Clinical trial results:
A Phase 2 Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Efficacy and Safety of GS-6624 Combined with Gemcitabine as First Line Treatment for Metastatic Pancreatic Adenocarcinoma

Summary

EudraCT number	2011-003753-26
Trial protocol	DE PL
Global end of trial date	28 January 2015

Results information

Result version number	v1 (current)
This version publication date	14 August 2016
First version publication date	14 August 2016

Trial information

Trial identification

Sponsor protocol code	GS-US-324-0101

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01472198
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	28 January 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare the additive efficacy of simtuzumab (SIM; GS-6624) versus placebo combined with gemcitabine as measured by improvement in progression-free survival (PFS) in adults with metastatic pancreatic adenocarcinoma.

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:

All participants received gemcitabine as background therapy.

Evidence for comparator: -

Actual start date of recruitment	22 November 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	Russian Federation: 83
Country: Number of subjects enrolled	United States: 167
Worldwide total number of subjects	250
EEA total number of subjects	0

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)	141
From 65 to 84 years	106
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in the United States and Russia. The first participant was screened on 22 November 2011. The last study visit occurred on 28 January 2015.

Pre-assignment

Screening details:

343 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	Subject, Investigator

Blinding implementation details:

Part A: open-label and non-randomized; Part B: double-blind and randomized.

Arms

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

Arm description:

Simtuzumab (SIM) 700 mg on Days 1 and 15 followed by gemcitabine on Days 1, 8, 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	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine administered at a dose of 1000 mg/m^2 over approximately 30 minutes

Arm title	SIM 200 mg (Part B)

Arm description:

SIM 200 mg on Days 1 and 15 followed by gemcitabine on Days 1, 8, 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	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine administered at a dose of 1000 mg/m^2 over approximately 30 minutes

Arm title	SIM 700 mg (Part B)

Arm description:

SIM 700 mg on Days 1 and 15 followed by gemcitabine on Days 1, 8, 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	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine administered at a dose of 1000 mg/m^2 over approximately 30 minutes

Arm title	Placebo (Part B)

Arm description:

Placebo on Days 1 and 15 followed by gemcitabine on Days 1, 8, and 15 of each 28-day cycle

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

Dosage and administration details:

Gemcitabine administered at a dose of 1000 mg/m^2 over approximately 30 minutes

Number of subjects in period 1[1]	SIM (Part A)	SIM 200 mg (Part B)	SIM 700 mg (Part B)
Started	10	76	79
Completed Follow-up	10	76	79
Completed	0	0	0
Not completed	10	76	79
Adverse event, serious fatal	1	3	4
Subject Withdrew Consent	1	5	9
Adverse event, non-fatal	-	4	3
Death	-	-	1
Investigator's Discretion	-	3	2
Study Discontinued by Sponsor	-	-	1
Lost to follow-up	-	-	1
Disease Progression	8	61	58

Number of subjects in period 1[1]	Placebo (Part B)
Started	81
Completed Follow-up	81
Completed	0
Not completed	81
Adverse event, serious fatal	4
Subject Withdrew Consent	7
Adverse event, non-fatal	6
Death	-
Investigator's Discretion	4
Study Discontinued by Sponsor	6
Lost to follow-up	-
Disease Progression	54

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: 4 participants who were randomized but not treated (2 withdrew consent, 1 discontinued due to physician decision, and 1 discontinued due to progressive disease) are not included in the subject disposition table.

Baseline characteristics

Reporting groups	
Reporting group title	SIM (Part A)
Reporting group description:	
Simtuzumab (SIM) 700 mg on Days 1 and 15 followed by gemcitabine on Days 1, 8, and 15 for one 28-day cycle	

Reporting group title	SIM 200 mg (Part B)
Reporting group description:	
SIM 200 mg on Days 1 and 15 followed by gemcitabine on Days 1, 8, and 15 of each 28-day cycle	

Reporting group title	SIM 700 mg (Part B)
Reporting group description:	
SIM 700 mg on Days 1 and 15 followed by gemcitabine on Days 1, 8, and 15 of each 28-day cycle	
Reporting group title	Placebo (Part B)
Reporting group description:	
Placebo on Days 1 and 15 followed by gemcitabine on Days 1, 8, 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	10	76	79
Age categorical Units: Subjects			
≥ 65 years	4	36	33
< 65 years	6	40	46
Age continuous Units: years			
arithmetic mean	62.2	63	63.1
standard deviation	± 7.71	± 10.11	± 11.04
Gender categorical Units: Subjects			
Female	6	34	30
Male	4	42	49
Race Units: Subjects			
White	9	68	66
Black or African Heritage	0	5	11
Asian	0	2	1
Native Hawaiian or Pacific Islander	0	1	0
Not Permitted	0	0	1
Other	1	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	3	2	4
Not Hispanic or Latino	7	70	74
Not Permitted	0	4	1

Reporting group values	Placebo (Part B)	Total	
Number of subjects	81	246	
Age categorical Units: Subjects			
≥ 65 years	34	107	
< 65 years	47	139	
Age continuous Units: years			
arithmetic mean	64.6		
standard deviation	± 9.53	-	
Gender categorical Units: Subjects			
Female	34	104	
Male	47	142	
Race Units: Subjects			
White	78	221	
Black or African Heritage	2	18	
Asian	1	4	
Native Hawaiian or Pacific Islander	0	1	
Not Permitted	0	1	
Other	0	1	
Ethnicity Units: Subjects			
Hispanic or Latino	2	11	
Not Hispanic or Latino	77	228	
Not Permitted	2	7	

End points

End points reporting groups

Reporting group title	SIM (Part A)
Reporting group description:	
Simtuzumab (SIM) 700 mg on Days 1 and 15 followed by gemcitabine on Days 1, 8, and 15 for one 28-day cycle	

Reporting group title	SIM 200 mg (Part B)
Reporting group description:	
SIM 200 mg on Days 1 and 15 followed by gemcitabine on Days 1, 8, and 15 of each 28-day cycle	

Reporting group title	SIM 700 mg (Part B)
Reporting group description:	
SIM 700 mg on Days 1 and 15 followed by gemcitabine on Days 1, 8, and 15 of each 28-day cycle	
Reporting group title	Placebo (Part B)
Reporting group description:	
Placebo on Days 1 and 15 followed by gemcitabine on Days 1, 8, 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. Full Analysis Set (participants who were randomized and received at least 1 dose of any study drug (SIM or placebo)) with available data were analyzed.	
End point type	Primary
End point timeframe:	
Up to 15 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	10	76	79	81
Units: Months				
median (confidence interval 95%)	4.3 (2.4 to 5.4)	3.5 (1.9 to 5.3)	3.7 (3.4 to 5.4)	3.7 (3.3 to 4.2)

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	SIM 200 mg (Part B) v Placebo (Part B)
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6148 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.66

Notes:

[1] - P-value was based on a two-sided log-rank test stratified based on the ECOG performance status and prior therapy of the pancreatic primary tumor 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	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7312 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.61

Notes:

[2] - P-value was based on a two-sided log-rank test stratified based on the ECOG performance status and prior therapy of the pancreatic primary tumor 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.

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

999 = NA; not reached.

End point type	Secondary

End point timeframe:

Up to 18 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	10	76	79	81
Units: months				
median (confidence interval 95%)	4.3 (2.4 to 999)	5.9 (4.6 to 7.3)	7.6 (6 to 9)	5.7 (4.1 to 7.3)

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 achieve a CR or PR.

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

End point type	Secondary

End point timeframe:

Up to 15 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	10	76	79	81
Units: percentage of participants				
number (confidence interval 95%)	20 (2.5 to 55.6)	14.5 (7.5 to 24.4)	13.9 (7.2 to 23.5)	23.5 (14.8 to 34.2)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 18 months

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	SIM (Part A)

Reporting group description:

Simtuzumab (SIM) 700 mg on Days 1 and 15 followed by gemcitabine on Days 1, 8, and 15 for one 28-day cycle

Reporting group title	SIM 200 mg (Part B)

Reporting group description:

SIM 200 mg on Days 1 and 15 followed by gemcitabine on Days 1, 8, and 15 of each 28-day cycle

Reporting group title	SIM 700 mg (Part B)

Reporting group description:

SIM 700 mg on Days 1 and 15 followed by gemcitabine on Days 1, 8, and 15 of each 28-day cycle

Reporting group title	Placebo (Part B)

Reporting group description:

Placebo on Days 1 and 15 followed by gemcitabine on Days 1, 8, and 15 of each 28-day cycle

Serious adverse events	SIM (Part A)	SIM 200 mg (Part B)	SIM 700 mg (Part B)
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 10 (80.00%)	27 / 76 (35.53%)	24 / 79 (30.38%)
number of deaths (all causes)	1	3	4
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatobiliary cancer			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	0 / 79 (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 / 10 (0.00%)	3 / 76 (3.95%)	2 / 79 (2.53%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	0 / 79 (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
Hypertension			
subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	0 / 79 (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
Hypertensive crisis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 76 (0.00%)	0 / 79 (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
Thrombophlebitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 10 (10.00%)	3 / 76 (3.95%)	2 / 79 (2.53%)
occurrences causally related to treatment / all	1 / 1	2 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 76 (1.32%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			

subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device dislocation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device failure			
subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device occlusion			
subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	0 / 79 (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
Generalised oedema			
subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	0 / 79 (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
Pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 76 (0.00%)	0 / 79 (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	1 / 10 (10.00%)	2 / 76 (2.63%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 10 (0.00%)	2 / 76 (2.63%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			

subjects affected / exposed	2 / 10 (20.00%)	1 / 76 (1.32%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	0 / 79 (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
Acute respiratory failure			
subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	0 / 79 (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
Hypoxia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	0 / 79 (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
Pulmonary artery thrombosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 10 (10.00%)	0 / 76 (0.00%)	2 / 79 (2.53%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			

subjects affected / exposed	1 / 10 (10.00%)	0 / 76 (0.00%)	0 / 79 (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
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	0 / 79 (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
International normalised ratio increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Febrile nonhaemolytic transfusion reaction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative stitch sinus			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			

subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Acute myocardial infarction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	2 / 79 (2.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure congestive			
subjects affected / exposed	1 / 10 (10.00%)	0 / 76 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	0 / 79 (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
Cardio-respiratory arrest			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Myocardial infarction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	0 / 79 (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
Tricuspid valve incompetence			

subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	0 / 79 (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			
Altered state of consciousness			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Convulsion			
subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic encephalopathy			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 10 (0.00%)	6 / 76 (7.89%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	1 / 7	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	0 / 79 (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
Thrombocytopenia			

subjects affected / exposed	0 / 10 (0.00%)	3 / 76 (3.95%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 10 (0.00%)	2 / 76 (2.63%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bandaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heparin-induced thrombocytopenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukocytosis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	0 / 79 (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
Splenic vein occlusion			
subjects affected / exposed	1 / 10 (10.00%)	0 / 76 (0.00%)	0 / 79 (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
Thrombocytosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 10 (10.00%)	2 / 76 (2.63%)	2 / 79 (2.53%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	2 / 10 (20.00%)	1 / 76 (1.32%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	3 / 10 (30.00%)	1 / 76 (1.32%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 10 (10.00%)	0 / 76 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Ascites			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Abdominal pain upper			
subjects affected / exposed	1 / 10 (10.00%)	0 / 76 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal wall haematoma			

subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal			
subjects affected / exposed	1 / 10 (10.00%)	0 / 76 (0.00%)	0 / 79 (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
Duodenal obstruction			
subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	0 / 79 (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
Duodenal ulcer			
subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	0 / 79 (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
Enteritis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal obstruction			
subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	0 / 79 (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
Haemorrhoids thrombosed			

subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstruction gastric			
subjects affected / exposed	1 / 10 (10.00%)	0 / 76 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic cyst rupture			
subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	0 / 79 (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
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice cholestatic			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute hepatic failure			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Bile duct obstruction			

subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 10 (0.00%)	2 / 76 (2.63%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 76 (0.00%)	0 / 79 (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

Muscular weakness			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 76 (0.00%)	0 / 79 (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
Osteoarthritis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 10 (20.00%)	3 / 76 (3.95%)	3 / 79 (3.80%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	2 / 10 (20.00%)	0 / 76 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 76 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 10 (10.00%)	1 / 76 (1.32%)	0 / 79 (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
Peritonitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			

subjects affected / exposed	0 / 10 (0.00%)	2 / 76 (2.63%)	0 / 79 (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
Appendicitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 76 (0.00%)	0 / 79 (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
Device related infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 76 (0.00%)	0 / 79 (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
Device related sepsis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	0 / 79 (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
Escherichia bacteraemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella sepsis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	0 / 79 (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
Liver abscess			
subjects affected / exposed	1 / 10 (10.00%)	0 / 76 (0.00%)	0 / 79 (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
Oral candidiasis			

subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	0 / 79 (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
Urosepsis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	0 / 79 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 10 (20.00%)	1 / 76 (1.32%)	2 / 79 (2.53%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	2 / 79 (2.53%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 76 (0.00%)	0 / 79 (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
Hypovolaemia			

subjects affected / exposed	1 / 10 (10.00%)	0 / 76 (0.00%)	0 / 79 (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
Metabolic acidosis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 76 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo (Part B)		
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 81 (43.21%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatobiliary cancer			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour pain			
subjects affected / exposed	0 / 81 (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	3 / 81 (3.70%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	2 / 81 (2.47%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypertension			

subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypertensive crisis				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thrombophlebitis				
subjects affected / exposed	0 / 81 (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	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Asthenia				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				
subjects affected / exposed	2 / 81 (2.47%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device dislocation				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device failure				

subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device occlusion				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Generalised oedema				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	0 / 81 (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	5 / 81 (6.17%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 1			
Dyspnoea				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute respiratory failure				

subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary artery thrombosis				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Respiratory failure				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Mental status changes				
subjects affected / exposed	2 / 81 (2.47%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Confusional state				
subjects affected / exposed	2 / 81 (2.47%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Anxiety				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Blood bilirubin increased				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
International normalised ratio				

increased				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transaminases increased				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
White blood cell count increased				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Febrile nonhaemolytic transfusion reaction				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Postoperative stitch sinus				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute coronary syndrome				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				

subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bradycardia				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardio-respiratory arrest				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tachycardia				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tricuspid valve incompetence				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Altered state of consciousness				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				

subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Convulsion				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic encephalopathy				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	2 / 81 (2.47%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	3 / 81 (3.70%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Leukopenia				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bandaemia				

subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Heparin-induced thrombocytopenia				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Leukocytosis				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Splenic vein occlusion				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thrombocytosis				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	4 / 81 (4.94%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	3 / 81 (3.70%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				

subjects affected / exposed	2 / 81 (2.47%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	2 / 81 (2.47%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal wall haematoma				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulum intestinal				

subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Duodenal obstruction				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Duodenal ulcer				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Enteritis				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal obstruction				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhoids thrombosed				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Obstruction gastric				

subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatic cyst rupture				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Jaundice				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Jaundice cholestatic				
subjects affected / exposed	2 / 81 (2.47%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Acute hepatic failure				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bile duct obstruction				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholangitis				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				

subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperbilirubinaemia				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Rash				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Renal failure				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal failure acute				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Arthralgia				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Muscular weakness				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myalgia				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Osteoarthritis				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Pneumonia				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	2 / 81 (2.47%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Cellulitis				
subjects affected / exposed	2 / 81 (2.47%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bacteraemia				

subjects affected / exposed	0 / 81 (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 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device related sepsis				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Escherichia bacteraemia				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Klebsiella sepsis				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Liver abscess				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oral candidiasis				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal infection				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urosepsis				

subjects affected / exposed	0 / 81 (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	7 / 81 (8.64%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malnutrition			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Decreased appetite			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypovolaemia			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolic acidosis			
subjects affected / exposed	0 / 81 (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	SIM (Part A)	SIM 200 mg (Part B)	SIM 700 mg (Part B)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	71 / 76 (93.42%)	72 / 79 (91.14%)
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 10 (0.00%)	7 / 76 (9.21%)	2 / 79 (2.53%)
occurrences (all)	0	7	3
Deep vein thrombosis			
subjects affected / exposed	0 / 10 (0.00%)	5 / 76 (6.58%)	1 / 79 (1.27%)
occurrences (all)	0	5	1
Hot flush			
subjects affected / exposed	0 / 10 (0.00%)	4 / 76 (5.26%)	0 / 79 (0.00%)
occurrences (all)	0	4	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 10 (50.00%)	35 / 76 (46.05%)	33 / 79 (41.77%)
occurrences (all)	7	41	39
Oedema peripheral			
subjects affected / exposed	1 / 10 (10.00%)	20 / 76 (26.32%)	18 / 79 (22.78%)
occurrences (all)	1	26	25
Pyrexia			
subjects affected / exposed	5 / 10 (50.00%)	13 / 76 (17.11%)	21 / 79 (26.58%)
occurrences (all)	9	23	35
Asthenia			
subjects affected / exposed	2 / 10 (20.00%)	10 / 76 (13.16%)	5 / 79 (6.33%)
occurrences (all)	2	10	17
Chills			
subjects affected / exposed	0 / 10 (0.00%)	4 / 76 (5.26%)	6 / 79 (7.59%)
occurrences (all)	0	4	7
Malaise			
subjects affected / exposed	3 / 10 (30.00%)	3 / 76 (3.95%)	2 / 79 (2.53%)
occurrences (all)	3	3	2
Peripheral swelling			

subjects affected / exposed	1 / 10 (10.00%)	2 / 76 (2.63%)	6 / 79 (7.59%)
occurrences (all)	2	2	7
Influenza like illness			
subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	6 / 79 (7.59%)
occurrences (all)	0	1	7
Pain			
subjects affected / exposed	1 / 10 (10.00%)	1 / 76 (1.32%)	1 / 79 (1.27%)
occurrences (all)	2	1	1
Thrombosis in device			
subjects affected / exposed	1 / 10 (10.00%)	0 / 76 (0.00%)	1 / 79 (1.27%)
occurrences (all)	1	0	1
Reproductive system and breast disorders			
Scrotal swelling			
subjects affected / exposed	1 / 10 (10.00%)	0 / 76 (0.00%)	0 / 79 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 10 (30.00%)	15 / 76 (19.74%)	9 / 79 (11.39%)
occurrences (all)	5	16	12
Pleural effusion			
subjects affected / exposed	1 / 10 (10.00%)	1 / 76 (1.32%)	2 / 79 (2.53%)
occurrences (all)	1	1	2
Cough			
subjects affected / exposed	0 / 10 (0.00%)	4 / 76 (5.26%)	6 / 79 (7.59%)
occurrences (all)	0	4	6
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 10 (10.00%)	8 / 76 (10.53%)	6 / 79 (7.59%)
occurrences (all)	1	8	6
Anxiety			
subjects affected / exposed	1 / 10 (10.00%)	5 / 76 (6.58%)	6 / 79 (7.59%)
occurrences (all)	1	5	6
Depression			
subjects affected / exposed	0 / 10 (0.00%)	5 / 76 (6.58%)	4 / 79 (5.06%)
occurrences (all)	0	5	4
Agitation			

subjects affected / exposed	1 / 10 (10.00%)	0 / 76 (0.00%)	1 / 79 (1.27%)
occurrences (all)	1	0	1
Investigations			
Platelet count decreased			
subjects affected / exposed	1 / 10 (10.00%)	14 / 76 (18.42%)	9 / 79 (11.39%)
occurrences (all)	2	27	24
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 10 (10.00%)	16 / 76 (21.05%)	12 / 79 (15.19%)
occurrences (all)	1	23	15
Alanine aminotransferase increased			
subjects affected / exposed	1 / 10 (10.00%)	15 / 76 (19.74%)	11 / 79 (13.92%)
occurrences (all)	1	19	13
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 10 (10.00%)	10 / 76 (13.16%)	10 / 79 (12.66%)
occurrences (all)	1	11	14
Weight decreased			
subjects affected / exposed	4 / 10 (40.00%)	5 / 76 (6.58%)	7 / 79 (8.86%)
occurrences (all)	4	6	7
Neutrophil count decreased			
subjects affected / exposed	0 / 10 (0.00%)	8 / 76 (10.53%)	5 / 79 (6.33%)
occurrences (all)	0	11	6
Blood bilirubin increased			
subjects affected / exposed	1 / 10 (10.00%)	5 / 76 (6.58%)	4 / 79 (5.06%)
occurrences (all)	1	6	6
White blood cell count decreased			
subjects affected / exposed	1 / 10 (10.00%)	5 / 76 (6.58%)	3 / 79 (3.80%)
occurrences (all)	1	13	3
Blood creatinine increased			
subjects affected / exposed	0 / 10 (0.00%)	8 / 76 (10.53%)	2 / 79 (2.53%)
occurrences (all)	0	9	2
Blood urine present			
subjects affected / exposed	1 / 10 (10.00%)	0 / 76 (0.00%)	0 / 79 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			

Tachycardia			
subjects affected / exposed	0 / 10 (0.00%)	4 / 76 (5.26%)	0 / 79 (0.00%)
occurrences (all)	0	4	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 10 (0.00%)	8 / 76 (10.53%)	6 / 79 (7.59%)
occurrences (all)	0	8	7
Dysgeusia			
subjects affected / exposed	1 / 10 (10.00%)	5 / 76 (6.58%)	6 / 79 (7.59%)
occurrences (all)	1	5	7
Dizziness			
subjects affected / exposed	0 / 10 (0.00%)	4 / 76 (5.26%)	6 / 79 (7.59%)
occurrences (all)	0	6	6
Hypoaesthesia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 76 (1.32%)	1 / 79 (1.27%)
occurrences (all)	1	1	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 10 (60.00%)	25 / 76 (32.89%)	28 / 79 (35.44%)
occurrences (all)	6	43	37
Thrombocytopenia			
subjects affected / exposed	4 / 10 (40.00%)	29 / 76 (38.16%)	22 / 79 (27.85%)
occurrences (all)	11	73	43
Neutropenia			
subjects affected / exposed	3 / 10 (30.00%)	18 / 76 (23.68%)	27 / 79 (34.18%)
occurrences (all)	4	52	62
Leukopenia			
subjects affected / exposed	0 / 10 (0.00%)	7 / 76 (9.21%)	11 / 79 (13.92%)
occurrences (all)	0	12	21
Leukocytosis			
subjects affected / exposed	0 / 10 (0.00%)	2 / 76 (2.63%)	6 / 79 (7.59%)
occurrences (all)	0	2	7
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 10 (0.00%)	0 / 76 (0.00%)	4 / 79 (5.06%)
occurrences (all)	0	0	4
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	6 / 10 (60.00%)	31 / 76 (40.79%)	33 / 79 (41.77%)
occurrences (all)	10	39	63
Vomiting			
subjects affected / exposed	4 / 10 (40.00%)	17 / 76 (22.37%)	14 / 79 (17.72%)
occurrences (all)	5	28	20
Constipation			
subjects affected / exposed	3 / 10 (30.00%)	18 / 76 (23.68%)	8 / 79 (10.13%)
occurrences (all)	3	23	9
Diarrhoea			
subjects affected / exposed	3 / 10 (30.00%)	13 / 76 (17.11%)	15 / 79 (18.99%)
occurrences (all)	3	14	17
Abdominal pain			
subjects affected / exposed	1 / 10 (10.00%)	17 / 76 (22.37%)	11 / 79 (13.92%)
occurrences (all)	3	19	11
Ascites			
subjects affected / exposed	1 / 10 (10.00%)	6 / 76 (7.89%)	6 / 79 (7.59%)
occurrences (all)	1	6	7
Dyspepsia			
subjects affected / exposed	2 / 10 (20.00%)	6 / 76 (7.89%)	8 / 79 (10.13%)
occurrences (all)	6	6	8
Abdominal pain upper			
subjects affected / exposed	0 / 10 (0.00%)	5 / 76 (6.58%)	4 / 79 (5.06%)
occurrences (all)	0	6	4
Abdominal distension			
subjects affected / exposed	2 / 10 (20.00%)	4 / 76 (5.26%)	1 / 79 (1.27%)
occurrences (all)	2	4	1
Dry mouth			
subjects affected / exposed	1 / 10 (10.00%)	4 / 76 (5.26%)	1 / 79 (1.27%)
occurrences (all)	1	4	1
Flatulence			
subjects affected / exposed	0 / 10 (0.00%)	2 / 76 (2.63%)	4 / 79 (5.06%)
occurrences (all)	0	2	5
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 10 (0.00%)	5 / 76 (6.58%)	0 / 79 (0.00%)
occurrences (all)	0	5	0

Retching			
subjects affected / exposed	1 / 10 (10.00%)	1 / 76 (1.32%)	0 / 79 (0.00%)
occurrences (all)	1	1	0
Haematochezia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 76 (1.32%)	0 / 79 (0.00%)
occurrences (all)	1	1	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 10 (10.00%)	7 / 76 (9.21%)	3 / 79 (3.80%)
occurrences (all)	1	8	3
Pruritus			
subjects affected / exposed	1 / 10 (10.00%)	2 / 76 (2.63%)	2 / 79 (2.53%)
occurrences (all)	1	2	2
Alopecia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 76 (1.32%)	4 / 79 (5.06%)
occurrences (all)	0	1	4
Ecchymosis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 76 (1.32%)	1 / 79 (1.27%)
occurrences (all)	1	1	1
Skin haemorrhage			
subjects affected / exposed	1 / 10 (10.00%)	0 / 76 (0.00%)	0 / 79 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	1 / 10 (10.00%)	3 / 76 (3.95%)	0 / 79 (0.00%)
occurrences (all)	1	3	0
Polyuria			
subjects affected / exposed	1 / 10 (10.00%)	0 / 76 (0.00%)	0 / 79 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 10 (10.00%)	5 / 76 (6.58%)	6 / 79 (7.59%)
occurrences (all)	1	6	6
Back pain			
subjects affected / exposed	0 / 10 (0.00%)	5 / 76 (6.58%)	5 / 79 (6.33%)
occurrences (all)	0	5	5

Muscular weakness			
subjects affected / exposed	1 / 10 (10.00%)	4 / 76 (5.26%)	2 / 79 (2.53%)
occurrences (all)	1	5	2
Musculoskeletal pain			
subjects affected / exposed	1 / 10 (10.00%)	6 / 76 (7.89%)	0 / 79 (0.00%)
occurrences (all)	1	6	0
Arthralgia			
subjects affected / exposed	1 / 10 (10.00%)	2 / 76 (2.63%)	1 / 79 (1.27%)
occurrences (all)	1	2	1
Joint swelling			
subjects affected / exposed	1 / 10 (10.00%)	1 / 76 (1.32%)	1 / 79 (1.27%)
occurrences (all)	2	1	1
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 10 (10.00%)	3 / 76 (3.95%)	5 / 79 (6.33%)
occurrences (all)	1	3	6
Influenza			
subjects affected / exposed	1 / 10 (10.00%)	1 / 76 (1.32%)	0 / 79 (0.00%)
occurrences (all)	1	1	0
Cystitis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 76 (1.32%)	0 / 79 (0.00%)
occurrences (all)	1	1	0
Localised infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 76 (0.00%)	0 / 79 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 10 (30.00%)	28 / 76 (36.84%)	16 / 79 (20.25%)
occurrences (all)	3	31	17
Hypokalaemia			
subjects affected / exposed	3 / 10 (30.00%)	5 / 76 (6.58%)	3 / 79 (3.80%)
occurrences (all)	4	12	5
Dehydration			
subjects affected / exposed	2 / 10 (20.00%)	7 / 76 (9.21%)	6 / 79 (7.59%)
occurrences (all)	2	8	7
Hyperglycaemia			

subjects affected / exposed	1 / 10 (10.00%)	8 / 76 (10.53%)	4 / 79 (5.06%)
occurrences (all)	1	9	4
Hypoalbuminaemia			
subjects affected / exposed	0 / 10 (0.00%)	6 / 76 (7.89%)	7 / 79 (8.86%)
occurrences (all)	0	6	8
Hyponatraemia			
subjects affected / exposed	0 / 10 (0.00%)	2 / 76 (2.63%)	2 / 79 (2.53%)
occurrences (all)	0	3	2
Hypoglycaemia			
subjects affected / exposed	1 / 10 (10.00%)	2 / 76 (2.63%)	2 / 79 (2.53%)
occurrences (all)	1	2	2

Non-serious adverse events	Placebo (Part B)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	77 / 81 (95.06%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	7 / 81 (8.64%)		
occurrences (all)	7		
Deep vein thrombosis			
subjects affected / exposed	6 / 81 (7.41%)		
occurrences (all)	6		
Hot flush			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	38 / 81 (46.91%)		
occurrences (all)	43		
Oedema peripheral			
subjects affected / exposed	22 / 81 (27.16%)		
occurrences (all)	24		
Pyrexia			
subjects affected / exposed	12 / 81 (14.81%)		
occurrences (all)	19		
Asthenia			

subjects affected / exposed	5 / 81 (6.17%)		
occurrences (all)	10		
Chills			
subjects affected / exposed	7 / 81 (8.64%)		
occurrences (all)	10		
Malaise			
subjects affected / exposed	2 / 81 (2.47%)		
occurrences (all)	2		
Peripheral swelling			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Influenza like illness			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	3 / 81 (3.70%)		
occurrences (all)	4		
Thrombosis in device			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Scrotal swelling			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	15 / 81 (18.52%)		
occurrences (all)	17		
Pleural effusion			
subjects affected / exposed	5 / 81 (6.17%)		
occurrences (all)	5		
Cough			
subjects affected / exposed	8 / 81 (9.88%)		
occurrences (all)	9		
Psychiatric disorders			

Insomnia			
subjects affected / exposed	6 / 81 (7.41%)		
occurrences (all)	6		
Anxiety			
subjects affected / exposed	5 / 81 (6.17%)		
occurrences (all)	5		
Depression			
subjects affected / exposed	6 / 81 (7.41%)		
occurrences (all)	6		
Agitation			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences (all)	0		
Investigations			
Platelet count decreased			
subjects affected / exposed	14 / 81 (17.28%)		
occurrences (all)	36		
Aspartate aminotransferase increased			
subjects affected / exposed	8 / 81 (9.88%)		
occurrences (all)	13		
Alanine aminotransferase increased			
subjects affected / exposed	9 / 81 (11.11%)		
occurrences (all)	15		
Blood alkaline phosphatase increased			
subjects affected / exposed	7 / 81 (8.64%)		
occurrences (all)	8		
Weight decreased			
subjects affected / exposed	5 / 81 (6.17%)		
occurrences (all)	5		
Neutrophil count decreased			
subjects affected / exposed	4 / 81 (4.94%)		
occurrences (all)	6		
Blood bilirubin increased			
subjects affected / exposed	4 / 81 (4.94%)		
occurrences (all)	4		
White blood cell count decreased			

subjects affected / exposed	3 / 81 (3.70%)		
occurrences (all)	6		
Blood creatinine increased			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Blood urine present			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 81 (6.17%)		
occurrences (all)	5		
Dysgeusia			
subjects affected / exposed	6 / 81 (7.41%)		
occurrences (all)	6		
Dizziness			
subjects affected / exposed	7 / 81 (8.64%)		
occurrences (all)	7		
Hypoaesthesia			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	30 / 81 (37.04%)		
occurrences (all)	50		
Thrombocytopenia			
subjects affected / exposed	27 / 81 (33.33%)		
occurrences (all)	48		
Neutropenia			
subjects affected / exposed	22 / 81 (27.16%)		
occurrences (all)	59		
Leukopenia			

subjects affected / exposed	12 / 81 (14.81%)		
occurrences (all)	29		
Leukocytosis			
subjects affected / exposed	3 / 81 (3.70%)		
occurrences (all)	3		
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	31 / 81 (38.27%)		
occurrences (all)	49		
Vomiting			
subjects affected / exposed	17 / 81 (20.99%)		
occurrences (all)	23		
Constipation			
subjects affected / exposed	22 / 81 (27.16%)		
occurrences (all)	22		
Diarrhoea			
subjects affected / exposed	17 / 81 (20.99%)		
occurrences (all)	20		
Abdominal pain			
subjects affected / exposed	13 / 81 (16.05%)		
occurrences (all)	16		
Ascites			
subjects affected / exposed	6 / 81 (7.41%)		
occurrences (all)	6		
Dyspepsia			
subjects affected / exposed	3 / 81 (3.70%)		
occurrences (all)	5		
Abdominal pain upper			
subjects affected / exposed	9 / 81 (11.11%)		
occurrences (all)	9		
Abdominal distension			

subjects affected / exposed	5 / 81 (6.17%)		
occurrences (all)	6		
Dry mouth			
subjects affected / exposed	3 / 81 (3.70%)		
occurrences (all)	3		
Flatulence			
subjects affected / exposed	3 / 81 (3.70%)		
occurrences (all)	3		
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 81 (2.47%)		
occurrences (all)	2		
Retching			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Haematochezia			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	7 / 81 (8.64%)		
occurrences (all)	9		
Pruritus			
subjects affected / exposed	5 / 81 (6.17%)		
occurrences (all)	5		
Alopecia			
subjects affected / exposed	2 / 81 (2.47%)		
occurrences (all)	2		
Ecchymosis			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Skin haemorrhage			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Proteinuria			

subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Polyuria			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	7 / 81 (8.64%)		
occurrences (all)	8		
Back pain			
subjects affected / exposed	6 / 81 (7.41%)		
occurrences (all)	8		
Muscular weakness			
subjects affected / exposed	5 / 81 (6.17%)		
occurrences (all)	5		
Musculoskeletal pain			
subjects affected / exposed	3 / 81 (3.70%)		
occurrences (all)	3		
Arthralgia			
subjects affected / exposed	2 / 81 (2.47%)		
occurrences (all)	2		
Joint swelling			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	8 / 81 (9.88%)		
occurrences (all)	8		
Influenza			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	3		
Cystitis			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences (all)	0		
Localised infection			

subjects affected / exposed	0 / 81 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	18 / 81 (22.22%)		
occurrences (all)	21		
Hypokalaemia			
subjects affected / exposed	12 / 81 (14.81%)		
occurrences (all)	16		
Dehydration			
subjects affected / exposed	7 / 81 (8.64%)		
occurrences (all)	9		
Hyperglycaemia			
subjects affected / exposed	4 / 81 (4.94%)		
occurrences (all)	4		
Hypoalbuminaemia			
subjects affected / exposed	4 / 81 (4.94%)		
occurrences (all)	5		
Hyponatraemia			
subjects affected / exposed	5 / 81 (6.17%)		
occurrences (all)	6		
Hypoglycaemia			
subjects affected / exposed	3 / 81 (3.70%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 November 2011	• Clarify monthly follow-up assessment was to be performed to determine overall survival • Define safety and tumor response could be followed every 8 weeks if study medication was discontinued but the subject continued on study
13 March 2012	• Exclusion criteria were added for subjects with planned combination treatment with erlotinib and gemcitabine and for subjects with uncontrolled hypertension at screening • Urinalysis was performed at screening and at the beginning of each cycle
10 September 2012	• Added inclusion of systemic biomarker sample analysis
12 March 2013	• Removal of the interim analysis • Clarification to the contraception section
07 March 2014	• Added text regarding treatment of subjects randomized to either 200 mg simtuzumab or 700 mg simtuzumab in Part B who continue on study after the determination of trial closure has been made by Gilead.

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: