



Clinical trial results:

A Randomized, Placebo-Controlled, Phase 1/2 Study of ARQ 197 in Combination with Irinotecan and Cetuximab in Subjects with Metastatic Colorectal Cancer with Wild-Type KRAS Who Have Received Front-Line Systemic Therapy

Summary

EudraCT number	2009-016025-34
Trial protocol	DE IT
Global end of trial date	16 December 2014

Results information

Result version number	v1 (current)
This version publication date	16 September 2016
First version publication date	16 September 2016
Summary attachment (see zip file)	Report Synopsis for ARQ197-A-U252 (ARQ197-A-U252 Synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	ARQ197-A-U252
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01075048
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Daiichi Sankyo Pharma Development
Sponsor organisation address	399 Thornall Street, Edison, United States, New Jersey 08837
Public contact	Jason Mann, Daiichi Sankyo Pharma Development, 399 Thornall Street, Edison, NJ 08837, United States, +001 732 5905011, jamann@dsi.com
Scientific contact	Jason Mann, Daiichi Sankyo Pharma Development, 399 Thornall Street, Edison, NJ 08837, United States, +001 732 5905011, jamann@dsi.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	16 December 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	16 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the safety and tolerability of ARQ197 when administered with irinotecan and cetuximab in subjects who had received front-line systemic therapy, to define the Recommended Phase 2 dose (RP2D) study in combination with irinotecan and cetuximab, to estimate the difference in progression-free survival (PFS) between the study and control arms in subjects with Colorectal cancer (CRC) with wild-type k-ras oncogene (KRAS) who have received front-line systemic therapy.

Protection of trial subjects:

The safety assessments included adverse events, clinical laboratory evaluations, coagulation, vital signs, 12-Lead eElectrocardiogram (ECG), physical examination, and Urinalysis.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 January 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Russian Federation: 39
Country: Number of subjects enrolled	United States: 76
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Italy: 5
Worldwide total number of subjects	131
EEA total number of subjects	16

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)	91
From 65 to 84 years	40
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study period: 26 Jan 2010 (First subject first visit) to 16 Dec 2014 (Last subject last visit)

Pre-assignment

Screening details:

Overall, 131 subjects were enrolled in the study, with 9 subjects enrolled into the Phase 1 cohort and 122 subjects randomly assigned to ARQ197 or placebo treatment in Phase 2. In Phase 2, 1 (1.7%) enrolled subject in the placebo group did not receive study drug and therefore was not included in the safety analysis set.

Period 1

Period 1 title	Phase 1
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Phase 1
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Arm description:

Subjects were administered with an oral dose of ARQ197 capsules twice daily (BID) with a meal, in escalating doses of 120 milligram (mg), 240 mg, and 360 mg to 3 separate cohorts on Day 1 of Cycle 1 and Cycle 2. Cetuximab 500 milligram per square meter (mg/m²) intravenous infusion over 120 minutes at the first cycle, then over 60-minutes at subsequent cycles. Followed by 60 minutes with Irinotecan 180 mg/m² intravenous infusion over 30 - 90 minutes. Cetuximab and Irinotecan are administered on Day 1 and Day 15 of each 28 day cycle.

Arm type	Experimental
Investigational medicinal product name	ARQ197
Investigational medicinal product code	ARQ197
Other name	Tivantinib
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects were administered with an oral dose of ARQ197 capsules twice daily (BID) with a meal, in escalating doses of 120 milligram (mg), 240 mg, and 360 mg to 3 separate cohorts on Day 1 of Cycle 1 and 2.

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

Dosage and administration details:

Subjects were administered with Cetuximab 500 mg/m² intravenous infusion over 120 minutes at the first cycle, then over 60-minutes at subsequent cycles on Day 1 and Day 15 of each 28 day cycle.

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

Dosage and administration details:

Subjects were administered with Irinotecan 180 mg/m² intravenous infusion over 30 - 90 minutes on Day 1 and Day 15 of each 28 day cycle.

Number of subjects in period 1 ^[1]	Phase 1
Started	9
Completed	0
Not completed	9
Consent withdrawn by subject	1
start of other or new therapy	4
Death	4

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: As baseline period included only for the Phase 1 subjects. Hence, the worldwide number enrolled in the trial differs with the number of subjects reported in the baseline period.

Period 2

Period 2 title	Phase 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	No
Arm title	Placebo

Arm description:

Subjects received placebo twice daily with Cetuximab and Irinotecan until disease progression, unacceptable toxicity or other discontinuation. Cetuximab 500 mg/ m² intravenous infusion over 120 minutes, then over 60 minutes at subsequent cycles. Followed 60 minutes later with Irinotecan 180 mg/m² intravenous infusion over 30 - 90 minutes. Cetuximab and Irinotecan are administered on Day 1 and Day 15 of each 28 day cycle.

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

Dosage and administration details:

Subjects were administered with placebo twice daily until disease progression, unacceptable toxicity or other discontinuation.

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

Dosage and administration details:

Subjects were administered with Cetuximab 500 mg/m² intravenous infusion until disease progression, unacceptable toxicity or other discontinuation.

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

Dosage and administration details:

Subjects were administered with Irinotecan 180 mg/m² intravenous infusion until disease progression, unacceptable toxicity or other discontinuation.

Arm title	ARQ197
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Arm description:

Subject received ARQ197 (recommended Phase 2 dose of 720 mg) daily with Cetuximab and Irinotecan until disease progression, unacceptable toxicity or other discontinuation. Cetuximab 500 mg/m² intravenous infusion over 120 minutes at the first cycle, then over 60-minutes at subsequent cycles. Followed 60 minutes later with Irinotecan 180 mg/m² intravenous infusion over 30 - 90 minutes. Cetuximab and Irinotecan are administered on Day 1 and Day 15 of each 28 day cycle.

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

Dosage and administration details:

Subjects were administered with Cetuximab 500 mg/m² intravenous infusion until disease progression, unacceptable toxicity or other discontinuation.

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

Dosage and administration details:

Subjects were administered with Irinotecan 180 mg/m² intravenous infusion until disease progression, unacceptable toxicity or other discontinuation.

Investigational medicinal product name	ARQ 197
Investigational medicinal product code	ARQ 197
Other name	Tivantinib
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects were administered with an oral dose of ARQ 197 capsules twice daily (BID) with a meal, until disease progression, unacceptable toxicity or other discontinuation.

Number of subjects in period 2	Placebo	ARQ197
Started	60	62
Completed	0	0
Not completed	60	62
Consent withdrawn by subject	6	3
start of other or new therapy	36	46
Death	17	12
Lost to follow-up	1	1

Baseline characteristics

Reporting groups

Reporting group title	Phase 1
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Reporting group description:

Subjects were administered with an oral dose of ARQ197 capsules twice daily (BID) with a meal, in escalating doses of 120 milligram (mg), 240 mg, and 360 mg to 3 separate cohorts on Day 1 of Cycle 1 and Cycle 2. Cetuximab 500 milligram per square meter (mg/m²) intravenous infusion over 120 minutes at the first cycle, then over 60-minutes at subsequent cycles. Followed by 60 minutes with Irinotecan 180 mg/m² intravenous infusion over 30 - 90 minutes. Cetuximab and Irinotecan are administered on Day 1 and Day 15 of each 28 day cycle.

Reporting group values	Phase 1	Total	
Number of subjects	9	9	
Age categorical			
Units: Subjects			
Adults (18-64 years)	6	6	
From 65-84 years	3	3	
Age continuous			
Units: years			
arithmetic mean	55.2		
standard deviation	± 14.69	-	
Gender categorical			
Units: Subjects			
Female	2	2	
Male	7	7	

End points

End points reporting groups

Reporting group title	Phase 1
Reporting group description:	
Subjects were administered with an oral dose of ARQ197 capsules twice daily (BID) with a meal, in escalating doses of 120 milligram (mg), 240 mg, and 360 mg to 3 separate cohorts on Day 1 of Cycle 1 and Cycle 2. Cetuximab 500 milligram per square meter (mg/m ²) intravenous infusion over 120 minutes at the first cycle, then over 60-minutes at subsequent cycles. Followed by 60 minutes with Irinotecan 180 mg/m ² intravenous infusion over 30 - 90 minutes. Cetuximab and Irinotecan are administered on Day 1 and Day 15 of each 28 day cycle.	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo twice daily with Cetuximab and Irinotecan until disease progression, unacceptable toxicity or other discontinuation. Cetuximab 500 mg/ m ² intravenous infusion over 120 minutes, then over 60 minutes at subsequent cycles. Followed 60 minutes later with Irinotecan 180 mg/m ² intravenous infusion over 30 - 90 minutes. Cetuximab and Irinotecan are administered on Day 1 and Day 15 of each 28 day cycle.	
Reporting group title	ARQ197
Reporting group description:	
Subject received ARQ197 (recommended Phase 2 dose of 720 mg) daily with Cetuximab and Irinotecan until disease progression, unacceptable toxicity or other discontinuation. Cetuximab 500 mg/m ² intravenous infusion over 120 minutes at the first cycle, then over 60-minutes at subsequent cycles. Followed 60 minutes later with Irinotecan 180 mg/m ² intravenous infusion over 30 - 90 minutes. Cetuximab and Irinotecan are administered on Day 1 and Day 15 of each 28 day cycle.	

Primary: Number of Subjects With Treatment Emergent Adverse Events (TEAEs) and Treatment Emergent Serious Adverse Events (TESEAs)

End point title	Number of Subjects With Treatment Emergent Adverse Events (TEAEs) and Treatment Emergent Serious Adverse Events (TESEAs) ^[1]
End point description:	
An adverse event (AE) was any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which did not necessarily have to have a causal relationship with that treatment. A TEAE was defined as an AE that Had an onset date on or after the first dose of Study Drug, cetuximab, or irinotecan up to and including 30 days after the last dose of any study drug, or Worsened in severity after the first dose of Study Drug relative to the pre-treatment state. Safety population included all subjects who received any amount of study drug and had at least one safety assessment.	
End point type	Primary
End point timeframe:	
Screening up to End of the Treatment (30 Days After Last Dose)	
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: Descriptive statistics were done, no inferential statistical analyses were performed.	

End point values	Phase 1	Placebo	ARQ197	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	59	62	
Units: Subjects				
TEAEs	9	59	62	
TESAEs	3	17	13	

Statistical analyses

No statistical analyses for this end point

Primary: Recommended Phase 2 Dose (RP2D) of ARQ 197

End point title	Recommended Phase 2 Dose (RP2D) of ARQ 197 ^[2]
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End point description:

RP2D of ARQ 197 was identified when administered along with irinotecan and cetuximab in Phase 1. All enrolled subjects received study drug and were included in the safety analysis set.

End point type	Primary
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End point timeframe:

Up to 4 weeks

Notes:

[2] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Phase 1			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: milligram				
number (not applicable)	720			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Progression-Free Survival (PFS)

End point title	Percentage of Subjects With Progression-Free Survival (PFS) ^[3]
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End point description:

Progression-free survival is defined as the time from randomization to the date of disease progression (PD) or death due to any cause. Full analysis set (FAS) included all subjects who were randomized in the Phase 2 portion of the study, received at least one dose of study drug, and had at least one assessment for the efficacy variable. Here '99999' indicates the parameter was not evaluated at that time point.

End point type	Primary
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End point timeframe:

Up to 80 weeks

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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Placebo	ARQ197		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	60		
Units: Months				
median (confidence interval 95%)	7.3 (5.3 to 9)	8.3 (5.6 to 10.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Best Overall Response and Objective Response Rate

End point title	Number of Subjects With Best Overall Response and Objective Response Rate
End point description:	
Best overall tumor response according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria assessed by CT/MRI. Complete Response (CR), Disappearance of all target lesions; Partial Response (PR), ≥ 30 percent (%) decrease in the longest diameter of target lesions; Overall Response (OR), CR+PR. All enrolled subjects received study drug and were included in the safety analysis set.	
End point type	Secondary
End point timeframe:	
Up to 2 years	

End point values	Placebo	ARQ197		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	60		
Units: Subjects				
number (not applicable)				
Complete Response	0	0		
Partial Response	19	27		
Stable Disease	22	22		
Progressive Disease	13	9		
Objective Response (CR + PR)	19	27		
Inevaluable	3	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Overall Survival (OS)

End point title	Percentage of Subjects With Overall Survival (OS)
End point description:	
Overall survival is defined as the time from randomization date to the date of death. Full analysis set (FAS) included all subjects who were randomized in the Phase 2 portion of the study, received at least	

one dose of study drug, and had at least one assessment for the efficacy variable. Here '99999' indicates the parameter was not evaluated at that time point.

End point type	Secondary
End point timeframe:	
Up to 3.8 years	

End point values	Placebo	ARQ197		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	60		
Units: months				
median (confidence interval 95%)	16.3 (11.6 to 20.4)	22.3 (15.4 to 27)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Screening up to End of the Treatment (30 Days After Last Dose)

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	13.0
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Reporting groups

Reporting group title	Phase 1
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Reporting group description:

Subjects were administered with an oral dose of ARQ 197 capsules twice daily (BID) with a meal, in escalating doses of 120 milligram (mg), 240 mg, and 360 mg to 3 separate cohorts on Day 1 of Cycle 1 and 2. Cetuximab 500 milligram per square meter (mg/m²) intravenous infusion over 120 minutes at the first cycle, then over 60-minutes at subsequent cycles. Followed by 60 minutes with Irinotecan 180 mg/m² intravenous infusion over 30 - 90 minutes. Cetuximab and Irinotecan are administered on Day 1 and Day 15 of each 28 day cycle.

Reporting group title	Placebo
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Reporting group description:

Subjects received placebo twice daily with Cetuximab and Irinotecan until disease progression, unacceptable toxicity or other discontinuation. Cetuximab 500 mg/m² intravenous infusion over 120 minutes, then over 60 minutes at subsequent cycles. Followed 60 minutes later with Irinotecan 180 mg/m² intravenous infusion over 30 - 90 minutes. Cetuximab and Irinotecan are administered on Day 1 and Day 15 of each 28 day cycle.

Reporting group title	ARQ197
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Reporting group description:

Subject received ARQ197 (recommended Phase 2 dose of 720 mg) daily with Cetuximab and Irinotecan until disease progression, unacceptable toxicity or other discontinuation. Cetuximab 500 mg/m² intravenous infusion over 120 minutes at the first cycle, then over 60-minutes at subsequent cycles. Followed 60 minutes later with Irinotecan 180 mg/m² intravenous infusion over 30 - 90 minutes. Cetuximab and Irinotecan are administered on Day 1 and Day 15 of each 28 day cycle.

Serious adverse events	Phase 1	Placebo	ARQ197
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 9 (33.33%)	17 / 59 (28.81%)	13 / 62 (20.97%)
number of deaths (all causes)	0	3	4
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (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
Colon cancer metastatic			

subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (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
Malignant neoplasm progression			
subjects affected / exposed	0 / 9 (0.00%)	2 / 59 (3.39%)	2 / 62 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 2
Metastases to bone			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (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
Hypovolaemic shock			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superior vena caval occlusion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (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
Multi-organ failure			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (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

Pneumatosis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (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
Pyrexia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 59 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (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
Hypersensitivity			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
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			
Dyspnoea			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (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
Pleural effusion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (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
Respiratory failure			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
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			
Facial bones fracture			
subjects affected / exposed	1 / 9 (11.11%)	0 / 59 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (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
Atrial fibrillation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiovascular insufficiency			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (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
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 9 (11.11%)	0 / 59 (0.00%)	0 / 62 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			

subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	2 / 62 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (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
Colitis ulcerative			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (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
Diarrhoea			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (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
Ileus			
subjects affected / exposed	0 / 9 (0.00%)	2 / 59 (3.39%)	0 / 62 (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
Nausea			
subjects affected / exposed	0 / 9 (0.00%)	2 / 59 (3.39%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumoperitoneum			

subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (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
Proctalgia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 9 (11.11%)	4 / 59 (6.78%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal perforation			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 9 (0.00%)	2 / 59 (3.39%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (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 acute			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	2 / 62 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Diverticulitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			

subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Urinary tract infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	2 / 62 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Phase 1	Placebo	ARQ197
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)	59 / 59 (100.00%)	62 / 62 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	1 / 62 (1.61%)
occurrences (all)	0	1	1
Flushing			

subjects affected / exposed	1 / 9 (11.11%)	1 / 59 (1.69%)	2 / 62 (3.23%)
occurrences (all)	1	1	2
Hot flush			
subjects affected / exposed	2 / 9 (22.22%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	3	0	1
Hypertension			
subjects affected / exposed	0 / 9 (0.00%)	2 / 59 (3.39%)	2 / 62 (3.23%)
occurrences (all)	0	3	3
Hypotension			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Lymphostasis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Phlebitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Thrombophlebitis superficial			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Varicose vein			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Vena cava thrombosis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 9 (0.00%)	6 / 59 (10.17%)	8 / 62 (12.90%)
occurrences (all)	0	19	12
Chest discomfort			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Chills			

subjects affected / exposed	1 / 9 (11.11%)	3 / 59 (5.08%)	2 / 62 (3.23%)
occurrences (all)	4	4	2
Fatigue			
subjects affected / exposed	7 / 9 (77.78%)	21 / 59 (35.59%)	26 / 62 (41.94%)
occurrences (all)	14	35	44
Feeling hot			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
General physical health deterioration			
subjects affected / exposed	0 / 9 (0.00%)	2 / 59 (3.39%)	1 / 62 (1.61%)
occurrences (all)	0	3	2
Hyperthermia			
subjects affected / exposed	0 / 9 (0.00%)	2 / 59 (3.39%)	4 / 62 (6.45%)
occurrences (all)	0	2	4
Inflammation			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Influenza like illness			
subjects affected / exposed	1 / 9 (11.11%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	1	1	0
Infusion related reaction			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	2 / 62 (3.23%)
occurrences (all)	0	1	3
Infusion site oedema			
subjects affected / exposed	1 / 9 (11.11%)	0 / 59 (0.00%)	0 / 62 (0.00%)
occurrences (all)	1	0	0
Local swelling			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Malaise			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Mucosal dryness			
subjects affected / exposed	0 / 9 (0.00%)	2 / 59 (3.39%)	0 / 62 (0.00%)
occurrences (all)	0	2	0
Mucosal inflammation			

subjects affected / exposed	1 / 9 (11.11%)	3 / 59 (5.08%)	5 / 62 (8.06%)
occurrences (all)	2	3	6
Non-cardiac chest pain			
subjects affected / exposed	1 / 9 (11.11%)	0 / 59 (0.00%)	0 / 62 (0.00%)
occurrences (all)	1	0	0
Oedema			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	3 / 62 (4.84%)
occurrences (all)	0	0	3
Oedema peripheral			
subjects affected / exposed	2 / 9 (22.22%)	5 / 59 (8.47%)	4 / 62 (6.45%)
occurrences (all)	3	14	5
Pain			
subjects affected / exposed	1 / 9 (11.11%)	2 / 59 (3.39%)	0 / 62 (0.00%)
occurrences (all)	2	2	0
Performance status decreased			
subjects affected / exposed	0 / 9 (0.00%)	2 / 59 (3.39%)	0 / 62 (0.00%)
occurrences (all)	0	2	0
Pyrexia			
subjects affected / exposed	2 / 9 (22.22%)	7 / 59 (11.86%)	4 / 62 (6.45%)
occurrences (all)	3	15	4
Xerosis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	2	0
Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Anaphylactic reaction			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Contrast media allergy			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	1 / 62 (1.61%)
occurrences (all)	0	1	1
Drug hypersensitivity			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	2 / 62 (3.23%)
occurrences (all)	0	1	3

Seasonal allergy subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	2 / 59 (3.39%) 2	1 / 62 (1.61%) 1
Reproductive system and breast disorders			
Vulvovaginal erythema subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 59 (0.00%) 0	1 / 62 (1.61%) 1
Vulvovaginal pruritus subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 59 (0.00%) 0	1 / 62 (1.61%) 1
Respiratory, thoracic and mediastinal disorders			
Bronchospasm subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 59 (0.00%) 0	1 / 62 (1.61%) 1
Cough subjects affected / exposed occurrences (all)	4 / 9 (44.44%) 4	7 / 59 (11.86%) 8	7 / 62 (11.29%) 7
Dry throat subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 59 (0.00%) 0	0 / 62 (0.00%) 0
Dysphonia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 59 (1.69%) 2	1 / 62 (1.61%) 1
Dyspnoea subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	7 / 59 (11.86%) 9	3 / 62 (4.84%) 6
Dyspnoea exertional subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 59 (1.69%) 1	0 / 62 (0.00%) 0
Epistaxis subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	2 / 59 (3.39%) 3	2 / 62 (3.23%) 2
Hiccups subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 59 (1.69%) 1	1 / 62 (1.61%) 1
Hyperventilation			

subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Nasal congestion			
subjects affected / exposed	2 / 9 (22.22%)	2 / 59 (3.39%)	0 / 62 (0.00%)
occurrences (all)	2	3	0
Oropharyngeal discomfort			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			
subjects affected / exposed	1 / 9 (11.11%)	2 / 59 (3.39%)	1 / 62 (1.61%)
occurrences (all)	1	2	1
Pleural effusion			
subjects affected / exposed	1 / 9 (11.11%)	0 / 59 (0.00%)	0 / 62 (0.00%)
occurrences (all)	1	0	0
Postnasal drip			
subjects affected / exposed	1 / 9 (11.11%)	0 / 59 (0.00%)	0 / 62 (0.00%)
occurrences (all)	1	0	0
Productive cough			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Pulmonary congestion			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Pulmonary embolism			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Rales			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Respiratory failure			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Respiratory tract congestion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Rhinitis allergic			

subjects affected / exposed	1 / 9 (11.11%)	0 / 59 (0.00%)	0 / 62 (0.00%)
occurrences (all)	1	0	0
Rhinitis seasonal			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	2 / 62 (3.23%)
occurrences (all)	0	0	2
Sinus congestion			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Sleep apnoea syndrome			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Wheezing			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Psychiatric disorders			
Adjustment disorder			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Agitation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Anxiety			
subjects affected / exposed	1 / 9 (11.11%)	2 / 59 (3.39%)	1 / 62 (1.61%)
occurrences (all)	1	2	1
Confusional state			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Depressed mood			
subjects affected / exposed	1 / 9 (11.11%)	0 / 59 (0.00%)	0 / 62 (0.00%)
occurrences (all)	1	0	0
Depression			
subjects affected / exposed	2 / 9 (22.22%)	4 / 59 (6.78%)	3 / 62 (4.84%)
occurrences (all)	2	4	5

Eating disorder subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 59 (0.00%) 0	1 / 62 (1.61%) 1
Insomnia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	4 / 59 (6.78%) 4	7 / 62 (11.29%) 11
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 59 (1.69%) 1	1 / 62 (1.61%) 1
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	2 / 59 (3.39%) 2	1 / 62 (1.61%) 1
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	3 / 59 (5.08%) 6	2 / 62 (3.23%) 3
Blood bilirubin increased subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 59 (0.00%) 0	1 / 62 (1.61%) 1
Blood chloride increased subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 59 (0.00%) 0	1 / 62 (1.61%) 1
Blood creatinine increased subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 59 (0.00%) 0	2 / 62 (3.23%) 3
Blood magnesium decreased subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	2 / 59 (3.39%) 2	3 / 62 (4.84%) 4
Blood phosphorus decreased subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 59 (0.00%) 0	1 / 62 (1.61%) 1
Blood pressure increased subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 59 (0.00%) 0	1 / 62 (1.61%) 1
Blood urea increased			

subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	1 / 62 (1.61%)
occurrences (all)	0	1	2
Cortisol free urine decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Creatinine renal clearance decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Haemoglobin decreased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	5 / 62 (8.06%)
occurrences (all)	0	1	10
Heart rate irregular			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Liver function test abnormal			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Neutrophil count decreased			
subjects affected / exposed	0 / 9 (0.00%)	3 / 59 (5.08%)	6 / 62 (9.68%)
occurrences (all)	0	3	10
Platelet count decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Prostatic specific antigen increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Pulse abnormal			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Weight decreased			

subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2	6 / 59 (10.17%) 7	3 / 62 (4.84%) 3
Weight increased subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 59 (1.69%) 2	1 / 62 (1.61%) 1
White blood cell count decreased subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	1 / 59 (1.69%) 1	4 / 62 (6.45%) 6
Blood calcium decreased subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 59 (0.00%) 0	1 / 62 (1.61%) 1
Injury, poisoning and procedural complications			
Animal bite subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 59 (1.69%) 1	0 / 62 (0.00%) 0
Contusion subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 59 (0.00%) 0	2 / 62 (3.23%) 2
Excoriation subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 59 (1.69%) 1	0 / 62 (0.00%) 0
Fall subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 59 (1.69%) 1	1 / 62 (1.61%) 1
Gastrointestinal stoma complication subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 59 (1.69%) 1	0 / 62 (0.00%) 0
Incision site pain subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 59 (0.00%) 0	1 / 62 (1.61%) 1
Joint sprain subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 59 (0.00%) 0	1 / 62 (1.61%) 1
Post procedural haemorrhage			

subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Postoperative hernia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Procedural pain			
subjects affected / exposed	1 / 9 (11.11%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	1	1	0
Road traffic accident			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Seroma			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	2
Skin laceration			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Wound			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Wound secretion			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	1 / 62 (1.61%)
occurrences (all)	0	1	1
Atrial fibrillation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Bradycardia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	3 / 62 (4.84%)
occurrences (all)	0	0	3
Cardiac disorder			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1

Extrasystoles			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Left ventricular dysfunction			
subjects affected / exposed	1 / 9 (11.11%)	0 / 59 (0.00%)	0 / 62 (0.00%)
occurrences (all)	1	0	0
Palpitations			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Sinus bradycardia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	3 / 62 (4.84%)
occurrences (all)	0	0	3
Sinus tachycardia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	1 / 62 (1.61%)
occurrences (all)	0	1	1
Supraventricular tachyarrhythmia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Tachycardia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	1 / 62 (1.61%)
occurrences (all)	0	1	1
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Aphasia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Balance disorder			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	1 / 9 (11.11%)	4 / 59 (6.78%)	2 / 62 (3.23%)
occurrences (all)	1	5	2
Dysarthria			

subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Dysgeusia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Grand mal convulsion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	2 / 9 (22.22%)	4 / 59 (6.78%)	7 / 62 (11.29%)
occurrences (all)	3	4	11
Hypoaesthesia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	1 / 62 (1.61%)
occurrences (all)	0	1	1
Hypotonia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Neuralgia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	2
Neuropathy peripheral			
subjects affected / exposed	0 / 9 (0.00%)	2 / 59 (3.39%)	2 / 62 (3.23%)
occurrences (all)	0	2	3
Paraesthesia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	1 / 62 (1.61%)
occurrences (all)	0	1	1
Parosmia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	2 / 62 (3.23%)
occurrences (all)	0	0	2
Polyneuropathy			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Radiculopathy			

subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Restless legs syndrome			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	2 / 62 (3.23%)
occurrences (all)	0	0	2
Sinus headache			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Syncope			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 9 (22.22%)	19 / 59 (32.20%)	7 / 62 (11.29%)
occurrences (all)	4	26	8
Febrile neutropenia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Haemorrhagic anaemia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Leukopenia			
subjects affected / exposed	2 / 9 (22.22%)	3 / 59 (5.08%)	5 / 62 (8.06%)
occurrences (all)	5	10	13
Lymphopenia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	3
Neutropenia			
subjects affected / exposed	4 / 9 (44.44%)	13 / 59 (22.03%)	17 / 62 (27.42%)
occurrences (all)	12	26	35
Pancytopenia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Thrombocytopenia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	5 / 62 (8.06%)
occurrences (all)	0	2	6

Thrombocytosis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 59 (1.69%) 1	0 / 62 (0.00%) 0
Ear and labyrinth disorders			
Ear discomfort subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 59 (1.69%) 1	0 / 62 (0.00%) 0
Vertigo subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 59 (0.00%) 0	1 / 62 (1.61%) 1
Eye disorder subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 59 (1.69%) 1	0 / 62 (0.00%) 0
Eye disorders			
Blepharitis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 59 (0.00%) 0	1 / 62 (1.61%) 1
Conjunctival irritation subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 2	0 / 59 (0.00%) 0	0 / 62 (0.00%) 0
Conjunctivitis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 59 (1.69%) 1	0 / 62 (0.00%) 0
Dry eye subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 59 (1.69%) 2	2 / 62 (3.23%) 3
Ectropion subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 59 (0.00%) 0	0 / 62 (0.00%) 0
Eye allergy subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 59 (0.00%) 0	1 / 62 (1.61%) 1
Eye pruritus subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 59 (0.00%) 0	1 / 62 (1.61%) 1
Growth of eyelashes			

subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Lacrimation increased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	1	0	1
Ocular hyperaemia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Photophobia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Vision blurred			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	2 / 62 (3.23%)
occurrences (all)	0	0	2
Visual acuity reduced			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 9 (0.00%)	2 / 59 (3.39%)	0 / 62 (0.00%)
occurrences (all)	0	2	0
Abdominal pain			
subjects affected / exposed	3 / 9 (33.33%)	16 / 59 (27.12%)	12 / 62 (19.35%)
occurrences (all)	6	23	14
Abdominal pain lower			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	3 / 62 (4.84%)
occurrences (all)	0	0	3
Abdominal pain upper			
subjects affected / exposed	1 / 9 (11.11%)	4 / 59 (6.78%)	7 / 62 (11.29%)
occurrences (all)	2	10	9
Cheilitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 59 (0.00%)	0 / 62 (0.00%)
occurrences (all)	1	0	0
Colitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	2

Colonic fistula			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	1 / 9 (11.11%)	11 / 59 (18.64%)	10 / 62 (16.13%)
occurrences (all)	1	19	20
Diarrhoea			
subjects affected / exposed	5 / 9 (55.56%)	30 / 59 (50.85%)	33 / 62 (53.23%)
occurrences (all)	13	87	88
Dry mouth			
subjects affected / exposed	1 / 9 (11.11%)	2 / 59 (3.39%)	0 / 62 (0.00%)
occurrences (all)	1	2	0
Dyspepsia			
subjects affected / exposed	1 / 9 (11.11%)	3 / 59 (5.08%)	3 / 62 (4.84%)
occurrences (all)	2	4	3
Dysphagia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Flatulence			
subjects affected / exposed	0 / 9 (0.00%)	5 / 59 (8.47%)	2 / 62 (3.23%)
occurrences (all)	0	6	2
Gastritis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	5 / 62 (8.06%)
occurrences (all)	0	0	6
Gingival pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Haematochezia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	2 / 62 (3.23%)
occurrences (all)	0	0	2
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 9 (11.11%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	1	0	3

Intestinal haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Lip dry			
subjects affected / exposed	1 / 9 (11.11%)	0 / 59 (0.00%)	0 / 62 (0.00%)
occurrences (all)	1	0	0
Lip exfoliation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Lip ulceration			
subjects affected / exposed	1 / 9 (11.11%)	0 / 59 (0.00%)	0 / 62 (0.00%)
occurrences (all)	1	0	0
Mesenteric vein thrombosis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Mouth ulceration			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	2 / 62 (3.23%)
occurrences (all)	0	0	3
Nausea			
subjects affected / exposed	6 / 9 (66.67%)	27 / 59 (45.76%)	28 / 62 (45.16%)
occurrences (all)	22	59	68
Oral pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Proctalgia			
subjects affected / exposed	0 / 9 (0.00%)	2 / 59 (3.39%)	1 / 62 (1.61%)
occurrences (all)	0	2	1
Rectal discharge			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	1 / 62 (1.61%)
occurrences (all)	0	1	1
Stomatitis			
subjects affected / exposed	1 / 9 (11.11%)	4 / 59 (6.78%)	7 / 62 (11.29%)
occurrences (all)	3	7	14
Toothache			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0

Vomiting subjects affected / exposed occurrences (all)	4 / 9 (44.44%) 6	17 / 59 (28.81%) 33	22 / 62 (35.48%) 42
Hepatobiliary disorders			
Cholestasis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 59 (1.69%) 1	0 / 62 (0.00%) 0
Hepatic pain subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 59 (1.69%) 1	0 / 62 (0.00%) 0
Hepatitis toxic subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 59 (0.00%) 0	1 / 62 (1.61%) 1
Hyperbilirubinaemia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 59 (1.69%) 2	0 / 62 (0.00%) 0
Jaundice subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 59 (1.69%) 1	0 / 62 (0.00%) 0
Skin and subcutaneous tissue disorders			
Acne subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 59 (1.69%) 1	2 / 62 (3.23%) 3
Actinic elastosis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 59 (0.00%) 0	1 / 62 (1.61%) 1
Alopecia subjects affected / exposed occurrences (all)	5 / 9 (55.56%) 5	14 / 59 (23.73%) 14	17 / 62 (27.42%) 19
Alopecia totalis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 59 (1.69%) 1	0 / 62 (0.00%) 0
Dermatitis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 59 (1.69%) 4	0 / 62 (0.00%) 0
Dermatitis acneiform			

subjects affected / exposed	4 / 9 (44.44%)	9 / 59 (15.25%)	8 / 62 (12.90%)
occurrences (all)	5	17	20
Dry skin			
subjects affected / exposed	4 / 9 (44.44%)	10 / 59 (16.95%)	11 / 62 (17.74%)
occurrences (all)	5	10	14
Erythema			
subjects affected / exposed	1 / 9 (11.11%)	2 / 59 (3.39%)	1 / 62 (1.61%)
occurrences (all)	2	6	1
Hair colour changes			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Hyperhidrosis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 59 (0.00%)	0 / 62 (0.00%)
occurrences (all)	2	0	0
Hypertrichosis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	2
Ichthyosis acquired			
subjects affected / exposed	1 / 9 (11.11%)	0 / 59 (0.00%)	0 / 62 (0.00%)
occurrences (all)	1	0	0
Nail bed inflammation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Nail disorder			
subjects affected / exposed	2 / 9 (22.22%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	10	0	2
Night sweats			
subjects affected / exposed	0 / 9 (0.00%)	2 / 59 (3.39%)	0 / 62 (0.00%)
occurrences (all)	0	2	0
Onychalgia			
subjects affected / exposed	2 / 9 (22.22%)	0 / 59 (0.00%)	0 / 62 (0.00%)
occurrences (all)	7	0	0
Onychoclasia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	2 / 62 (3.23%)
occurrences (all)	0	0	2
Palmar-plantar erythrodysesthesia			

syndrome			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	4 / 62 (6.45%)
occurrences (all)	0	0	10
Photosensitivity reaction			
subjects affected / exposed	1 / 9 (11.11%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	1	1	0
Pruritus			
subjects affected / exposed	1 / 9 (11.11%)	4 / 59 (6.78%)	6 / 62 (9.68%)
occurrences (all)	1	5	6
Purpura			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	6 / 9 (66.67%)	34 / 59 (57.63%)	36 / 62 (58.06%)
occurrences (all)	14	69	69
Rash generalised			
subjects affected / exposed	2 / 9 (22.22%)	1 / 59 (1.69%)	6 / 62 (9.68%)
occurrences (all)	4	1	10
Rash maculo-papular			
subjects affected / exposed	1 / 9 (11.11%)	1 / 59 (1.69%)	4 / 62 (6.45%)
occurrences (all)	1	1	8
Rash pruritic			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Rash vesicular			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Scab			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Skin atrophy			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Skin disorder			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1

Skin exfoliation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Skin fissures			
subjects affected / exposed	3 / 9 (33.33%)	3 / 59 (5.08%)	5 / 62 (8.06%)
occurrences (all)	3	4	7
Skin lesion			
subjects affected / exposed	1 / 9 (11.11%)	1 / 59 (1.69%)	2 / 62 (3.23%)
occurrences (all)	1	1	2
Skin ulcer			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Urticaria			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	3 / 62 (4.84%)
occurrences (all)	0	6	4
Xeroderma			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	1 / 62 (1.61%)
occurrences (all)	0	1	1
Haematuria			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Nephrolithiasis			
subjects affected / exposed	0 / 9 (0.00%)	2 / 59 (3.39%)	0 / 62 (0.00%)
occurrences (all)	0	3	0
Pollakiuria			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Proteinuria			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	3 / 62 (4.84%)
occurrences (all)	0	0	7
Renal pain			

subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Urinary incontinence			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	1 / 62 (1.61%)
occurrences (all)	0	1	1
Urinary tract pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	2 / 62 (3.23%)
occurrences (all)	0	1	4
Arthritis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	1 / 62 (1.61%)
occurrences (all)	0	1	1
Back pain			
subjects affected / exposed	1 / 9 (11.11%)	3 / 59 (5.08%)	3 / 62 (4.84%)
occurrences (all)	1	5	4
Bone pain			
subjects affected / exposed	1 / 9 (11.11%)	0 / 59 (0.00%)	0 / 62 (0.00%)
occurrences (all)	1	0	0
Exostosis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Flank pain			
subjects affected / exposed	1 / 9 (11.11%)	0 / 59 (0.00%)	0 / 62 (0.00%)
occurrences (all)	1	0	0
Groin pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	2 / 62 (3.23%)
occurrences (all)	0	0	2
Intervertebral disc disorder			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Muscle spasms			

subjects affected / exposed	1 / 9 (11.11%)	1 / 59 (1.69%)	2 / 62 (3.23%)
occurrences (all)	1	1	3
Muscular weakness			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	1 / 62 (1.61%)
occurrences (all)	0	1	2
Musculoskeletal stiffness			
subjects affected / exposed	2 / 9 (22.22%)	0 / 59 (0.00%)	0 / 62 (0.00%)
occurrences (all)	2	0	0
Myalgia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Neck pain			
subjects affected / exposed	1 / 9 (11.11%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	1	0	1
Pain in extremity			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	3 / 62 (4.84%)
occurrences (all)	0	1	3
Pain in jaw			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Abscess jaw			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Abscess neck			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Acute sinusitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1

Bronchitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	3 / 62 (4.84%)
occurrences (all)	0	1	3
Candidiasis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 59 (0.00%)	0 / 62 (0.00%)
occurrences (all)	1	0	0
Cellulitis			
subjects affected / exposed	1 / 9 (11.11%)	1 / 59 (1.69%)	2 / 62 (3.23%)
occurrences (all)	1	1	2
Cystitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Device related infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 59 (0.00%)	0 / 62 (0.00%)
occurrences (all)	1	0	0
Diverticulitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Ear infection			
subjects affected / exposed	0 / 9 (0.00%)	2 / 59 (3.39%)	0 / 62 (0.00%)
occurrences (all)	0	2	0
Eye infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	2 / 62 (3.23%)
occurrences (all)	0	0	2
Folliculitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Fungal infection			
subjects affected / exposed	1 / 9 (11.11%)	1 / 59 (1.69%)	1 / 62 (1.61%)
occurrences (all)	1	1	1
Herpes simplex			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	2	0
Herpes zoster			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	1 / 62 (1.61%)
occurrences (all)	0	1	1

Hordeolum			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	0 / 9 (0.00%)	3 / 59 (5.08%)	1 / 62 (1.61%)
occurrences (all)	0	6	1
Kidney infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 59 (0.00%)	0 / 62 (0.00%)
occurrences (all)	1	0	0
Labyrinthitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Laryngitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	5
Localised infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	2	0
Nail infection			
subjects affected / exposed	2 / 9 (22.22%)	1 / 59 (1.69%)	1 / 62 (1.61%)
occurrences (all)	2	1	1
Nasopharyngitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	2 / 62 (3.23%)
occurrences (all)	0	1	2
Oral pustule			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Paronychia			
subjects affected / exposed	0 / 9 (0.00%)	5 / 59 (8.47%)	6 / 62 (9.68%)
occurrences (all)	0	9	16
Pharyngitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 59 (0.00%)	0 / 62 (0.00%)
occurrences (all)	1	0	0

Pneumonia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Pyoderma			
subjects affected / exposed	0 / 9 (0.00%)	2 / 59 (3.39%)	1 / 62 (1.61%)
occurrences (all)	0	5	1
Rash pustular			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	1 / 62 (1.61%)
occurrences (all)	0	1	1
Respiratory tract infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	2 / 62 (3.23%)
occurrences (all)	0	0	2
Respiratory tract infection viral			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	2 / 62 (3.23%)
occurrences (all)	0	1	6
Rhinitis			
subjects affected / exposed	0 / 9 (0.00%)	2 / 59 (3.39%)	0 / 62 (0.00%)
occurrences (all)	0	4	0
Sinusitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	2 / 62 (3.23%)
occurrences (all)	0	0	3
Skin infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	1 / 62 (1.61%)
occurrences (all)	0	1	2
Tooth abscess			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	2	0
Tooth infection			
subjects affected / exposed	0 / 9 (0.00%)	2 / 59 (3.39%)	0 / 62 (0.00%)
occurrences (all)	0	3	0
Tracheitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Tracheobronchitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	2 / 62 (3.23%)
occurrences (all)	0	0	3

Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 59 (0.00%) 0	3 / 62 (4.84%) 3
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	3 / 59 (5.08%) 3	1 / 62 (1.61%) 1
Viral infection subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 59 (0.00%) 0	1 / 62 (1.61%) 1
Metabolism and nutrition disorders			
Cachexia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 59 (1.69%) 1	0 / 62 (0.00%) 0
Decreased appetite subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2	7 / 59 (11.86%) 11	11 / 62 (17.74%) 14
Dehydration subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	6 / 59 (10.17%) 9	6 / 62 (9.68%) 6
Hyperglycaemia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	7 / 59 (11.86%) 9	4 / 62 (6.45%) 4
Hyperkalaemia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 59 (1.69%) 1	1 / 62 (1.61%) 1
Hyperuricaemia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 59 (0.00%) 0	1 / 62 (1.61%) 1
Hypoalbuminaemia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	2 / 59 (3.39%) 2	0 / 62 (0.00%) 0
Hypocalcaemia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	3 / 59 (5.08%) 4	0 / 62 (0.00%) 0
Hypokalaemia			

subjects affected / exposed	0 / 9 (0.00%)	5 / 59 (8.47%)	3 / 62 (4.84%)
occurrences (all)	0	6	3
Hypomagnesaemia			
subjects affected / exposed	2 / 9 (22.22%)	6 / 59 (10.17%)	6 / 62 (9.68%)
occurrences (all)	2	6	10
Hyponatraemia			
subjects affected / exposed	0 / 9 (0.00%)	2 / 59 (3.39%)	1 / 62 (1.61%)
occurrences (all)	0	2	2
Hypophosphataemia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 59 (1.69%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Hypouricaemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Polydipsia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1
Vitamin D deficiency			
subjects affected / exposed	0 / 9 (0.00%)	0 / 59 (0.00%)	1 / 62 (1.61%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 December 2009	The amendment was included to clarify the administration of ARQ 197 was changed to be with a meal. A summary of results of a food-effect study (ARQ197-A-U151) was added. Tumor re-evaluation was clarified. The schedule of events was updated to be consistent with changes made to the protocol body text. The entry for the functional assessment of cancer therapy-colorectal (FACT-C) questionnaire in the schedule of assessments was annotated to clarify the testing schedule. Population pharmacokinetic (PK) analysis was changed to population PK/pharmacodynamic analysis.
20 April 2011	The amendment was included to address changed the last possible study follow-up contact from "12 months after the end of treatment visit" to "12 months after the end of treatment visit for the last subject on the study." Number of study sites was increased from 25 to 40. Clarified inclusion criteria from "Subjects with surgically unresectable locally advanced or metastatic disease who have received one prior line of chemotherapy. (The Phase 1 portion of the study will be open for enrollment for subjects who received 1 or more prior therapies). Both relapsed and refractory Colorectal cancer (CRC) are allowed." to "Subjects with surgically unresectable locally advanced or metastatic disease who have received one prior line of chemotherapy, including irinotecan-based chemotherapy. Subjects who received only adjuvant treatment will be eligible if disease progressed less than 6 months after completion of adjuvant therapy. (The Phase 1 portion of the study will be open for enrollment for subjects who received 1 or more prior therapies). Both relapsed and refractory CRC are allowed. Subjects must have radiologically documented disease progression prior to enrollment". Clarified Exclusion Criteria from "Previous administration of ARQ 197." to "Previous administration of ARQ 197 (or other known c-MET inhibitor)". Added the PK analysis of irinotecan and SN-38.

Notes:

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.

Descriptive statistics on PK parameters were not performed. The original sample size was reduced after early termination of enrollment.

Notes: