosis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
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	1 / 37 (2.70%)	1 / 222 (0.45%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fistula			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			

subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Muscle tightness			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periostitis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 222 (0.00%)	0 / 216 (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
Infections and infestations			
Peritonitis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	0 / 216 (0.00%)
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	1 / 37 (2.70%)	5 / 222 (2.25%)	3 / 216 (1.39%)
occurrences causally related to treatment / all	0 / 1	0 / 7	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Bacteraemia			
subjects affected / exposed	0 / 37 (0.00%)	4 / 222 (1.80%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			

subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrintestinal infection			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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 / 37 (0.00%)	1 / 222 (0.45%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Cholangitis infective			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Biliary tract infection			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal wall abscess			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Urosepsis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound abscess			

subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Campylobacter gastroenteritis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial sepsis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 222 (0.00%)	0 / 216 (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
Anal abscess			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess limb			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	0 / 216 (0.00%)
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 abscess			
subjects affected / exposed	1 / 37 (2.70%)	1 / 222 (0.45%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related sepsis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 37 (0.00%)	4 / 222 (1.80%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			

subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Clostridial infection			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis infectious			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	0 / 216 (0.00%)
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 / 37 (0.00%)	2 / 222 (0.90%)	0 / 216 (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
Ophthalmic herpes zoster			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Lung infection			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Kidney infection			
subjects affected / exposed	1 / 37 (2.70%)	0 / 222 (0.00%)	0 / 216 (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
Infectious colitis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			

subjects affected / exposed	2 / 37 (5.41%)	0 / 222 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes simplex			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile infection			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia bacteraemia			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	0 / 216 (0.00%)
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 / 37 (0.00%)	3 / 222 (1.35%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Pyelonephritis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	0 / 216 (0.00%)
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 / 37 (0.00%)	1 / 222 (0.45%)	3 / 216 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection bacterial			
subjects affected / exposed	1 / 37 (2.70%)	0 / 222 (0.00%)	0 / 216 (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
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 37 (0.00%)	2 / 222 (0.90%)	0 / 216 (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
Streptococcal bacteraemia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Streptococcal infection			
subjects affected / exposed	1 / 37 (2.70%)	0 / 222 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	4 / 37 (10.81%)	5 / 222 (2.25%)	6 / 216 (2.78%)
occurrences causally related to treatment / all	0 / 5	0 / 7	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
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			
Decreased appetite			
subjects affected / exposed	1 / 37 (2.70%)	0 / 222 (0.00%)	0 / 216 (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
Dehydration			

subjects affected / exposed	1 / 37 (2.70%)	2 / 222 (0.90%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 1	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoalbuminaemia			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cachexia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Electrolyte imbalance			
subjects affected / exposed	0 / 37 (0.00%)	1 / 222 (0.45%)	0 / 216 (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
Hypercalcaemia			
subjects affected / exposed	0 / 37 (0.00%)	0 / 222 (0.00%)	0 / 216 (0.00%)
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 / 37 (0.00%)	0 / 222 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase 3:Control Arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	78 / 193 (40.41%)		
number of deaths (all causes)	29		
number of deaths resulting from adverse events	8		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant melanoma			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metastases to central nervous system			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transitional cell carcinoma			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tumour associated fever			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumor haemorrhage			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Tumour pain			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Peripheral artery stenosis			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Jugular vein thrombosis			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Analgesic therapy			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pain			

subjects affected / exposed	3 / 193 (1.55%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Catheter site thrombosis				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Non-cardiac chest pain				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Malaise				
subjects affected / exposed	0 / 193 (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	2 / 193 (1.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Perforation			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Drug hypersensitivity			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Female genital tract fistula			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pelvic pain			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	3 / 193 (1.55%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	1 / 1		
Aspiration			

subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Interstitial lung disease			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	5 / 193 (2.59%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumomediastinum			

subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pleuritic pain				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Anxiety				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Confusional state				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Product issues				
Device occlusion				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Blood creatine phosphokinase increased				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Alanine aminotransferase increased				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				

subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood bilirubin increased				
subjects affected / exposed	0 / 193 (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 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
International normalised ratio increased				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Body temperature increased				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Rib fracture				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Radiation inflammation				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infusion related reaction				
subjects affected / exposed	2 / 193 (1.04%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Anastomotic ulcer				

subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anastomotic haemorrhage				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Toxicity to various agents				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Cardio-respiratory arrest				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiac arrest				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				

subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sinus tachycardia				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pericarditis				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pericardial effusion				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebral ischaemia				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Epilepsy				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ischaemic stroke				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic encephalopathy				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hemiparesis				

subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cognitive disorder			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebral haematoma			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lethargy			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal cord compression			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	0 / 193 (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 / 193 (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	1 / 193 (0.52%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	5 / 193 (2.59%)			
occurrences causally related to treatment / all	5 / 5			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
Vertigo				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Diarrhoea				
subjects affected / exposed	10 / 193 (5.18%)			
occurrences causally related to treatment / all	9 / 11			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	4 / 193 (2.07%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal perforation				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	4 / 193 (2.07%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Subileus				

subjects affected / exposed	4 / 193 (2.07%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 1			
Gastrointestinal haemorrhage				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large intestine perforation				
subjects affected / exposed	2 / 193 (1.04%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	7 / 193 (3.63%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	4 / 193 (2.07%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Duodenal obstruction				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspepsia				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastritis				

subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haematemesis			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	4 / 193 (2.07%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	0 / 193 (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 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Enterocolitis			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
intestinal perforation			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anal haemorrhage			

subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal hernia			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatitis relapsing			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rectal stenosis			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Melaena			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Proctalgia			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Large intestine ulcer			

subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Impaired gastric emptying				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal distension				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large intestinal ulcer hemorrhage				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhoids				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anal fistula				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower gastrointestinal hemorrhage				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Esophageal ulcer hemorrhage				

subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Mallory-Weiss syndrome				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Malabsorption				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Proctitis				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rectal hemorrhage				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Small intestinal perforation				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal hemorrhage				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large intestinal haemorrhage				

subjects affected / exposed	37 / 193 (19.17%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal ulcer haemorrhage				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal obstruction				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Duodenal perforation				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophageal ulcer haemorrhage				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hepatic failure				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Jaundice				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperbilirubinaemia				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic function abnormal				

subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Bile duct obstruction				
subjects affected / exposed	2 / 193 (1.04%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bile duct stenosis				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Biliary dilatation				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholangitis				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholangitis acute				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Pruritus generalised				
subjects affected / exposed	0 / 193 (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	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nephritis				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hydronephrosis				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haematuria				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary retention				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Prerenal failure				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal colic				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract obstruction				

subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Chondrocalcinosis			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bone pain			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fistula			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal chest pain			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Muscle tightness			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Periostitis			

subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rhabdomyolysis				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Peritonitis				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Sepsis				
subjects affected / exposed	3 / 193 (1.55%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Bacteraemia				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrintestinal infection				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Erysipelas				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Endocarditis				

subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholangitis infective			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Biliary tract infection			
subjects affected / exposed	0 / 193 (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 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wound abscess			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Campylobacter gastroenteritis			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bacterial sepsis			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anal abscess			

subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abscess limb				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal abscess				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device related sepsis				
subjects affected / exposed	0 / 193 (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 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cystitis				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Clostridial infection				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Enteritis infectious				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal infection				

subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ophthalmic herpes zoster				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Kidney infection				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infectious colitis				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Herpes simplex				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Febrile infection				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Escherichia bacteraemia				

subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumocystis jirovecii pneumonia				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Septic shock				
subjects affected / exposed	2 / 193 (1.04%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis acute				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection bacterial				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Staphylococcal bacteraemia				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Streptococcal bacteraemia				

subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Streptococcal infection				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin infection				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Decreased appetite				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoalbuminaemia				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypokalaemia				
subjects affected / exposed	2 / 193 (1.04%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				

subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Malnutrition				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cachexia				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Electrolyte imbalance				
subjects affected / exposed	0 / 193 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypercalcaemia				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperglycaemia				
subjects affected / exposed	0 / 193 (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	Combined Safety Lead-in	Phase 3: Triplet Arm	Phase 3: Doublet Arm
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 37 (97.30%)	218 / 222 (98.20%)	212 / 216 (98.15%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	1 / 37 (2.70%)	1 / 222 (0.45%)	34 / 216 (15.74%)
occurrences (all)	1	2	39
Tumour Pain			

subjects affected / exposed	4 / 37 (10.81%)	3 / 222 (1.35%)	1 / 216 (0.46%)
occurrences (all)	4	3	2
Skin papilloma			
subjects affected / exposed	1 / 37 (2.70%)	0 / 222 (0.00%)	15 / 216 (6.94%)
occurrences (all)	11	0	17
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 37 (10.81%)	8 / 222 (3.60%)	8 / 216 (3.70%)
occurrences (all)	7	11	12
Hypotension			
subjects affected / exposed	3 / 37 (8.11%)	9 / 222 (4.05%)	9 / 216 (4.17%)
occurrences (all)	3	11	9
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 37 (16.22%)	63 / 222 (28.38%)	51 / 216 (23.61%)
occurrences (all)	16	163	92
Fatigue			
subjects affected / exposed	20 / 37 (54.05%)	74 / 222 (33.33%)	74 / 216 (34.26%)
occurrences (all)	57	142	152
Pyrexia			
subjects affected / exposed	16 / 37 (43.24%)	53 / 222 (23.87%)	43 / 216 (19.91%)
occurrences (all)	30	103	52
Malaise			
subjects affected / exposed	7 / 37 (18.92%)	5 / 222 (2.25%)	6 / 216 (2.78%)
occurrences (all)	18	8	7
Chills			
subjects affected / exposed	6 / 37 (16.22%)	15 / 222 (6.76%)	6 / 216 (2.78%)
occurrences (all)	12	19	8
Oedema peripheral			
subjects affected / exposed	6 / 37 (16.22%)	30 / 222 (13.51%)	24 / 216 (11.11%)
occurrences (all)	8	36	30
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	13 / 37 (35.14%)	22 / 222 (9.91%)	30 / 216 (13.89%)
occurrences (all)	17	26	44
Cough			

subjects affected / exposed	5 / 37 (13.51%)	26 / 222 (11.71%)	22 / 216 (10.19%)
occurrences (all)	8	31	29
Pulmonary embolism			
subjects affected / exposed	2 / 37 (5.41%)	4 / 222 (1.80%)	1 / 216 (0.46%)
occurrences (all)	2	4	1
Epistaxis			
subjects affected / exposed	1 / 37 (2.70%)	8 / 222 (3.60%)	16 / 216 (7.41%)
occurrences (all)	1	9	19
Dysphonia			
subjects affected / exposed	2 / 37 (5.41%)	5 / 222 (2.25%)	12 / 216 (5.56%)
occurrences (all)	2	5	12
Rhinnorrhoea			
subjects affected / exposed	3 / 37 (8.11%)	5 / 222 (2.25%)	6 / 216 (2.78%)
occurrences (all)	3	5	9
Rhinitis allergic			
subjects affected / exposed	3 / 37 (8.11%)	1 / 222 (0.45%)	3 / 216 (1.39%)
occurrences (all)	3	1	3
Pleural effusion			
subjects affected / exposed	2 / 37 (5.41%)	1 / 222 (0.45%)	3 / 216 (1.39%)
occurrences (all)	2	1	3
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 37 (5.41%)	15 / 222 (6.76%)	25 / 216 (11.57%)
occurrences (all)	2	16	29
Depression			
subjects affected / exposed	2 / 37 (5.41%)	5 / 222 (2.25%)	5 / 216 (2.31%)
occurrences (all)	2	5	5
Investigations			
Weight decreased			
subjects affected / exposed	3 / 37 (8.11%)	25 / 222 (11.26%)	26 / 216 (12.04%)
occurrences (all)	4	29	26
Neutrophil count decreased			
subjects affected / exposed	0 / 37 (0.00%)	2 / 222 (0.90%)	1 / 216 (0.46%)
occurrences (all)	0	2	3
Blood creatine phosphokinase increased			

subjects affected / exposed	13 / 37 (35.14%)	26 / 222 (11.71%)	3 / 216 (1.39%)
occurrences (all)	56	81	4
Blood creatine increased			
subjects affected / exposed	11 / 37 (29.73%)	25 / 222 (11.26%)	6 / 216 (2.78%)
occurrences (all)	57	52	15
Alanine aminotransferase increased			
subjects affected / exposed	6 / 37 (16.22%)	16 / 222 (7.21%)	15 / 216 (6.94%)
occurrences (all)	9	22	21
Aspartate aminotransferase increased			
subjects affected / exposed	7 / 37 (18.92%)	14 / 222 (6.31%)	7 / 216 (3.24%)
occurrences (all)	9	22	11
Ejection fraction decreased			
subjects affected / exposed	5 / 37 (13.51%)	8 / 222 (3.60%)	0 / 216 (0.00%)
occurrences (all)	5	11	0
Blood bilirubin increased			
subjects affected / exposed	3 / 37 (8.11%)	5 / 222 (2.25%)	9 / 216 (4.17%)
occurrences (all)	3	10	12
White blood cell count decrease			
subjects affected / exposed	0 / 37 (0.00%)	2 / 222 (0.90%)	2 / 216 (0.93%)
occurrences (all)	0	3	3
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 37 (0.00%)	6 / 222 (2.70%)	7 / 216 (3.24%)
occurrences (all)	0	11	10
Injury, poisoning and procedural complications			
Wound			
subjects affected / exposed	2 / 37 (5.41%)	1 / 222 (0.45%)	1 / 216 (0.46%)
occurrences (all)	2	1	1
Infusion related reaction			
subjects affected / exposed	1 / 37 (2.70%)	5 / 222 (2.25%)	18 / 216 (8.33%)
occurrences (all)	1	5	21
Cardiac disorders			
Palpitations			
subjects affected / exposed	2 / 37 (5.41%)	3 / 222 (1.35%)	4 / 216 (1.85%)
occurrences (all)	3	3	4
Nervous system disorders			

Headache			
subjects affected / exposed	7 / 37 (18.92%)	21 / 222 (9.46%)	43 / 216 (19.91%)
occurrences (all)	12	45	51
Dizziness			
subjects affected / exposed	8 / 37 (21.62%)	16 / 222 (7.21%)	16 / 216 (7.41%)
occurrences (all)	8	21	17
Neuropathy peripheral			
subjects affected / exposed	1 / 37 (2.70%)	13 / 222 (5.86%)	11 / 216 (5.09%)
occurrences (all)	1	15	22
Dysgeusia			
subjects affected / exposed	6 / 37 (16.22%)	11 / 222 (4.95%)	10 / 216 (4.63%)
occurrences (all)	7	12	12
Peripheral sensory neuropathy			
subjects affected / exposed	6 / 37 (16.22%)	7 / 222 (3.15%)	5 / 216 (2.31%)
occurrences (all)	11	10	8
Nervous system disorder			
subjects affected / exposed	2 / 37 (5.41%)	0 / 222 (0.00%)	0 / 216 (0.00%)
occurrences (all)	2	0	0
Restless legs syndrome			
subjects affected / exposed	2 / 37 (5.41%)	1 / 222 (0.45%)	10 / 216 (4.63%)
occurrences (all)	3	1	11
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	16 / 37 (43.24%)	105 / 222 (47.30%)	44 / 216 (20.37%)
occurrences (all)	49	376	126
Neutropenia			
subjects affected / exposed	1 / 37 (2.70%)	3 / 222 (1.35%)	4 / 216 (1.85%)
occurrences (all)	1	5	8
Eye disorders			
Vision blurred			
subjects affected / exposed	12 / 37 (32.43%)	27 / 222 (12.16%)	10 / 216 (4.63%)
occurrences (all)	16	33	14
Dry eye			
subjects affected / exposed	5 / 37 (13.51%)	9 / 222 (4.05%)	11 / 216 (5.09%)
occurrences (all)	6	11	13
Retinal detachment			

subjects affected / exposed	2 / 37 (5.41%)	6 / 222 (2.70%)	1 / 216 (0.46%)
occurrences (all)	5	7	1
Vitreous floaters			
subjects affected / exposed	4 / 37 (10.81%)	3 / 222 (1.35%)	4 / 216 (1.85%)
occurrences (all)	4	3	4
Visual impairment			
subjects affected / exposed	3 / 37 (8.11%)	4 / 222 (1.80%)	5 / 216 (2.31%)
occurrences (all)	3	7	5
Trichomegaly			
subjects affected / exposed	2 / 37 (5.41%)	6 / 222 (2.70%)	1 / 216 (0.46%)
occurrences (all)	2	6	1
Trichiasis			
subjects affected / exposed	4 / 37 (10.81%)	1 / 222 (0.45%)	0 / 216 (0.00%)
occurrences (all)	4	1	0
Chorioretinopathy			
subjects affected / exposed	2 / 37 (5.41%)	3 / 222 (1.35%)	0 / 216 (0.00%)
occurrences (all)	3	4	0
Macular oedema			
subjects affected / exposed	3 / 37 (8.11%)	1 / 222 (0.45%)	1 / 216 (0.46%)
occurrences (all)	4	1	1
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	22 / 37 (59.46%)	107 / 222 (48.20%)	80 / 216 (37.04%)
occurrences (all)	57	227	113
Constipation			
subjects affected / exposed	14 / 37 (37.84%)	64 / 222 (28.83%)	39 / 216 (18.06%)
occurrences (all)	22	99	52
Diarrhoea			
subjects affected / exposed	29 / 37 (78.38%)	150 / 222 (67.57%)	85 / 216 (39.35%)
occurrences (all)	91	399	158
Abdominal pain			
subjects affected / exposed	14 / 37 (37.84%)	74 / 222 (33.33%)	60 / 216 (27.78%)
occurrences (all)	27	130	111
Vomiting			
subjects affected / exposed	19 / 37 (51.35%)	99 / 222 (44.59%)	58 / 216 (26.85%)
occurrences (all)	33	198	100

Flatulence			
subjects affected / exposed	0 / 37 (0.00%)	15 / 222 (6.76%)	6 / 216 (2.78%)
occurrences (all)	0	17	7
Dyspepsia			
subjects affected / exposed	4 / 37 (10.81%)	18 / 222 (8.11%)	9 / 216 (4.17%)
occurrences (all)	6	24	9
Abdominal pain upper			
subjects affected / exposed	5 / 37 (13.51%)	24 / 222 (10.81%)	22 / 216 (10.19%)
occurrences (all)	6	26	27
Rectal haemorrhage			
subjects affected / exposed	2 / 37 (5.41%)	21 / 222 (9.46%)	6 / 216 (2.78%)
occurrences (all)	3	25	7
Gastroesophageal reflux disease			
subjects affected / exposed	2 / 37 (5.41%)	10 / 222 (4.50%)	6 / 216 (2.78%)
occurrences (all)	2	10	8
Abdominal distension			
subjects affected / exposed	2 / 37 (5.41%)	10 / 222 (4.50%)	16 / 216 (7.41%)
occurrences (all)	3	11	17
Dry Mouth			
subjects affected / exposed	2 / 37 (5.41%)	11 / 222 (4.95%)	10 / 216 (4.63%)
occurrences (all)	2	13	12
Anal haemorrhage			
subjects affected / exposed	2 / 37 (5.41%)	6 / 222 (2.70%)	1 / 216 (0.46%)
occurrences (all)	2	6	2
Ascites			
subjects affected / exposed	2 / 37 (5.41%)	5 / 222 (2.25%)	2 / 216 (0.93%)
occurrences (all)	4	6	3
Colitis			
subjects affected / exposed	2 / 37 (5.41%)	1 / 222 (0.45%)	0 / 216 (0.00%)
occurrences (all)	3	3	0
Stomatitis			
subjects affected / exposed	6 / 37 (16.22%)	32 / 222 (14.41%)	13 / 216 (6.02%)
occurrences (all)	7	40	15
Abdominal pain lower			
subjects affected / exposed	2 / 37 (5.41%)	5 / 222 (2.25%)	4 / 216 (1.85%)
occurrences (all)	2	7	5

Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	25 / 37 (67.57%)	113 / 222 (50.90%)	65 / 216 (30.09%)
occurrences (all)	44	255	116
Rash			
subjects affected / exposed	3 / 37 (8.11%)	49 / 222 (22.07%)	35 / 216 (16.20%)
occurrences (all)	10	97	54
Dry Skin			
subjects affected / exposed	19 / 37 (51.35%)	49 / 222 (22.07%)	28 / 216 (12.96%)
occurrences (all)	23	65	36
Pruritus			
subjects affected / exposed	3 / 37 (8.11%)	35 / 222 (15.77%)	24 / 216 (11.11%)
occurrences (all)	5	47	37
Palmar-planar erythrodysaesthesia			
subjects affected / exposed	6 / 37 (16.22%)	31 / 222 (13.96%)	11 / 216 (5.09%)
occurrences (all)	7	54	18
Rash maculo-papular			
subjects affected / exposed	6 / 37 (16.22%)	19 / 222 (8.56%)	19 / 216 (8.80%)
occurrences (all)	8	33	23
Skin fissures			
subjects affected / exposed	9 / 37 (24.32%)	21 / 222 (9.46%)	9 / 216 (4.17%)
occurrences (all)	12	35	9
Erythema			
subjects affected / exposed	2 / 37 (5.41%)	9 / 222 (4.05%)	13 / 216 (6.02%)
occurrences (all)	2	13	14
Eczema			
subjects affected / exposed	2 / 37 (5.41%)	5 / 222 (2.25%)	2 / 216 (0.93%)
occurrences (all)	2	5	2
Skin hyperpigmentation			
subjects affected / exposed	2 / 37 (5.41%)	1 / 222 (0.45%)	16 / 216 (7.41%)
occurrences (all)	2	1	16
Skin lesion			
subjects affected / exposed	0 / 37 (0.00%)	2 / 222 (0.90%)	17 / 216 (7.87%)
occurrences (all)	0	2	24
Pruritus generalised			

subjects affected / exposed	2 / 37 (5.41%)	6 / 222 (2.70%)	12 / 216 (5.56%)
occurrences (all)	2	7	16
Alopecia			
subjects affected / exposed	1 / 37 (2.70%)	6 / 222 (2.70%)	10 / 216 (4.63%)
occurrences (all)	1	7	11
Hyperkeratosis			
subjects affected / exposed	1 / 37 (2.70%)	1 / 222 (0.45%)	12 / 216 (5.56%)
occurrences (all)	1	1	17
Hypertrichosis			
subjects affected / exposed	3 / 37 (8.11%)	4 / 222 (1.80%)	5 / 216 (2.31%)
occurrences (all)	3	5	5
Nail disorder			
subjects affected / exposed	2 / 37 (5.41%)	4 / 222 (1.80%)	3 / 216 (1.39%)
occurrences (all)	2	4	3
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	2 / 37 (5.41%)	16 / 222 (7.21%)	6 / 216 (2.78%)
occurrences (all)	3	16	8
Urinary incontinence			
subjects affected / exposed	2 / 37 (5.41%)	1 / 222 (0.45%)	5 / 216 (2.31%)
occurrences (all)	2	1	6
Proteinuria			
subjects affected / exposed	3 / 37 (8.11%)	5 / 222 (2.25%)	6 / 216 (2.78%)
occurrences (all)	5	5	10
Pollakiuria			
subjects affected / exposed	4 / 37 (10.81%)	4 / 222 (1.80%)	8 / 216 (3.70%)
occurrences (all)	4	4	8
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	8 / 37 (21.62%)	36 / 222 (16.22%)	32 / 216 (14.81%)
occurrences (all)	14	48	46
Pain in extremity			
subjects affected / exposed	3 / 37 (8.11%)	19 / 222 (8.56%)	26 / 216 (12.04%)
occurrences (all)	4	28	37
Myalgia			

subjects affected / exposed	9 / 37 (24.32%)	23 / 222 (10.36%)	35 / 216 (16.20%)
occurrences (all)	19	33	45
Arthralgia			
subjects affected / exposed	9 / 37 (24.32%)	26 / 222 (11.71%)	52 / 216 (24.07%)
occurrences (all)	22	42	84
Musculoskeletal pain			
subjects affected / exposed	2 / 37 (5.41%)	12 / 222 (5.41%)	32 / 216 (14.81%)
occurrences (all)	2	15	43
Muscle spasms			
subjects affected / exposed	2 / 37 (5.41%)	22 / 222 (9.91%)	5 / 216 (2.31%)
occurrences (all)	4	40	6
Bone pain			
subjects affected / exposed	2 / 37 (5.41%)	2 / 222 (0.90%)	3 / 216 (1.39%)
occurrences (all)	3	2	3
Flank pain			
subjects affected / exposed	3 / 37 (8.11%)	2 / 222 (0.90%)	1 / 216 (0.46%)
occurrences (all)	4	2	1
Musculoskeletal chest pain			
subjects affected / exposed	2 / 37 (5.41%)	7 / 222 (3.15%)	5 / 216 (2.31%)
occurrences (all)	2	10	16
Infections and infestations			
Cystitis			
subjects affected / exposed	2 / 37 (5.41%)	6 / 222 (2.70%)	2 / 216 (0.93%)
occurrences (all)	2	7	5
Conjunctivitis			
subjects affected / exposed	2 / 37 (5.41%)	16 / 222 (7.21%)	12 / 216 (5.56%)
occurrences (all)	2	21	18
Rash pustular			
subjects affected / exposed	6 / 37 (16.22%)	13 / 222 (5.86%)	4 / 216 (1.85%)
occurrences (all)	9	25	5
Paronychia			
subjects affected / exposed	6 / 37 (16.22%)	21 / 222 (9.46%)	13 / 216 (6.02%)
occurrences (all)	13	39	22
Urinary tract infection			
subjects affected / exposed	7 / 37 (18.92%)	26 / 222 (11.71%)	16 / 216 (7.41%)
occurrences (all)	11	43	20

Nasopharyngitis			
subjects affected / exposed	3 / 37 (8.11%)	12 / 222 (5.41%)	15 / 216 (6.94%)
occurrences (all)	3	15	19
Upper respiratory tract infection			
subjects affected / exposed	1 / 37 (2.70%)	4 / 222 (1.80%)	9 / 216 (4.17%)
occurrences (all)	1	6	12
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	15 / 37 (40.54%)	67 / 222 (30.18%)	68 / 216 (31.48%)
occurrences (all)	35	106	96
Hypokalaemia			
subjects affected / exposed	3 / 37 (8.11%)	16 / 222 (7.21%)	14 / 216 (6.48%)
occurrences (all)	5	21	17
Hypomagnesaemia			
subjects affected / exposed	6 / 37 (16.22%)	29 / 222 (13.06%)	28 / 216 (12.96%)
occurrences (all)	12	56	34
Hypoalbuminaemia			
subjects affected / exposed	4 / 37 (10.81%)	20 / 222 (9.01%)	6 / 216 (2.78%)
occurrences (all)	7	29	9
Iron deficiency			
subjects affected / exposed	3 / 37 (8.11%)	2 / 222 (0.90%)	3 / 216 (1.39%)
occurrences (all)	10	3	4
Hypophosphataemia			
subjects affected / exposed	2 / 37 (5.41%)	7 / 222 (3.15%)	3 / 216 (1.39%)
occurrences (all)	2	17	5
Hypocalcaemia			
subjects affected / exposed	2 / 37 (5.41%)	10 / 222 (4.50%)	5 / 216 (2.31%)
occurrences (all)	3	13	5

Non-serious adverse events	Phase 3:Control Arm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	187 / 193 (96.89%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences (all)	0		
Tumour Pain			

subjects affected / exposed	1 / 193 (0.52%)		
occurrences (all)	1		
Skin papilloma			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 193 (3.11%)		
occurrences (all)	10		
Hypotension			
subjects affected / exposed	3 / 193 (1.55%)		
occurrences (all)	3		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	52 / 193 (26.94%)		
occurrences (all)	128		
Fatigue			
subjects affected / exposed	54 / 193 (27.98%)		
occurrences (all)	85		
Pyrexia			
subjects affected / exposed	30 / 193 (15.54%)		
occurrences (all)	42		
Malaise			
subjects affected / exposed	11 / 193 (5.70%)		
occurrences (all)	16		
Chills			
subjects affected / exposed	3 / 193 (1.55%)		
occurrences (all)	3		
Oedema peripheral			
subjects affected / exposed	14 / 193 (7.25%)		
occurrences (all)	16		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	20 / 193 (10.36%)		
occurrences (all)	30		
Cough			

subjects affected / exposed	12 / 193 (6.22%)		
occurrences (all)	16		
Pulmonary embolism			
subjects affected / exposed	5 / 193 (2.59%)		
occurrences (all)	5		
Epistaxis			
subjects affected / exposed	8 / 193 (4.15%)		
occurrences (all)	10		
Dysphonia			
subjects affected / exposed	3 / 193 (1.55%)		
occurrences (all)	3		
Rhinnorrhoea			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences (all)	1		
Rhinitis allergic			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences (all)	1		
Pleural effusion			
subjects affected / exposed	2 / 193 (1.04%)		
occurrences (all)	3		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	13 / 193 (6.74%)		
occurrences (all)	13		
Depression			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences (all)	1		
Investigations			
Weight decreased			
subjects affected / exposed	12 / 193 (6.22%)		
occurrences (all)	14		
Neutrophil count decreased			
subjects affected / exposed	21 / 193 (10.88%)		
occurrences (all)	36		
Blood creatine phosphokinase increased			

subjects affected / exposed	4 / 193 (2.07%)		
occurrences (all)	6		
Blood creatine increased			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences (all)	3		
Alanine aminotransferase increased			
subjects affected / exposed	14 / 193 (7.25%)		
occurrences (all)	18		
Aspartate aminotransferase increased			
subjects affected / exposed	14 / 193 (7.25%)		
occurrences (all)	20		
Ejection fraction decreased			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences (all)	0		
Blood bilirubin increased			
subjects affected / exposed	8 / 193 (4.15%)		
occurrences (all)	10		
White blood cell count decrease			
subjects affected / exposed	14 / 193 (7.25%)		
occurrences (all)	22		
Blood alkaline phosphatase increased			
subjects affected / exposed	10 / 193 (5.18%)		
occurrences (all)	14		
Injury, poisoning and procedural complications			
Wound			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences (all)	1		
Infusion related reaction			
subjects affected / exposed	13 / 193 (6.74%)		
occurrences (all)	13		
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences (all)	1		
Nervous system disorders			

Headache			
subjects affected / exposed	5 / 193 (2.59%)		
occurrences (all)	6		
Dizziness			
subjects affected / exposed	16 / 193 (8.29%)		
occurrences (all)	19		
Neuropathy peripheral			
subjects affected / exposed	5 / 193 (2.59%)		
occurrences (all)	5		
Dysgeusia			
subjects affected / exposed	8 / 193 (4.15%)		
occurrences (all)	8		
Peripheral sensory neuropathy			
subjects affected / exposed	4 / 193 (2.07%)		
occurrences (all)	4		
Nervous system disorder			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences (all)	0		
Restless legs syndrome			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	37 / 193 (19.17%)		
occurrences (all)	109		
Neutropenia			
subjects affected / exposed	36 / 193 (18.65%)		
occurrences (all)	87		
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences (all)	1		
Dry eye			
subjects affected / exposed	3 / 193 (1.55%)		
occurrences (all)	3		
Retinal detachment			

subjects affected / exposed	0 / 193 (0.00%)		
occurrences (all)	0		
Vitreous floaters			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences (all)	0		
Visual impairment			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences (all)	0		
Trichomegaly			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences (all)	0		
Trichiasis			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences (all)	0		
Chorioretinopathy			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences (all)	0		
Macular oedema			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	84 / 193 (43.52%)		
occurrences (all)	162		
Constipation			
subjects affected / exposed	39 / 193 (20.21%)		
occurrences (all)	48		
Diarrhoea			
subjects affected / exposed	96 / 193 (49.74%)		
occurrences (all)	252		
Abdominal pain			
subjects affected / exposed	54 / 193 (27.98%)		
occurrences (all)	101		
Vomiting			
subjects affected / exposed	59 / 193 (30.57%)		
occurrences (all)	91		

Flatulence				
subjects affected / exposed	3 / 193 (1.55%)			
occurrences (all)	3			
Dyspepsia				
subjects affected / exposed	7 / 193 (3.63%)			
occurrences (all)	7			
Abdominal pain upper				
subjects affected / exposed	15 / 193 (7.77%)			
occurrences (all)	15			
Rectal haemorrhage				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences (all)	1			
Gastroesophageal reflux disease				
subjects affected / exposed	6 / 193 (3.11%)			
occurrences (all)	6			
Abdominal distension				
subjects affected / exposed	8 / 193 (4.15%)			
occurrences (all)	11			
Dry Mouth				
subjects affected / exposed	8 / 193 (4.15%)			
occurrences (all)	8			
Anal haemorrhage				
subjects affected / exposed	2 / 193 (1.04%)			
occurrences (all)	2			
Ascites				
subjects affected / exposed	4 / 193 (2.07%)			
occurrences (all)	4			
Colitis				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences (all)	1			
Stomatitis				
subjects affected / exposed	45 / 193 (23.32%)			
occurrences (all)	84			
Abdominal pain lower				
subjects affected / exposed	2 / 193 (1.04%)			
occurrences (all)	2			

Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	77 / 193 (39.90%)		
occurrences (all)	138		
Rash			
subjects affected / exposed	28 / 193 (14.51%)		
occurrences (all)	55		
Dry Skin			
subjects affected / exposed	17 / 193 (8.81%)		
occurrences (all)	20		
Pruritus			
subjects affected / exposed	10 / 193 (5.18%)		
occurrences (all)	12		
Palmar-planar erythrodysaesthesia			
subjects affected / exposed	15 / 193 (7.77%)		
occurrences (all)	21		
Rash maculo-papular			
subjects affected / exposed	11 / 193 (5.70%)		
occurrences (all)	14		
Skin fissures			
subjects affected / exposed	13 / 193 (6.74%)		
occurrences (all)	16		
Erythema			
subjects affected / exposed	4 / 193 (2.07%)		
occurrences (all)	4		
Eczema			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences (all)	1		
Skin hyperpigmentation			
subjects affected / exposed	2 / 193 (1.04%)		
occurrences (all)	2		
Skin lesion			
subjects affected / exposed	3 / 193 (1.55%)		
occurrences (all)	3		
Pruritus generalised			

subjects affected / exposed occurrences (all)	3 / 193 (1.55%) 5		
Alopecia subjects affected / exposed occurrences (all)	21 / 193 (10.88%) 23		
Hyperkeratosis subjects affected / exposed occurrences (all)	0 / 193 (0.00%) 0		
Hypertrichosis subjects affected / exposed occurrences (all)	1 / 193 (0.52%) 1		
Nail disorder subjects affected / exposed occurrences (all)	2 / 193 (1.04%) 2		
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	4 / 193 (2.07%) 4		
Urinary incontinence subjects affected / exposed occurrences (all)	2 / 193 (1.04%) 2		
Proteinuria subjects affected / exposed occurrences (all)	1 / 193 (0.52%) 1		
Pollakiuria subjects affected / exposed occurrences (all)	0 / 193 (0.00%) 0		
Musculoskeletal and connective tissue disorders Back Pain subjects affected / exposed occurrences (all)	27 / 193 (13.99%) 32		
Pain in extremity subjects affected / exposed occurrences (all)	2 / 193 (1.04%) 3		
Myalgia			

subjects affected / exposed	4 / 193 (2.07%)		
occurrences (all)	7		
Arthralgia			
subjects affected / exposed	3 / 193 (1.55%)		
occurrences (all)	4		
Musculoskeletal pain			
subjects affected / exposed	5 / 193 (2.59%)		
occurrences (all)	5		
Muscle spasms			
subjects affected / exposed	4 / 193 (2.07%)		
occurrences (all)	7		
Bone pain			
subjects affected / exposed	2 / 193 (1.04%)		
occurrences (all)	5		
Flank pain			
subjects affected / exposed	3 / 193 (1.55%)		
occurrences (all)	6		
Musculoskeletal chest pain			
subjects affected / exposed	2 / 193 (1.04%)		
occurrences (all)	2		
Infections and infestations			
Cystitis			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences (all)	1		
Conjunctivitis			
subjects affected / exposed	3 / 193 (1.55%)		
occurrences (all)	3		
Rash pustular			
subjects affected / exposed	4 / 193 (2.07%)		
occurrences (all)	6		
Paronychia			
subjects affected / exposed	20 / 193 (10.36%)		
occurrences (all)	28		
Urinary tract infection			
subjects affected / exposed	5 / 193 (2.59%)		
occurrences (all)	6		

Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 193 (1.55%) 3		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	10 / 193 (5.18%) 13		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	56 / 193 (29.02%) 74		
Hypokalaemia subjects affected / exposed occurrences (all)	25 / 193 (12.95%) 41		
Hypomagnesaemia subjects affected / exposed occurrences (all)	19 / 193 (9.84%) 36		
Hypoalbuminaemia subjects affected / exposed occurrences (all)	6 / 193 (3.11%) 6		
Iron deficiency subjects affected / exposed occurrences (all)	1 / 193 (0.52%) 1		
Hypophosphataemia subjects affected / exposed occurrences (all)	4 / 193 (2.07%) 6		
Hypocalcaemia subjects affected / exposed occurrences (all)	9 / 193 (4.66%) 14		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Total number of deaths is reported for safety set under Adverse Events section. However, actual number of deaths were, for combined safety lead-in: 30; for Phase 3: Triplet arm: 209; for Phase 3: Doublet arm: 193 and for Phase 3: Control arm: 198.

Notes: