Clinical trial results:
A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of GS-6624 Combined with FOLFIRI as Second Line Treatment for Metastatic KRAS Mutant Colorectal Adenocarcinoma that has Progressed Following a First Line Oxaliplatin- and Fluoropyrimidine-Containing Regimen

Summary

EudraCT number	2011-003754-61
Trial protocol	IT ES DE PL
Global end of trial date	27 February 2015
Results information	
Result version number	v2 (current)
This version publication date	03 April 2019
First version publication date	15 July 2016
Version creation reason	• Correction of full data set Adding 1 missing SAE and typo to a non-serious AE.

Trial information

Trial identification	
Sponsor protocol code	GS-US-295-0203
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01479465
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, CA, United States, 94404
Public contact	Clinical Trial Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com
Scientific contact	Clinical Trial Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.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	27 February 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 February 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This study was to compare the additive efficacy of simtuzumab (SIM; GS-6624) versus placebo in combination with FOLFIRI (fluorouracil, leucovorin, and irinotecan) as measured by improvement in progression-free survival (PFS) in adults with metastatic KRAS mutant colorectal adenocarcinoma who have progressed following a first line oxaliplatin- and fluoropyrimidine-containing regimen.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 December 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 17
Country: Number of subjects enrolled	Spain: 30
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	Italy: 18
Country: Number of subjects enrolled	United States: 148
Country: Number of subjects enrolled	Russian Federation: 29
Worldwide total number of subjects	266
EEA total number of subjects	89

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)	175
From 65 to 84 years	90
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in the United States, Russia, and the European Union (EU). The first participant was screened on 15 December 2011. The last study visit occurred on 27 February 2015.

Pre-assignment

Screening details:

358 participants were screened.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Blinding implementation details:

Note: Part A was open-label and nonrandomized, while Part B was randomized and double-blind.

Arms

Are arms mutually exclusive?	Yes
Arm title	SIM (Part A)

Arm description:

SIM 700 mg followed by FOLFIRI on Days 1 and 15 for one 28-day cycle

Arm type	Experimental
Investigational medicinal product name	Simtuzumab
Investigational medicinal product code	
Other name	GS-6624
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Simtuzumab 700 mg prepared by reconstituting vials of simtuzumab in sterile 0.9% sodium chloride USP solution

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

Dosage and administration details:

FOLFIRI consisted of l-leucovorin (LV) 200 mg/m^2 or dl-LV 400 mg/m^2 as a 2-hour infusion, and irinotecan 180 mg/m^2 given as a 90-minute infusion in 500 mL dextrose 5% via a Y-connector, followed by bolus fluorouracil (FU) 400 mg/m^2 and a 46-hour infusion FU 2400 mg/m^2

Arm title	SIM 200 mg (Part B)

Arm description:

SIM 200 mg followed by FOLFIRI on Days 1 and 15 of each 28-day cycle

Arm type	Experimental
Investigational medicinal product name	Simtuzumab
Investigational medicinal product code	
Other name	GS-6624
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Simtuzumab 200 mg prepared by reconstituting vials of simtuzumab and placebo in sterile 0.9% sodium chloride USP solution

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

Dosage and administration details:

FOLFIRI consisted of LV 200 mg/m^2 or dl-LV 400 mg/m^2 as a 2-hour infusion, and irinotecan 180 mg/m^2 given as a 90-minute infusion in 500 mL dextrose 5% via a Y-connector, followed by bolus FU 400 mg/m^2 and a 46-hour infusion FU 2400 mg/m^2

Arm title	SIM 700 mg (Part B)

Arm description:

SIM 700 mg followed by FOLFIRI on Days 1 and 15 of each 28-day cycle

Arm type	Experimental
Investigational medicinal product name	Simtuzumab
Investigational medicinal product code	
Other name	GS-6624
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Simtuzumab 700 mg prepared by reconstituting vials of simtuzumab in sterile 0.9% sodium chloride USP solution

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

Dosage and administration details:

FOLFIRI consisted of LV 200 mg/m^2 or dl-LV 400 mg/m^2 as a 2-hour infusion, and irinotecan 180 mg/m^2 given as a 90-minute infusion in 500 mL dextrose 5% via a Y-connector, followed by bolus FU 400 mg/m^2 and a 46-hour infusion FU 2400 mg/m^2

Arm title	Placebo (Part B)

Arm description:

Placebo followed by FOLFIRI on Days 1 and 15 of each 28-day cycle

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

Dosage and administration details:

Placebo prepared by reconstituting vials of simtuzumab placebo in sterile 0.9% sodium chloride USP solution

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

Dosage and administration details:

FOLFIRI consisted of LV 200 mg/m^2 or dl-LV 400 mg/m^2 as a 2-hour infusion, and irinotecan 180 mg/m^2 given as a 90-minute infusion in 500 mL dextrose 5% via a Y-connector, followed by bolus FU

400 mg/m^2 and a 46-hour infusion FU 2400 mg/m^2

Number of subjects in period 1[1]	SIM (Part A)	SIM 200 mg (Part B)	SIM 700 mg (Part B)
Started	11	85	84
Completed Follow-up	11	85	84
Completed	0	0	0
Not completed	11	85	84
Adverse event, serious fatal	-	2	1
Subject Withdrew Consent	-	2	1
Adverse event, non-fatal	-	4	3
Death	-	-	1
Investigator's Discretion	1	2	4
Study Discontinued by Sponsor	-	5	3
Subject Request	1	4	2
Lost to follow-up	-	1	-
Disease Progression	9	65	69

Number of subjects in period 1[1]	Placebo (Part B)
Started	80
Completed Follow-up	80
Completed	0
Not completed	80
Adverse event, serious fatal	2
Subject Withdrew Consent	4
Adverse event, non-fatal	-
Death	-
Investigator's Discretion	3
Study Discontinued by Sponsor	7
Subject Request	3
Lost to follow-up	-
Disease Progression	61

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: 6 participants who were randomized but not treated are not included in the subject disposition table.

Baseline characteristics

Reporting groups	
Reporting group title	SIM (Part A)
Reporting group description:	
SIM 700 mg followed by FOLFIRI on Days 1 and 15 for one 28-day cycle	

Reporting group title	SIM 200 mg (Part B)
Reporting group description:	
SIM 200 mg followed by FOLFIRI on Days 1 and 15 of each 28-day cycle	
Reporting group title	SIM 700 mg (Part B)
Reporting group description:	
SIM 700 mg followed by FOLFIRI on Days 1 and 15 of each 28-day cycle	

Reporting group title	Placebo (Part B)
Reporting group description:	
Placebo followed by FOLFIRI on Days 1 and 15 of each 28-day cycle	

Reporting group values	SIM (Part A)	SIM 200 mg (Part B)	SIM 700 mg (Part B)
Number of subjects	11	85	84
Age categorical Units: Subjects			
≥ 65 years	4	36	28
< 65 years	7	49	56
Age continuous Units: years			
arithmetic mean	57.3	62.6	60.1
standard deviation	± 14.09	± 11.39	± 9.76
Gender categorical Units: Subjects			
Female	6	32	48
Male	5	53	36
Race Units: Subjects			
White	8	74	71
Black or African American	2	5	7
Asian	1	5	1
Native Hawaiian or Pacific Islander	0	0	1
Not Permitted	0	1	3
Missing	0	0	1
Ethnicity Units: Subjects			
Hispanic or Latino	3	7	8
Not Hispanic or Latino	8	75	73
Not Permitted	0	3	3

Reporting group values	Placebo (Part B)	Total	
Number of subjects	80	260	

Age categorical Units: Subjects			
≥ 65 years	23	91	
< 65 years	57	169	
Age continuous Units: years			
arithmetic mean	58.8		
standard deviation	± 11.78	-	
Gender categorical Units: Subjects			
Female	41	127	
Male	39	133	
Race Units: Subjects			
White	67	220	
Black or African American	8	22	
Asian	1	8	
Native Hawaiian or Pacific Islander	1	2	
Not Permitted	3	7	
Missing	0	1	
Ethnicity Units: Subjects			
Hispanic or Latino	5	23	
Not Hispanic or Latino	70	226	
Not Permitted	5	11	

End points

End points reporting groups

Reporting group title	SIM (Part A)
Reporting group description:	
SIM 700 mg followed by FOLFIRI on Days 1 and 15 for one 28-day cycle	

Reporting group title	SIM 200 mg (Part B)
Reporting group description:	
SIM 200 mg followed by FOLFIRI on Days 1 and 15 of each 28-day cycle	

Reporting group title	SIM 700 mg (Part B)
Reporting group description:	
SIM 700 mg followed by FOLFIRI on Days 1 and 15 of each 28-day cycle	

Reporting group title	Placebo (Part B)
Reporting group description:	
Placebo followed by FOLFIRI on Days 1 and 15 of each 28-day cycle	

Primary: Progression-Free Survival

End point title	Progression-Free Survival
End point description:	
Progression-free survival (PFS) was defined as the time from the date of randomization to the earliest event time of a) death regardless of cause, or b) first indication of disease progression. PFS was analyzed using Kaplan-Meier (KM) estimates. Participants in the Full Analysis Set (participants who were randomized and received at least 1 dose of study drug) with available data were analyzed.	
End point type	Primary
End point timeframe:	
Up to 27 months	

End point values	SIM (Part A)	SIM 200 mg (Part B)	SIM 700 mg (Part B)	Placebo (Part B)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	85	84	80
Units: Months				
median (confidence interval 95%)	5.7 (1.8 to 10)	5.4 (3.4 to 5.6)	5.5 (4 to 7.1)	5.8 (4.9 to 9)

Statistical analyses

Statistical analysis title	PFS - SIM 200 mg vs Placebo
Statistical analysis description:	
The difference in PFS among the treatment groups was assessed using Kaplan-Meier methods and the stratified log-rank test, adjusted for the stratification factors.	
Comparison groups	Placebo (Part B) v SIM 200 mg (Part B)

Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0395 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	2.06

Notes:

[1] - P-value was based on a two-sided log-rank test stratified based on the 2 level Eastern Cooperative Oncology Group (ECOG) performance status (0 or > 0) at randomization.

Statistical analysis title	PFS - SIM 700 mg vs Placebo

Statistical analysis description:

The difference in PFS among the treatment groups was assessed using Kaplan-Meier methods and the stratified log-rank test, adjusted for the stratification factors.

Comparison groups	SIM 700 mg (Part B) v Placebo (Part B)
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1042 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	1.89

Notes:

[2] - P-value was based on a two-sided log-rank test stratified based on the 2 level ECOG performance status (0 or > 0) at randomization.

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survivial (OS) was defined as the time from the date of randomization to death regardless of cause. The OS was analyzed using KM estimates.

Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Up to 33 months

End point values	SIM (Part A)	SIM 200 mg (Part B)	SIM 700 mg (Part B)	Placebo (Part B)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	85	84	80
Units: months				
median (confidence interval 95%)	9.8 (3.5 to 22.3)	10.5 (9.2 to 12.6)	11.4 (9.7 to 15.6)	16.3 (12 to 19.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate

End point title	Objective Response Rate

End point description:

Objective response was assessed by the RECIST criteria (ver. 1.1) as Complete Response (CR), Partial Response (PR), Stable Disease (SD), or Progressive Disease (PD). Objective response rate (ORR) was defined as the proportion of participants who achieved a CR or PR.

Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Up to 27 months

End point values	SIM (Part A)	SIM 200 mg (Part B)	SIM 700 mg (Part B)	Placebo (Part B)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	85	84	80
Units: percentage of participants				
number (confidence interval 95%)	9.1 (0.2 to 41.3)	5.9 (1.9 to 13.2)	11.9 (5.9 to 20.8)	10 (4.4 to 18.8)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 33 months	
Adverse event reporting additional description:	
Safety Analysis Set: participants in the Full Analysis Set grouped for analyses with treatment assignments designated according to the actual study drug received.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Placebo (Part B)
Reporting group description:	
Placebo followed by FOLFIRI on Days 1 and 15 of each 28-day cycle	
Reporting group title	SIM 200 mg (Part B)
Reporting group description:	
SIM 200 mg followed by FOLFIRI on Days 1 and 15 of each 28-day cycle	
Reporting group title	SIM 700 mg (Part B)
Reporting group description:	
SIM 700 mg followed by FOLFIRI on Days 1 and 15 of each 28-day cycle	
Reporting group title	SIM (Part A)
Reporting group description:	
SIM 700 mg followed by FOLFIRI on Days 1 and 15 for one 28-day cycle	

Serious adverse events	Placebo (Part B)	SIM 200 mg (Part B)	SIM 700 mg (Part B)
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 80 (33.75%)	24 / 85 (28.24%)	17 / 84 (20.24%)
number of deaths (all causes)	3	2	2
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant ascites			
subjects affected / exposed	0 / 80 (0.00%)	1 / 85 (1.18%)	0 / 84 (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
Metastases to central nervous system			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	1 / 84 (1.19%)
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 thrombosis			

subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 80 (0.00%)	1 / 85 (1.18%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superior vena cava occlusion			
subjects affected / exposed	1 / 80 (1.25%)	0 / 85 (0.00%)	0 / 84 (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
Venous thrombosis			
subjects affected / exposed	1 / 80 (1.25%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	2 / 84 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 80 (0.00%)	1 / 85 (1.18%)	0 / 84 (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
Death			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
General physical health deterioration			
subjects affected / exposed	1 / 80 (1.25%)	0 / 85 (0.00%)	0 / 84 (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			
Hypersensitivity			
subjects affected / exposed	1 / 80 (1.25%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	4 / 80 (5.00%)	2 / 85 (2.35%)	2 / 84 (2.38%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract inflammation			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary infarction			
subjects affected / exposed	1 / 80 (1.25%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	1 / 84 (1.19%)
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			
Confusional state			

subjects affected / exposed	0 / 80 (0.00%)	1 / 85 (1.18%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	0 / 80 (0.00%)	1 / 85 (1.18%)	0 / 84 (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
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 80 (0.00%)	1 / 85 (1.18%)	0 / 84 (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
Urine output decreased			
subjects affected / exposed	0 / 80 (0.00%)	1 / 85 (1.18%)	0 / 84 (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
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 80 (0.00%)	1 / 85 (1.18%)	0 / 84 (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
Hip fracture			
subjects affected / exposed	1 / 80 (1.25%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 80 (0.00%)	1 / 85 (1.18%)	0 / 84 (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

Radius fracture			
subjects affected / exposed	1 / 80 (1.25%)	0 / 85 (0.00%)	0 / 84 (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 coronary syndrome			
subjects affected / exposed	1 / 80 (1.25%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 80 (0.00%)	1 / 85 (1.18%)	0 / 84 (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
Cardiac failure			
subjects affected / exposed	1 / 80 (1.25%)	0 / 85 (0.00%)	0 / 84 (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
Tachycardia			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	1 / 84 (1.19%)
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			
Cerebrovascular accident			
subjects affected / exposed	1 / 80 (1.25%)	0 / 85 (0.00%)	0 / 84 (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
Presyncope			
subjects affected / exposed	0 / 80 (0.00%)	1 / 85 (1.18%)	0 / 84 (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			
Febrile neutropenia			
subjects affected / exposed	2 / 80 (2.50%)	3 / 85 (3.53%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	2 / 2	1 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Neutropenia			
subjects affected / exposed	3 / 80 (3.75%)	1 / 85 (1.18%)	2 / 84 (2.38%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	0 / 80 (0.00%)	1 / 85 (1.18%)	3 / 84 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 80 (0.00%)	1 / 85 (1.18%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 80 (1.25%)	0 / 85 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	3 / 80 (3.75%)	2 / 85 (2.35%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	2 / 3	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	2 / 80 (2.50%)	0 / 85 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 80 (1.25%)	3 / 85 (3.53%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Intestinal obstruction			
subjects affected / exposed	0 / 80 (0.00%)	1 / 85 (1.18%)	2 / 84 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	2 / 80 (2.50%)	0 / 85 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction			
subjects affected / exposed	0 / 80 (0.00%)	1 / 85 (1.18%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 80 (1.25%)	1 / 85 (1.18%)	0 / 84 (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
Subileus			
subjects affected / exposed	2 / 80 (2.50%)	0 / 85 (0.00%)	0 / 84 (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
Anal fistula			
subjects affected / exposed	1 / 80 (1.25%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	1 / 80 (1.25%)	0 / 85 (0.00%)	0 / 84 (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
Intestinal perforation			
subjects affected / exposed	1 / 80 (1.25%)	0 / 85 (0.00%)	0 / 84 (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
Renal and urinary disorders			

Nephrolithiasis			
subjects affected / exposed	1 / 80 (1.25%)	0 / 85 (0.00%)	0 / 84 (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
Renal failure acute			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract disorder			
subjects affected / exposed	0 / 80 (0.00%)	1 / 85 (1.18%)	0 / 84 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 80 (1.25%)	0 / 85 (0.00%)	3 / 84 (3.57%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 80 (2.50%)	0 / 85 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 80 (1.25%)	0 / 85 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastroenteritis			
subjects affected / exposed	2 / 80 (2.50%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 80 (1.25%)	0 / 85 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 80 (0.00%)	1 / 85 (1.18%)	0 / 84 (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
Diverticulitis			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	1 / 80 (1.25%)	0 / 85 (0.00%)	0 / 84 (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
Herpes zoster			
subjects affected / exposed	0 / 80 (0.00%)	1 / 85 (1.18%)	0 / 84 (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
Influenza			
subjects affected / exposed	0 / 80 (0.00%)	1 / 85 (1.18%)	0 / 84 (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
Klebsiella infection			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			

subjects affected / exposed	0 / 80 (0.00%)	1 / 85 (1.18%)	0 / 84 (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
Pyelonephritis			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 80 (0.00%)	1 / 85 (1.18%)	0 / 84 (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
Urinary tract infection			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	1 / 84 (1.19%)
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	2 / 80 (2.50%)	1 / 85 (1.18%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 80 (0.00%)	1 / 85 (1.18%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			

subjects affected / exposed	1 / 80 (1.25%)	0 / 85 (0.00%)	0 / 84 (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
Hyponatraemia			
subjects affected / exposed	1 / 80 (1.25%)	0 / 85 (0.00%)	0 / 84 (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
Hypophosphataemia			
subjects affected / exposed	0 / 80 (0.00%)	1 / 85 (1.18%)	0 / 84 (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

Serious adverse events	SIM (Part A)		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 11 (36.36%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant ascites			
subjects affected / exposed	0 / 11 (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 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tumour thrombosis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Superior vena cava occlusion				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Venous thrombosis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Pyrexia				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Asthenia				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Hypersensitivity				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute respiratory failure			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract inflammation			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary infarction			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Delirium			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Mental status changes			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urine output decreased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Post procedural haemorrhage			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Radius fracture			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute coronary syndrome			

subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tachycardia				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebrovascular accident				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Presyncope				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Febrile neutropenia				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutropenia				

subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anaemia				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Leukopenia				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Vomiting				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				

subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large intestinal obstruction				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subileus				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anal fistula				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Enteritis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal perforation				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Nephrolithiasis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal failure acute				

subjects affected / exposed	1 / 11 (9.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal impairment				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract disorder				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Back pain				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Sepsis				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Urosepsis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bacteraemia				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis viral				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Klebsiella infection				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				

subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypokalaemia				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diabetic ketoacidosis				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Electrolyte imbalance				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoglycaemia				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				

subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypophosphataemia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo (Part B)	SIM 200 mg (Part B)	SIM 700 mg (Part B)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	76 / 80 (95.00%)	80 / 85 (94.12%)	79 / 84 (94.05%)
Vascular disorders			
Hypotension			
subjects affected / exposed	3 / 80 (3.75%)	2 / 85 (2.35%)	4 / 84 (4.76%)
occurrences (all)	3	2	5
Flushing			
subjects affected / exposed	0 / 80 (0.00%)	2 / 85 (2.35%)	0 / 84 (0.00%)
occurrences (all)	0	2	0
Peripheral coldness			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	34 / 80 (42.50%)	38 / 85 (44.71%)	43 / 84 (51.19%)
occurrences (all)	47	55	70
Asthenia			
subjects affected / exposed	12 / 80 (15.00%)	13 / 85 (15.29%)	12 / 84 (14.29%)
occurrences (all)	22	33	26
Mucosal inflammation			
subjects affected / exposed	10 / 80 (12.50%)	14 / 85 (16.47%)	7 / 84 (8.33%)
occurrences (all)	11	17	18
Pyrexia			

subjects affected / exposed	11 / 80 (13.75%)	10 / 85 (11.76%)	11 / 84 (13.10%)
occurrences (all)	21	11	17
Oedema peripheral			
subjects affected / exposed	4 / 80 (5.00%)	14 / 85 (16.47%)	10 / 84 (11.90%)
occurrences (all)	4	15	12
Chest pain			
subjects affected / exposed	3 / 80 (3.75%)	1 / 85 (1.18%)	5 / 84 (5.95%)
occurrences (all)	4	1	5
Malaise			
subjects affected / exposed	1 / 80 (1.25%)	1 / 85 (1.18%)	5 / 84 (5.95%)
occurrences (all)	1	2	5
Catheter site pain			
subjects affected / exposed	1 / 80 (1.25%)	0 / 85 (0.00%)	1 / 84 (1.19%)
occurrences (all)	1	0	1
Chest discomfort			
subjects affected / exposed	1 / 80 (1.25%)	0 / 85 (0.00%)	1 / 84 (1.19%)
occurrences (all)	1	0	1
Catheter site rash			
subjects affected / exposed	0 / 80 (0.00%)	1 / 85 (1.18%)	0 / 84 (0.00%)
occurrences (all)	0	1	0
Feeling abnormal			
subjects affected / exposed	0 / 80 (0.00%)	1 / 85 (1.18%)	0 / 84 (0.00%)
occurrences (all)	0	1	0
Axillary pain			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences (all)	0	0	0
Feeling jittery			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	10 / 80 (12.50%)	10 / 85 (11.76%)	14 / 84 (16.67%)
occurrences (all)	10	10	18
Dyspnoea			

subjects affected / exposed	10 / 80 (12.50%)	9 / 85 (10.59%)	11 / 84 (13.10%)
occurrences (all)	11	11	13
Epistaxis			
subjects affected / exposed	10 / 80 (12.50%)	5 / 85 (5.88%)	4 / 84 (4.76%)
occurrences (all)	13	5	4
Oropharyngeal pain			
subjects affected / exposed	3 / 80 (3.75%)	0 / 85 (0.00%)	8 / 84 (9.52%)
occurrences (all)	4	0	9
Rhinorrhoea			
subjects affected / exposed	2 / 80 (2.50%)	2 / 85 (2.35%)	4 / 84 (4.76%)
occurrences (all)	3	2	4
Hiccups			
subjects affected / exposed	1 / 80 (1.25%)	1 / 85 (1.18%)	1 / 84 (1.19%)
occurrences (all)	1	1	1
Dyspnoea exertional			
subjects affected / exposed	0 / 80 (0.00%)	3 / 85 (3.53%)	0 / 84 (0.00%)
occurrences (all)	0	3	0
Atelectasis			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences (all)	0	0	0
Throat tightness			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	9 / 80 (11.25%)	5 / 85 (5.88%)	8 / 84 (9.52%)
occurrences (all)	10	5	10
Anxiety			
subjects affected / exposed	5 / 80 (6.25%)	5 / 85 (5.88%)	4 / 84 (4.76%)
occurrences (all)	6	5	5
Depression			
subjects affected / exposed	2 / 80 (2.50%)	3 / 85 (3.53%)	3 / 84 (3.57%)
occurrences (all)	2	4	3
Agitation			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences (all)	0	0	0

Anger			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences (all)	0	0	0
Mood swings			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences (all)	0	0	0
Investigations			
Weight decreased			
subjects affected / exposed	7 / 80 (8.75%)	9 / 85 (10.59%)	6 / 84 (7.14%)
occurrences (all)	9	11	6
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 80 (6.25%)	6 / 85 (7.06%)	4 / 84 (4.76%)
occurrences (all)	5	6	4
Blood alkaline phosphatase increased			
subjects affected / exposed	6 / 80 (7.50%)	4 / 85 (4.71%)	4 / 84 (4.76%)
occurrences (all)	7	4	4
Alanine aminotransferase increased			
subjects affected / exposed	4 / 80 (5.00%)	4 / 85 (4.71%)	5 / 84 (5.95%)
occurrences (all)	4	4	6
Neutrophil count decreased			
subjects affected / exposed	5 / 80 (6.25%)	3 / 85 (3.53%)	3 / 84 (3.57%)
occurrences (all)	6	3	4
International normalised ratio increased			
subjects affected / exposed	2 / 80 (2.50%)	2 / 85 (2.35%)	1 / 84 (1.19%)
occurrences (all)	3	5	1
White blood cell count increased			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences (all)	0	0	0
Atrial fibrillation			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences (all)	0	0	0
Cardiac failure congestive			

subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences (all)	0	0	0
Palpitations			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	7 / 80 (8.75%)	9 / 85 (10.59%)	13 / 84 (15.48%)
occurrences (all)	9	11	20
Dysgeusia			
subjects affected / exposed	6 / 80 (7.50%)	6 / 85 (7.06%)	8 / 84 (9.52%)
occurrences (all)	6	7	9
Neuropathy peripheral			
subjects affected / exposed	5 / 80 (6.25%)	7 / 85 (8.24%)	7 / 84 (8.33%)
occurrences (all)	5	7	7
Headache			
subjects affected / exposed	4 / 80 (5.00%)	3 / 85 (3.53%)	6 / 84 (7.14%)
occurrences (all)	4	4	8
Peripheral sensory neuropathy			
subjects affected / exposed	4 / 80 (5.00%)	2 / 85 (2.35%)	3 / 84 (3.57%)
occurrences (all)	4	2	3
Parosmia			
subjects affected / exposed	1 / 80 (1.25%)	1 / 85 (1.18%)	0 / 84 (0.00%)
occurrences (all)	1	1	0
Dizziness postural			
subjects affected / exposed	1 / 80 (1.25%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences (all)	1	0	0
VIIth nerve paralysis			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	35 / 80 (43.75%)	42 / 85 (49.41%)	40 / 84 (47.62%)
occurrences (all)	81	77	91
Anaemia			

subjects affected / exposed	19 / 80 (23.75%)	23 / 85 (27.06%)	18 / 84 (21.43%)
occurrences (all)	30	27	34
Leukopenia			
subjects affected / exposed	9 / 80 (11.25%)	13 / 85 (15.29%)	13 / 84 (15.48%)
occurrences (all)	35	24	43
Thrombocytopenia			
subjects affected / exposed	6 / 80 (7.50%)	10 / 85 (11.76%)	11 / 84 (13.10%)
occurrences (all)	12	13	16
Eye disorders			
Ocular hyperaemia			
subjects affected / exposed	0 / 80 (0.00%)	1 / 85 (1.18%)	0 / 84 (0.00%)
occurrences (all)	0	1	0
Eye pain			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	43 / 80 (53.75%)	36 / 85 (42.35%)	42 / 84 (50.00%)
occurrences (all)	93	58	92
Nausea			
subjects affected / exposed	37 / 80 (46.25%)	38 / 85 (44.71%)	42 / 84 (50.00%)
occurrences (all)	93	60	100
Vomiting			
subjects affected / exposed	25 / 80 (31.25%)	21 / 85 (24.71%)	23 / 84 (27.38%)
occurrences (all)	50	30	37
Abdominal pain			
subjects affected / exposed	18 / 80 (22.50%)	16 / 85 (18.82%)	22 / 84 (26.19%)
occurrences (all)	31	21	28
Constipation			
subjects affected / exposed	17 / 80 (21.25%)	18 / 85 (21.18%)	21 / 84 (25.00%)
occurrences (all)	23	23	37
Stomatitis			
subjects affected / exposed	17 / 80 (21.25%)	14 / 85 (16.47%)	9 / 84 (10.71%)
occurrences (all)	58	19	17
Abdominal pain upper			

subjects affected / exposed	6 / 80 (7.50%)	8 / 85 (9.41%)	6 / 84 (7.14%)
occurrences (all)	7	8	6
Dyspepsia			
subjects affected / exposed	7 / 80 (8.75%)	4 / 85 (4.71%)	4 / 84 (4.76%)
occurrences (all)	9	6	4
Dry mouth			
subjects affected / exposed	7 / 80 (8.75%)	2 / 85 (2.35%)	3 / 84 (3.57%)
occurrences (all)	7	3	3
Abdominal distension			
subjects affected / exposed	4 / 80 (5.00%)	2 / 85 (2.35%)	1 / 84 (1.19%)
occurrences (all)	4	2	1
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 80 (3.75%)	3 / 85 (3.53%)	1 / 84 (1.19%)
occurrences (all)	3	3	1
Abdominal pain lower			
subjects affected / exposed	5 / 80 (6.25%)	0 / 85 (0.00%)	2 / 84 (2.38%)
occurrences (all)	6	0	2
Dysphagia			
subjects affected / exposed	4 / 80 (5.00%)	0 / 85 (0.00%)	1 / 84 (1.19%)
occurrences (all)	4	0	1
Oral pain			
subjects affected / exposed	2 / 80 (2.50%)	3 / 85 (3.53%)	1 / 84 (1.19%)
occurrences (all)	2	5	1
Abdominal discomfort			
subjects affected / exposed	2 / 80 (2.50%)	2 / 85 (2.35%)	0 / 84 (0.00%)
occurrences (all)	2	2	0
Haematochezia			
subjects affected / exposed	2 / 80 (2.50%)	1 / 85 (1.18%)	0 / 84 (0.00%)
occurrences (all)	2	1	0
Salivary hypersecretion			
subjects affected / exposed	1 / 80 (1.25%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences (all)	1	0	0
Oral mucosal erythema			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	21 / 80 (26.25%)	20 / 85 (23.53%)	22 / 84 (26.19%)
occurrences (all)	21	20	22
Dry skin			
subjects affected / exposed	5 / 80 (6.25%)	2 / 85 (2.35%)	5 / 84 (5.95%)
occurrences (all)	5	4	6
Rash			
subjects affected / exposed	3 / 80 (3.75%)	4 / 85 (4.71%)	3 / 84 (3.57%)
occurrences (all)	13	7	3
Hyperhidrosis			
subjects affected / exposed	3 / 80 (3.75%)	2 / 85 (2.35%)	3 / 84 (3.57%)
occurrences (all)	3	2	4
Night sweats			
subjects affected / exposed	4 / 80 (5.00%)	1 / 85 (1.18%)	3 / 84 (3.57%)
occurrences (all)	4	1	3
Skin hyperpigmentation			
subjects affected / exposed	1 / 80 (1.25%)	2 / 85 (2.35%)	2 / 84 (2.38%)
occurrences (all)	1	2	3
Swelling face			
subjects affected / exposed	1 / 80 (1.25%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences (all)	1	0	0
Skin disorder			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences (all)	0	0	0
Skin wrinkling			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	5 / 80 (6.25%)	3 / 85 (3.53%)	0 / 84 (0.00%)
occurrences (all)	7	3	0
Micturition urgency			
subjects affected / exposed	1 / 80 (1.25%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences (all)	1	0	0
Nocturia			

subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	6 / 80 (7.50%)	9 / 85 (10.59%)	9 / 84 (10.71%)
occurrences (all)	6	10	11
Arthralgia			
subjects affected / exposed	4 / 80 (5.00%)	4 / 85 (4.71%)	5 / 84 (5.95%)
occurrences (all)	4	5	5
Muscle spasms			
subjects affected / exposed	5 / 80 (6.25%)	0 / 85 (0.00%)	5 / 84 (5.95%)
occurrences (all)	7	0	8
Pain in extremity			
subjects affected / exposed	3 / 80 (3.75%)	1 / 85 (1.18%)	6 / 84 (7.14%)
occurrences (all)	5	1	7
Musculoskeletal pain			
subjects affected / exposed	3 / 80 (3.75%)	1 / 85 (1.18%)	5 / 84 (5.95%)
occurrences (all)	8	1	5
Bone pain			
subjects affected / exposed	2 / 80 (2.50%)	0 / 85 (0.00%)	2 / 84 (2.38%)
occurrences (all)	2	0	3
Muscular weakness			
subjects affected / exposed	0 / 80 (0.00%)	2 / 85 (2.35%)	0 / 84 (0.00%)
occurrences (all)	0	2	0
Muscle atrophy			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences (all)	0	0	0
Muscle tightness			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	6 / 80 (7.50%)	5 / 85 (5.88%)	9 / 84 (10.71%)
occurrences (all)	8	7	9
Upper respiratory tract infection			

subjects affected / exposed	5 / 80 (6.25%)	4 / 85 (4.71%)	2 / 84 (2.38%)
occurrences (all)	5	4	2
Nasopharyngitis			
subjects affected / exposed	1 / 80 (1.25%)	2 / 85 (2.35%)	2 / 84 (2.38%)
occurrences (all)	1	2	2
Pneumonia			
subjects affected / exposed	2 / 80 (2.50%)	2 / 85 (2.35%)	0 / 84 (0.00%)
occurrences (all)	2	2	0
Respiratory tract infection			
subjects affected / exposed	1 / 80 (1.25%)	1 / 85 (1.18%)	0 / 84 (0.00%)
occurrences (all)	1	1	0
Infection			
subjects affected / exposed	1 / 80 (1.25%)	0 / 85 (0.00%)	0 / 84 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	22 / 80 (27.50%)	14 / 85 (16.47%)	21 / 84 (25.00%)
occurrences (all)	29	17	35
Hypokalaemia			
subjects affected / exposed	8 / 80 (10.00%)	8 / 85 (9.41%)	10 / 84 (11.90%)
occurrences (all)	11	11	13
Dehydration			
subjects affected / exposed	4 / 80 (5.00%)	5 / 85 (5.88%)	6 / 84 (7.14%)
occurrences (all)	5	6	7
Hyperglycaemia			
subjects affected / exposed	2 / 80 (2.50%)	4 / 85 (4.71%)	3 / 84 (3.57%)
occurrences (all)	2	4	5
Hypomagnesaemia			
subjects affected / exposed	5 / 80 (6.25%)	2 / 85 (2.35%)	3 / 84 (3.57%)
occurrences (all)	8	2	7
Hypophosphataemia			
subjects affected / exposed	1 / 80 (1.25%)	2 / 85 (2.35%)	2 / 84 (2.38%)
occurrences (all)	1	2	2
Hypoalbuminaemia			
subjects affected / exposed	0 / 80 (0.00%)	1 / 85 (1.18%)	1 / 84 (1.19%)
occurrences (all)	0	1	1

Hypocalcaemia			
subjects affected / exposed	0 / 80 (0.00%)	0 / 85 (0.00%)	2 / 84 (2.38%)
occurrences (all)	0	0	2

Non-serious adverse events	SIM (Part A)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 11 (100.00%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Flushing			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Peripheral coldness			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	9 / 11 (81.82%)		
occurrences (all)	19		
Asthenia			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Mucosal inflammation			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	5		
Pyrexia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Chest pain			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Malaise			

subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Catheter site pain			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Chest discomfort			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Catheter site rash			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Feeling abnormal			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Axillary pain			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Feeling jittery			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Rhinorrhoea			

subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Hiccups			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Dyspnoea exertional			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Atelectasis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Throat tightness			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	5 / 11 (45.45%)		
occurrences (all)	6		
Anxiety			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	3		
Depression			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Agitation			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Anger			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Mood swings			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Investigations			
Weight decreased			

subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Alanine aminotransferase increased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Neutrophil count decreased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
International normalised ratio increased			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
White blood cell count increased			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Atrial fibrillation			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Cardiac failure congestive			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Palpitations			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Nervous system disorders			

Dizziness subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1			
Dysgeusia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 2			
Neuropathy peripheral subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 2			
Headache subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1			
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 3			
Parosmia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1			
Dizziness postural subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1			
VIIth nerve paralysis subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1			
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all)	6 / 11 (54.55%) 14			
Anaemia subjects affected / exposed occurrences (all)	3 / 11 (27.27%) 4			
Leukopenia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 5			
Thrombocytopenia				

subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Eye disorders			
Ocular hyperaemia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Eye pain			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	9 / 11 (81.82%)		
occurrences (all)	15		
Nausea			
subjects affected / exposed	9 / 11 (81.82%)		
occurrences (all)	17		
Vomiting			
subjects affected / exposed	5 / 11 (45.45%)		
occurrences (all)	12		
Abdominal pain			
subjects affected / exposed	4 / 11 (36.36%)		
occurrences (all)	7		
Constipation			
subjects affected / exposed	4 / 11 (36.36%)		
occurrences (all)	5		
Stomatitis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Abdominal pain upper			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	3		
Dyspepsia			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	3		
Dry mouth			

subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Abdominal distension			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	3		
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Abdominal pain lower			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Dysphagia			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Oral pain			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Abdominal discomfort			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Haematochezia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Salivary hypersecretion			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Oral mucosal erythema			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	6 / 11 (54.55%)		
occurrences (all)	6		
Dry skin			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		

Rash			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Hyperhidrosis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Night sweats			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Skin hyperpigmentation			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Swelling face			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Skin disorder			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Skin wrinkling			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Micturition urgency			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Nocturia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	3		
Arthralgia			

subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Musculoskeletal pain			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Bone pain			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Muscular weakness			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Muscle atrophy			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Muscle tightness			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		

Respiratory tract infection			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Infection			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 11 (45.45%)		
occurrences (all)	7		
Hypokalaemia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Dehydration			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	3		
Hyperglycaemia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Hypomagnesaemia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Hypophosphataemia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Hypoalbuminaemia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Hypocalcaemia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 September 2011	The protocol was revised to provide specific guidance on dose modification for study drug and FOLFIRI.
07 November 2011	The protocol was revised to exclude subjects with metastatic BRAF mutant colorectal adenocarcinoma, to further clarify the dose modification for FOLFIRI, to specify enrolled subjects must have experienced radiographic disease progression following first line therapy, and to clarify that prior irinotecan therapy for metastatic disease was not permitted, but prior adjuvant therapy with irinotecan was allowed.
08 March 2012	The protocol was revised in response to questions received during the European Voluntary Harmonization Procedure assessment (to specify that the KRAS mutated, histologically confirmed adenocarcinoma of the colon or rectum was not to be amenable to complete surgical resection, to specify that the subject must have received first-line combination therapy containing oxaliplatin and a fluoropyrimidine with or without bevacizumab for metastatic disease, to specify that the subject must not be a candidate for further oxaliplatin, to clarify cardiac conditions and define hypertension parameters that would exclude subjects from the study, to describe emergency unblinding procedures, and to add an interim analysis.
05 September 2012	The protocol was revised to include analyses for systemic biomarkers related to complete response (CR) pathophysiology or GS-6624 mechanism of action such as circulating LOXL2 and TIMP-1 levels and to clarify inclusion/exclusion criteria.
20 March 2014	The protocol was revised to change the assessment of progressive disease for PFS from Independent Radiology Review to determination by Principal Investigator, to remove the interim analysis, and to indicate that Gilead would assess the continuation of the development of SIM in colorectal cancer if the primary objective of the study was not met and could decide to prematurely discontinue the study.

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.

There were no limitations affecting the analysis or results.

Notes: