

**Clinical trial results:****A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, 3-Arm Study of SAR302503 in Patients with Intermediate-2 or High-Risk Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis with Splenomegaly****Summary**

EudraCT number	2011-001897-25
Trial protocol	BE GB HU LT PT ES DE SE AT IT CZ IE
Global end of trial date	09 June 2014

Results information

Result version number	v1 (current)
This version publication date	23 May 2016
First version publication date	06 August 2015

Trial information**Trial identification**

Sponsor protocol code	EFC12153
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01437787
WHO universal trial number (UTN)	U1111-1121-7170

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly-Mazarin, France, 91380
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.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	24 July 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	09 June 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of daily oral doses of 400 mg or 500 mg of SAR302503 compared to placebo in the reduction of spleen volume as determined by magnetic resonance imaging (MRI) (or computed tomography scan in subjects with contraindications for MRI).

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency.

Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 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	Australia: 12
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Brazil: 4
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	France: 27
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Hungary: 17
Country: Number of subjects enrolled	Ireland: 3
Country: Number of subjects enrolled	Israel: 12
Country: Number of subjects enrolled	Italy: 27
Country: Number of subjects enrolled	Lithuania: 9
Country: Number of subjects enrolled	Poland: 17
Country: Number of subjects enrolled	Portugal: 11
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 11

Country: Number of subjects enrolled	Romania: 15
Country: Number of subjects enrolled	Russian Federation: 17
Country: Number of subjects enrolled	Singapore: 9
Country: Number of subjects enrolled	South Africa: 3
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	Taiwan: 4
Country: Number of subjects enrolled	United Kingdom: 36
Country: Number of subjects enrolled	United States: 24
Worldwide total number of subjects	289
EEA total number of subjects	185

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)	140
From 65 to 84 years	147
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 101 sites in 25 countries. A total of 351 subjects were screened between 22 December 2011 and 24 August 2012.

Pre-assignment

Screening details:

Of 351 screened subjects, 62 were screen failures and 289 were randomized.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Placebo

Arm description:

Placebo up to 6 cycles (1 cycle=28 days - median exposure= 24 weeks).

At the end of cycle 6, subjects were crossed-over to SAR302503 400 or 500 mg until disease progression or unacceptable toxicity.

Arm type	Placebo
Investigational medicinal product name	Placebo (for SAR302503)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to SAR302503 once daily on an empty stomach.

Arm title	SAR302503 400 mg
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Arm description:

SAR302503 400 mg until disease progression and/or unacceptable toxicity (median exposure= 62.1 weeks).

Arm type	Experimental
Investigational medicinal product name	Fedratinib
Investigational medicinal product code	SAR302503
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

SAR302503 400 mg once daily on an empty stomach.

Arm title	SAR302503 500 mg
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Arm description:

SAR302503 500 mg until disease progression and/or unacceptable toxicity (median exposure =59.7 weeks).

Arm type	Experimental
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Investigational medicinal product name	Fedratinib
Investigational medicinal product code	SAR302503
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

SAR302503 500 mg once daily on an empty stomach.

Number of subjects in period 1	Placebo	SAR302503 400 mg	SAR302503 500 mg
Started	96	96	97
Treated	95	96	97
Completed	61	0	0
Not completed	35	96	97
Consent withdrawn by subject	-	-	3
Disease progression	4	6	3
Poor compliance	-	1	1
Adverse event	8	26	35
Other than specified	12	10	7
'Randomized, but not treated '	1	-	-
Subject request	-	2	3
Study termination by sponsor	-	51	45
Early crossover	10	-	-

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description: Placebo up to 6 cycles (1 cycle=28 days - median exposure= 24 weeks). At the end of cycle 6, subjects were crossed-over to SAR302503 400 or 500 mg until disease progression or unacceptable toxicity.	
Reporting group title	SAR302503 400 mg
Reporting group description: SAR302503 400 mg until disease progression and/or unacceptable toxicity (median exposure= 62.1 weeks).	
Reporting group title	SAR302503 500 mg
Reporting group description: SAR302503 500 mg until disease progression and/or unacceptable toxicity (median exposure =59.7 weeks).	

Reporting group values	Placebo	SAR302503 400 mg	SAR302503 500 mg
Number of subjects	96	96	97
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	64.9 ± 9.5	62.9 ± 9.6	64.7 ± 9.3
Gender categorical Units: Subjects			
Female	41	42	36
Male	55	54	61
Re-randomization			
Subjects in placebo group were re-randomized to SAR302503 400 mg or 500 mg after cycle 6 or earlier (if a subject experienced progressive disease PD prior to completing the first 6 cycles).			
Units: Subjects			
SAR302503 400 mg	35	0	0
SAR302503 500 mg	36	0	0
Not applicable	25	96	97

Reporting group values	Total		
Number of subjects	289		
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	119		

Male	170		
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Re-randomization			
Subjects in placebo group were re-randomized to SAR302503 400 mg or 500 mg after cycle 6 or earlier (if a subject experienced progressive disease PD prior to completing the first 6 cycles).			
Units: Subjects			
SAR302503 400 mg	35		
SAR302503 500 mg	36		
Not applicable	218		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Placebo up to 6 cycles (1 cycle=28 days - median exposure= 24 weeks). At the end of cycle 6, subjects were crossed-over to SAR302503 400 or 500 mg until disease progression or unacceptable toxicity.	
Reporting group title	SAR302503 400 mg
Reporting group description: SAR302503 400 mg until disease progression and/or unacceptable toxicity (median exposure= 62.1 weeks).	
Reporting group title	SAR302503 500 mg
Reporting group description: SAR302503 500 mg until disease progression and/or unacceptable toxicity (median exposure =59.7 weeks).	

Primary: Response Rate (RR): Percentage of Subjects Who Had a $\geq 35\%$ Reduction From Baseline in Volume of Spleen Size at The End Cycle 6

End point title	Response Rate (RR): Percentage of Subjects Who Had a $\geq 35\%$ Reduction From Baseline in Volume of Spleen Size at The End Cycle 6
End point description: Spleen volume was determined by magnetic resonance imaging (MRI) (or computed tomography scan in subjects with contraindications for MRI) at baseline and at the end of cycle 6 with a confirmatory scan approximately 4 weeks after the end of Cycle 6. The MRI or CT imaging results reviewed in a blinded manner by an Independent Review Committee (IRC). Analysis was performed on intent-to-treat (ITT) population defined as all randomized subjects who signed ICF.	
End point type	Primary
End point timeframe: Baseline, Week 24	

End point values	Placebo	SAR302503 400 mg	SAR302503 500 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	96	96	97	
Units: percentage of subjects				
number (confidence interval 95%)	1 (0 to 3.1)	36.5 (26.8 to 46.1)	40.2 (30.4 to 50)	

Statistical analyses

Statistical analysis title	SAR302503 400 mg vs placebo
Statistical analysis description: A Chi-squared test was performed to compare the response rate at each dose to the placebo.	
Comparison groups	SAR302503 400 mg v Placebo

Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[1]
Method	Chi-squared
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.2416
upper limit	0.4667

Notes:

[1] - Threshold for significance was 0.025.

Statistical analysis title	SAR302503 500 mg vs placebo
Statistical analysis description: A Chi-squared test was performed to compare the response rate at each dose to the placebo.	
Comparison groups	SAR302503 500 mg v Placebo
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[2]
Method	Chi-squared
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.2777
upper limit	0.5056

Notes:

[2] - Threshold for significance was 0.025.

Secondary: Symptom Response Rate (SRR): Percentage of Subjects with $\geq 50\%$ Reduction From Baseline in the Total Symptom Score at End of Cycle 6

End point title	Symptom Response Rate (SRR): Percentage of Subjects with $\geq 50\%$ Reduction From Baseline in the Total Symptom Score at End of Cycle 6
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End point description:

Total symptom score is the averaged value of the daily scores for each of 6 key Myelofibrosis (MF) associated Symptom items (night sweats, pruritus, abdominal discomfort, early satiety [filling up quickly when you eat], pain under ribs on left side, and bone or muscle pain), each item measured on a scale from 0 (absent) to 10 (worst imaginable). A higher score indicates worse symptoms. Analysis was performed on ITT population. Number of subjects analysed= subjects with available data at end of cycle 6.

End point type	Secondary
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End point timeframe:

Baseline, Week 24

End point values	Placebo	SAR302503 400 mg	SAR302503 500 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	91	91	
Units: percentage of subjects				
number (confidence interval 95%)	7.1 (1.6 to 12.5)	36.3 (26.4 to 46.1)	34.1 (24.3 to 43.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
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End point description:

Overall survival was defined as the time interval from the date of randomization to the date of death due to any cause.

End point type	Secondary
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End point timeframe:

Week 92

End point values	Placebo	SAR302503 400 mg	SAR302503 500 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[3]	0 ^[4]	0 ^[5]	
Units: months				
number (not applicable)				

Notes:

[3] - Overall survival analysis was not performed due to short follow-up period.

[4] - Overall survival analysis was not performed due to short follow-up period.

[5] - Overall survival analysis was not performed due to short follow-up period.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)
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End point description:

Disease progression was defined as: - Progressive splenomegaly, defined as enlargement of spleen volume confirmed by MRI (or CT scan in subjects with contraindications for MRI) of $\geq 25\%$ compared to baseline value. - Leukemic transformation, confirmed by a bone marrow blast count of $\geq 20\%$ or the occurrence of a granulocytic sarcoma (chloroma). - An increase in peripheral blood blast percentage of $\geq 20\%$ that persists for at least 1 week. PFS was defined as the time interval from the date of randomization to the date of the first Investigator-assessed disease progression or the date of death due to any cause, whichever came first.

End point type	Secondary
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End point timeframe:

Week 24

End point values	Placebo	SAR302503 400 mg	SAR302503 500 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[6]	0 ^[7]	0 ^[8]	
Units: months				
number (not applicable)				

Notes:

[6] - PFS analysis was not performed due to short follow-up period.

[7] - PFS analysis was not performed due to short follow-up period.

[8] - PFS analysis was not performed due to short follow-up period.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects who had $\geq 25\%$ Reduction From Baseline in Volume of Spleen Size at End of Cycle 6

End point title	Percentage of Subjects who had $\geq 25\%$ Reduction From Baseline in Volume of Spleen Size at End of Cycle 6
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End point description:

Spleen volume was determined by magnetic resonance imaging (MRI) (or computed tomography scan in subjects with contraindications for MRI) at baseline and at the end of cycle 6 with a confirmatory scan approximately 4 weeks after the end of Cycle 6. Analysis was performed on ITT population.

End point type	Secondary
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End point timeframe:

Baseline, Week 24

End point values	Placebo	SAR302503 400 mg	SAR302503 500 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	96	96	97	
Units: percentage of subjects				
number (confidence interval 95%)	2.1 (0 to 4.9)	49 (39 to 59)	51.5 (41.6 to 61.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response in Spleen Volume by Central Imaging MRI/CT Scan

End point title	Duration of Response in Spleen Volume by Central Imaging MRI/CT Scan
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End point description:

Response was measured by MRI (or CT scan). The duration of response was defined as the time from

the date of the first response by independent review committee (IRC) to the date of the subsequent progressive disease by IRC or death, whichever was earlier. Data for this endpoint was analysed up to study completion. Analysis was performed on ITT population.

End point type	Secondary
End point timeframe:	
From the first response up to disease progression or death (Up to Week 92)	

End point values	Placebo	SAR302503 400 mg	SAR302503 500 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	54	57	
Units: month				
median (full range (min-max))	16.7 (16.7 to 16.7)	10.4 (0 to 18.2)	10.4 (0 to 19.7)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (Up to 92 Weeks) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported adverse events and deaths are treatment-emergent that is AEs that developed/worsened or deaths that occurred during the 'on treatment period' (from the first dose of IMP up to 30 days after the last dose).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Placebo
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Reporting group description:

Placebo up to 6 cycles (1 cycle=28 days) (median duration of exposure= 24 weeks).

Reporting group title	SAR302503 400 mg
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Reporting group description:

SAR302503 400 mg (from first dose after initial randomization to the end of study, median duration of exposure= 62.1 weeks).

Reporting group title	SAR302503 500 mg
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Reporting group description:

SAR302503 500 mg (from first dose after initial randomization to the end of study, median duration of exposure= 59.7 weeks).

Reporting group title	SAR302503 400 mg after cross-over
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Reporting group description:

SAR302503 400 mg (from first dose after re-randomization to the end of study, median duration of exposure= 43.9 weeks).

Reporting group title	SAR302503 500 mg after cross-over
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Reporting group description:

SAR302503 500 mg (from first dose after re-randomization to the end of study, median duration of exposure= 44.2 weeks).

Serious adverse events	Placebo	SAR302503 400 mg	SAR302503 500 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 95 (23.16%)	37 / 96 (38.54%)	43 / 97 (44.33%)
number of deaths (all causes)	6	5	6
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute Leukaemia			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0

Acute Myeloid Leukaemia			
subjects affected / exposed	2 / 95 (2.11%)	2 / 96 (2.08%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Adenocarcinoma Of Colon			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal Cell Carcinoma			
subjects affected / exposed	1 / 95 (1.05%)	0 / 96 (0.00%)	0 / 97 (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
Chronic Lymphocytic Leukaemia			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukaemia			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
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 Neoplasm Malignant			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate Cancer			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal Adenocarcinoma			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous Cell Carcinoma			

subjects affected / exposed	1 / 95 (1.05%)	0 / 96 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic Stenosis			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral Artery Thrombosis			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock Haemorrhagic			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	0 / 97 (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
General disorders and administration site conditions			
Disease Progression			
subjects affected / exposed	1 / 95 (1.05%)	2 / 96 (2.08%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Localised Oedema			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multi-Organ Failure			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Pyrexia			
subjects affected / exposed	1 / 95 (1.05%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign Prostatic Hyperplasia			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal Haemorrhage			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute Pulmonary Oedema			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 95 (1.05%)	0 / 96 (0.00%)	0 / 97 (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
Epistaxis			
subjects affected / exposed	1 / 95 (1.05%)	0 / 96 (0.00%)	0 / 97 (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
Lung Disorder			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural Effusion			

subjects affected / exposed	1 / 95 (1.05%)	0 / 96 (0.00%)	0 / 97 (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
Pneumonitis			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Productive Cough			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	0 / 97 (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 Embolism			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pulmonary Hypertension			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	0 / 97 (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 Oedema			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
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 Distress			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	0 / 97 (0.00%)
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 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Investigations			
Alanine Aminotransferase Increased			

subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	2 / 97 (2.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Amylase Increased			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	2 / 97 (2.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipase Increased			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver Function Test Abnormal			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Occult Blood			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Adrenal Haematoma			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	0 / 97 (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
Contusion			
subjects affected / exposed	1 / 95 (1.05%)	0 / 96 (0.00%)	0 / 97 (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
Femur Fracture			

subjects affected / exposed	1 / 95 (1.05%)	0 / 96 (0.00%)	0 / 97 (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
Muscle Rupture			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	0 / 97 (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
Post Procedural Haemorrhage			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	0 / 97 (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
Procedural Intestinal Perforation			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transfusion-Related Acute Lung Injury			
subjects affected / exposed	1 / 95 (1.05%)	0 / 96 (0.00%)	0 / 97 (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
Cardiac disorders			
Acute Coronary Syndrome			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	0 / 97 (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 Left Ventricular Failure			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	0 / 97 (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 Myocardial Infarction			
subjects affected / exposed	1 / 95 (1.05%)	0 / 96 (0.00%)	2 / 97 (2.06%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina Unstable			

subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial Fibrillation			
subjects affected / exposed	0 / 95 (0.00%)	2 / 96 (2.08%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Arrest			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac Disorder			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	0 / 97 (0.00%)
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 Failure			
subjects affected / exposed	3 / 95 (3.16%)	5 / 96 (5.21%)	3 / 97 (3.09%)
occurrences causally related to treatment / all	0 / 3	1 / 6	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac Failure Congestive			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	2 / 97 (2.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-Respiratory Arrest			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	0 / 97 (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
Cardiogenic Shock			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Left Ventricular Dysfunction			

subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial Ischaemia			
subjects affected / exposed	1 / 95 (1.05%)	1 / 96 (1.04%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Right Ventricular Failure			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	0 / 97 (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			
Cerebrovascular Accident			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
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 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	0 / 97 (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
Encephalopathy			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage Intracranial			
subjects affected / exposed	1 / 95 (1.05%)	0 / 96 (0.00%)	0 / 97 (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
Haemorrhagic Stroke			

subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	0 / 97 (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
Headache			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	0 / 97 (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
Hypoglycaemic Coma			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wernicke's Encephalopathy			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 95 (1.05%)	4 / 96 (4.17%)	5 / 97 (5.15%)
occurrences causally related to treatment / all	0 / 4	2 / 5	19 / 23
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated Intravascular Coagulation			
subjects affected / exposed	0 / 95 (0.00%)	2 / 96 (2.08%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Haemorrhagic Anaemia			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	0 / 97 (0.00%)
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	1 / 95 (1.05%)	1 / 96 (1.04%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Neutropenia			

subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic Haemorrhage			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic Infarction			
subjects affected / exposed	2 / 95 (2.11%)	0 / 96 (0.00%)	2 / 97 (2.06%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenomegaly			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	0 / 97 (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 / 95 (0.00%)	1 / 96 (1.04%)	2 / 97 (2.06%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Amaurosis Fugax			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periorbital Oedema			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous Haemorrhage			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	0 / 97 (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 disorders			

Abdominal Pain			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Pain Upper			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Wall Haematoma			
subjects affected / exposed	1 / 95 (1.05%)	0 / 96 (0.00%)	0 / 97 (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
Ascites			
subjects affected / exposed	3 / 95 (3.16%)	0 / 96 (0.00%)	2 / 97 (2.06%)
occurrences causally related to treatment / all	0 / 3	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
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 Haemorrhage			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal Polyp Haemorrhage			

subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Ileus Paralytic			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	0 / 97 (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
Rectal Haemorrhage			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small Intestinal Perforation			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical Hernia			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	0 / 97 (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
Volvulus			

subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocholecystitis			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertransaminasaemia			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal Colic			
subjects affected / exposed	1 / 95 (1.05%)	0 / 96 (0.00%)	0 / 97 (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 Cyst			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Failure Acute			

subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Failure Chronic			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Retention			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal Haemorrhage			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	0 / 97 (0.00%)
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			
Back Pain			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	0 / 97 (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 Pain			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological Fracture			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	0 / 97 (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
Infections and infestations			
Abscess Limb			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Abscess Oral			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal Abscess			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial Pyelonephritis			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Bronchitis			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	0 / 97 (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
Bronchopneumonia			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis Escherichia			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	0 / 97 (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
Enterocolitis Infectious			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			

subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Implant Site Infection			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	0 / 97 (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
Infective Exacerbation Of Chronic Obstructive Airways Disease			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella Sepsis			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower Respiratory Tract Infection			
subjects affected / exposed	1 / 95 (1.05%)	0 / 96 (0.00%)	0 / 97 (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
Lower Respiratory Tract Infection Viral			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
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 Abscess			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung Infection			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	2 / 97 (2.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic Sepsis			

subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 95 (2.11%)	4 / 96 (4.17%)	3 / 97 (3.09%)
occurrences causally related to treatment / all	0 / 2	1 / 4	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 95 (1.05%)	2 / 96 (2.08%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Septic Shock			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal Sepsis			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheobronchitis			
subjects affected / exposed	1 / 95 (1.05%)	0 / 96 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 95 (1.05%)	0 / 96 (0.00%)	0 / 97 (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
Hyperkalaemia			

subjects affected / exposed	1 / 95 (1.05%)	1 / 96 (1.04%)	2 / 97 (2.06%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	0 / 97 (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
Hyponatraemia			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	2 / 97 (2.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	SAR302503 400 mg after cross-over	SAR302503 500 mg after cross-over	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 35 (37.14%)	13 / 36 (36.11%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute Leukaemia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Myeloid Leukaemia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma Of Colon			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal Cell Carcinoma			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chronic Lymphocytic Leukaemia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukaemia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Neoplasm Malignant			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate Cancer			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Adenocarcinoma			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous Cell Carcinoma			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic Stenosis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Artery Thrombosis			

subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock Haemorrhagic			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Disease Progression			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised Oedema			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-Organ Failure			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign Prostatic Hyperplasia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal Haemorrhage			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Acute Pulmonary Oedema			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Disorder			
subjects affected / exposed	0 / 35 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Productive Cough			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary Hypertension			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Oedema			
subjects affected / exposed	0 / 35 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Distress			
subjects affected / exposed	0 / 35 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory Failure			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amylase Increased			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase Increased			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Liver Function Test Abnormal subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Occult Blood subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Adrenal Haematoma subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur Fracture subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle Rupture subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post Procedural Haemorrhage subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural Intestinal Perforation subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Transfusion-Related Acute Lung Injury			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Coronary Syndrome			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Left Ventricular Failure			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Myocardial Infarction			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina Unstable			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Fibrillation			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Arrest			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Disorder			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac Failure			
subjects affected / exposed	0 / 35 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Congestive			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-Respiratory Arrest			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic Shock			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left Ventricular Dysfunction			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Ischaemia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right Ventricular Failure			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular Accident			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			

subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage Intracranial			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic Stroke			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic Coma			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wernicke's Encephalopathy			
subjects affected / exposed	0 / 35 (0.00%)	2 / 36 (5.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	3 / 35 (8.57%)	2 / 36 (5.56%)	
occurrences causally related to treatment / all	5 / 6	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated Intravascular Coagulation			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic Anaemia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic Haemorrhage			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic Infarction			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenomegaly			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			

subjects affected / exposed	1 / 35 (2.86%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Amaurosis Fugax			
subjects affected / exposed	0 / 35 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital Oedema			
subjects affected / exposed	0 / 35 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous Haemorrhage			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Pain Upper			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Wall Haematoma			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			

subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Polyp Haemorrhage			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus Paralytic			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Haemorrhage			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small Intestinal Perforation			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical Hernia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Volvulus			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 35 (2.86%)	2 / 36 (5.56%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocholecystis			

subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertransaminasaemia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal Colic			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Cyst			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure Acute			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure Chronic			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Retention			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal Haemorrhage			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue			

disorders			
Back Pain			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal Pain			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological Fracture			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess Limb			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess Oral			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal Abscess			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial Pyelonephritis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bronchitis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis Escherichia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis Infectious			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implant Site Infection			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective Exacerbation Of Chronic Obstructive Airways Disease			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella Sepsis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Respiratory Tract Infection			

subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Respiratory Tract Infection Viral			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Abscess			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Infection			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic Sepsis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 35 (2.86%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic Shock			

subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal Sepsis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	SAR302503 400 mg	SAR302503 500 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	76 / 95 (80.00%)	96 / 96 (100.00%)	94 / 97 (96.91%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 95 (1.05%)	4 / 96 (4.17%)	6 / 97 (6.19%)
occurrences (all)	1	5	7
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 95 (6.32%)	13 / 96 (13.54%)	16 / 97 (16.49%)
occurrences (all)	6	19	19
Fatigue			
subjects affected / exposed	9 / 95 (9.47%)	24 / 96 (25.00%)	14 / 97 (14.43%)
occurrences (all)	9	28	22
Local Swelling			
subjects affected / exposed	1 / 95 (1.05%)	5 / 96 (5.21%)	0 / 97 (0.00%)
occurrences (all)	1	5	0
Oedema Peripheral			
subjects affected / exposed	8 / 95 (8.42%)	13 / 96 (13.54%)	9 / 97 (9.28%)
occurrences (all)	8	14	10
Pain			
subjects affected / exposed	0 / 95 (0.00%)	3 / 96 (3.13%)	2 / 97 (2.06%)
occurrences (all)	0	4	2
Pyrexia			
subjects affected / exposed	2 / 95 (2.11%)	7 / 96 (7.29%)	6 / 97 (6.19%)
occurrences (all)	3	9	10
Social circumstances			
Blood Product Transfusion Dependent			
subjects affected / exposed	2 / 95 (2.11%)	10 / 96 (10.42%)	12 / 97 (12.37%)
occurrences (all)	2	10	12
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 95 (6.32%)	14 / 96 (14.58%)	14 / 97 (14.43%)
occurrences (all)	6	17	14
Dyspnoea			

subjects affected / exposed	6 / 95 (6.32%)	11 / 96 (11.46%)	13 / 97 (13.40%)
occurrences (all)	6	12	16
Dyspnoea Exertional			
subjects affected / exposed	0 / 95 (0.00%)	5 / 96 (5.21%)	2 / 97 (2.06%)
occurrences (all)	0	5	2
Epistaxis			
subjects affected / exposed	6 / 95 (6.32%)	7 / 96 (7.29%)	4 / 97 (4.12%)
occurrences (all)	8	9	4
Oropharyngeal Pain			
subjects affected / exposed	0 / 95 (0.00%)	5 / 96 (5.21%)	4 / 97 (4.12%)
occurrences (all)	0	5	4
Pleural Effusion			
subjects affected / exposed	0 / 95 (0.00%)	4 / 96 (4.17%)	1 / 97 (1.03%)
occurrences (all)	0	4	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 95 (0.00%)	5 / 96 (5.21%)	1 / 97 (1.03%)
occurrences (all)	0	6	1
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 95 (1.05%)	12 / 96 (12.50%)	7 / 97 (7.22%)
occurrences (all)	1	16	7
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 95 (0.00%)	6 / 96 (6.25%)	8 / 97 (8.25%)
occurrences (all)	0	7	9
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	1 / 95 (1.05%)	6 / 96 (6.25%)	2 / 97 (2.06%)
occurrences (all)	1	6	3
Blood Creatinine Increased			
subjects affected / exposed	1 / 95 (1.05%)	11 / 96 (11.46%)	17 / 97 (17.53%)
occurrences (all)	1	12	26
Lipase Increased			
subjects affected / exposed	1 / 95 (1.05%)	8 / 96 (8.33%)	7 / 97 (7.22%)
occurrences (all)	1	8	10
Weight Decreased			

subjects affected / exposed occurrences (all)	5 / 95 (5.26%) 5	5 / 96 (5.21%) 6	12 / 97 (12.37%) 12
Weight Increased subjects affected / exposed occurrences (all)	4 / 95 (4.21%) 4	12 / 96 (12.50%) 12	8 / 97 (8.25%) 8
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	1 / 95 (1.05%) 1	5 / 96 (5.21%) 6	2 / 97 (2.06%) 2
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	3 / 95 (3.16%) 3	12 / 96 (12.50%) 16	10 / 97 (10.31%) 11
Headache subjects affected / exposed occurrences (all)	1 / 95 (1.05%) 1	13 / 96 (13.54%) 13	6 / 97 (6.19%) 6
Lethargy subjects affected / exposed occurrences (all)	0 / 95 (0.00%) 0	0 / 96 (0.00%) 0	1 / 97 (1.03%) 1
Paraesthesia subjects affected / exposed occurrences (all)	1 / 95 (1.05%) 1	1 / 96 (1.04%) 1	3 / 97 (3.09%) 3
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	13 / 95 (13.68%) 15	50 / 96 (52.08%) 79	43 / 97 (44.33%) 77
Leukopenia subjects affected / exposed occurrences (all)	0 / 95 (0.00%) 0	1 / 96 (1.04%) 2	3 / 97 (3.09%) 3
Neutropenia subjects affected / exposed occurrences (all)	0 / 95 (0.00%) 0	6 / 96 (6.25%) 10	12 / 97 (12.37%) 17
Thrombocytopenia subjects affected / exposed occurrences (all)	8 / 95 (8.42%) 9	15 / 96 (15.63%) 22	20 / 97 (20.62%) 28
Ear and labyrinth disorders			

Vertigo subjects affected / exposed occurrences (all)	1 / 95 (1.05%) 1	2 / 96 (2.08%) 2	0 / 97 (0.00%) 0
Gastrointestinal disorders			
Abdominal Discomfort subjects affected / exposed occurrences (all)	1 / 95 (1.05%) 1	2 / 96 (2.08%) 2	3 / 97 (3.09%) 4
Abdominal Distension subjects affected / exposed occurrences (all)	2 / 95 (2.11%) 2	5 / 96 (5.21%) 6	6 / 97 (6.19%) 7
Abdominal Pain subjects affected / exposed occurrences (all)	15 / 95 (15.79%) 17	15 / 96 (15.63%) 23	14 / 97 (14.43%) 19
Abdominal Pain Upper subjects affected / exposed occurrences (all)	5 / 95 (5.26%) 6	10 / 96 (10.42%) 12	5 / 97 (5.15%) 6
Constipation subjects affected / exposed occurrences (all)	7 / 95 (7.37%) 7	12 / 96 (12.50%) 13	19 / 97 (19.59%) 23
Diarrhoea subjects affected / exposed occurrences (all)	15 / 95 (15.79%) 19	67 / 96 (69.79%) 106	57 / 97 (58.76%) 87
Dyspepsia subjects affected / exposed occurrences (all)	2 / 95 (2.11%) 2	7 / 96 (7.29%) 9	6 / 97 (6.19%) 7
Flatulence subjects affected / exposed occurrences (all)	0 / 95 (0.00%) 0	3 / 96 (3.13%) 3	1 / 97 (1.03%) 1
Nausea subjects affected / exposed occurrences (all)	15 / 95 (15.79%) 15	64 / 96 (66.67%) 89	51 / 97 (52.58%) 62
Vomiting subjects affected / exposed occurrences (all)	5 / 95 (5.26%) 5	44 / 96 (45.83%) 83	53 / 97 (54.64%) 107
Skin and subcutaneous tissue disorders			

Dry Skin			
subjects affected / exposed	2 / 95 (2.11%)	6 / 96 (6.25%)	5 / 97 (5.15%)
occurrences (all)	2	7	6
Night Sweats			
subjects affected / exposed	2 / 95 (2.11%)	6 / 96 (6.25%)	4 / 97 (4.12%)
occurrences (all)	2	7	6
Pruritus			
subjects affected / exposed	2 / 95 (2.11%)	6 / 96 (6.25%)	7 / 97 (7.22%)
occurrences (all)	2	6	8
Pruritus Generalised			
subjects affected / exposed	6 / 95 (6.32%)	6 / 96 (6.25%)	3 / 97 (3.09%)
occurrences (all)	6	6	3
Rash			
subjects affected / exposed	0 / 95 (0.00%)	4 / 96 (4.17%)	5 / 97 (5.15%)
occurrences (all)	0	4	5
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 95 (0.00%)	6 / 96 (6.25%)	0 / 97 (0.00%)
occurrences (all)	0	7	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 95 (6.32%)	7 / 96 (7.29%)	2 / 97 (2.06%)
occurrences (all)	7	8	2
Back Pain			
subjects affected / exposed	2 / 95 (2.11%)	3 / 96 (3.13%)	3 / 97 (3.09%)
occurrences (all)	2	3	3
Bone Pain			
subjects affected / exposed	2 / 95 (2.11%)	13 / 96 (13.54%)	8 / 97 (8.25%)
occurrences (all)	2	17	13
Muscle Spasms			
subjects affected / exposed	1 / 95 (1.05%)	15 / 96 (15.63%)	8 / 97 (8.25%)
occurrences (all)	1	21	11
Pain In Extremity			
subjects affected / exposed	4 / 95 (4.21%)	12 / 96 (12.50%)	3 / 97 (3.09%)
occurrences (all)	4	13	3
Infections and infestations			

Bronchitis			
subjects affected / exposed	1 / 95 (1.05%)	4 / 96 (4.17%)	3 / 97 (3.09%)
occurrences (all)	1	6	3
Conjunctivitis			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	1 / 97 (1.03%)
occurrences (all)	0	1	1
Gastroenteritis			
subjects affected / exposed	0 / 95 (0.00%)	5 / 96 (5.21%)	0 / 97 (0.00%)
occurrences (all)	0	6	0
Nasopharyngitis			
subjects affected / exposed	3 / 95 (3.16%)	5 / 96 (5.21%)	6 / 97 (6.19%)
occurrences (all)	3	7	7
Tooth Abscess			
subjects affected / exposed	1 / 95 (1.05%)	0 / 96 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Upper Respiratory Tract Infection			
subjects affected / exposed	4 / 95 (4.21%)	8 / 96 (8.33%)	6 / 97 (6.19%)
occurrences (all)	4	10	7
Urinary Tract Infection			
subjects affected / exposed	1 / 95 (1.05%)	9 / 96 (9.38%)	10 / 97 (10.31%)
occurrences (all)	1	14	13
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	3 / 95 (3.16%)	6 / 96 (6.25%)	9 / 97 (9.28%)
occurrences (all)	3	6	10
Hyperglycaemia			
subjects affected / exposed	0 / 95 (0.00%)	6 / 96 (6.25%)	2 / 97 (2.06%)
occurrences (all)	0	6	2
Hyperkalaemia			
subjects affected / exposed	1 / 95 (1.05%)	5 / 96 (5.21%)	9 / 97 (9.28%)
occurrences (all)	1	5	14
Hyperuricaemia			
subjects affected / exposed	4 / 95 (4.21%)	9 / 96 (9.38%)	3 / 97 (3.09%)
occurrences (all)	4	11	6
Hypocalcaemia			

subjects affected / exposed	1 / 95 (1.05%)	4 / 96 (4.17%)	3 / 97 (3.09%)
occurrences (all)	1	4	4

Non-serious adverse events	SAR302503 400 mg after cross-over	SAR302503 500 mg after cross-over	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 35 (94.29%)	36 / 36 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 35 (2.86%)	1 / 36 (2.78%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 35 (8.57%)	7 / 36 (19.44%)	
occurrences (all)	4	9	
Fatigue			
subjects affected / exposed	7 / 35 (20.00%)	5 / 36 (13.89%)	
occurrences (all)	10	7	
Local Swelling			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences (all)	0	0	
Oedema Peripheral			
subjects affected / exposed	3 / 35 (8.57%)	2 / 36 (5.56%)	
occurrences (all)	3	2	
Pain			
subjects affected / exposed	1 / 35 (2.86%)	2 / 36 (5.56%)	
occurrences (all)	1	2	
Pyrexia			
subjects affected / exposed	2 / 35 (5.71%)	3 / 36 (8.33%)	
occurrences (all)	4	3	
Social circumstances			
Blood Product Transfusion Dependent			
subjects affected / exposed	3 / 35 (8.57%)	1 / 36 (2.78%)	
occurrences (all)	3	1	
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 4	3 / 36 (8.33%) 3	
Dyspnoea subjects affected / exposed occurrences (all)	4 / 35 (11.43%) 5	4 / 36 (11.11%) 4	
Dyspnoea Exertional subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	1 / 36 (2.78%) 2	
Epistaxis subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 3	1 / 36 (2.78%) 1	
Oropharyngeal Pain subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 36 (0.00%) 0	
Pleural Effusion subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	1 / 36 (2.78%) 1	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 36 (0.00%) 0	
Investigations Alanine Aminotransferase Increased subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	4 / 36 (11.11%) 5	
Aspartate Aminotransferase Increased subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	1 / 36 (2.78%) 1	
Blood Alkaline Phosphatase Increased subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	2 / 36 (5.56%) 2	
Blood Creatinine Increased subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	4 / 36 (11.11%) 4	
Lipase Increased			

subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	2 / 36 (5.56%) 2	
Weight Decreased subjects affected / exposed occurrences (all)	6 / 35 (17.14%) 6	3 / 36 (8.33%) 3	
Weight Increased subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	3 / 36 (8.33%) 3	
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	1 / 36 (2.78%) 1	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	1 / 36 (2.78%) 1	
Headache subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	1 / 36 (2.78%) 1	
Lethargy subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	2 / 36 (5.56%) 2	
Paraesthesia subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 2	2 / 36 (5.56%) 3	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	21 / 35 (60.00%) 34	19 / 36 (52.78%) 32	
Leukopenia subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 3	0 / 36 (0.00%) 0	
Neutropenia subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 6	3 / 36 (8.33%) 3	
Thrombocytopenia			

subjects affected / exposed occurrences (all)	8 / 35 (22.86%) 9	12 / 36 (33.33%) 13	
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	0 / 36 (0.00%) 0	
Gastrointestinal disorders Abdominal Discomfort subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	2 / 36 (5.56%) 2	
Abdominal Distension subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 36 (0.00%) 0	
Abdominal Pain subjects affected / exposed occurrences (all)	4 / 35 (11.43%) 5	6 / 36 (16.67%) 7	
Abdominal Pain Upper subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	4 / 36 (11.11%) 4	
Constipation subjects affected / exposed occurrences (all)	7 / 35 (20.00%) 8	3 / 36 (8.33%) 3	
Diarrhoea subjects affected / exposed occurrences (all)	10 / 35 (28.57%) 15	14 / 36 (38.89%) 18	
Dyspepsia subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	0 / 36 (0.00%) 0	
Flatulence subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	2 / 36 (5.56%) 4	
Nausea subjects affected / exposed occurrences (all)	20 / 35 (57.14%) 26	16 / 36 (44.44%) 30	
Vomiting			

subjects affected / exposed occurrences (all)	13 / 35 (37.14%) 22	14 / 36 (38.89%) 26	
Skin and subcutaneous tissue disorders			
Dry Skin			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences (all)	0	0	
Night Sweats			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences (all)	1	0	
Pruritus Generalised			
subjects affected / exposed	2 / 35 (5.71%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
Rash			
subjects affected / exposed	1 / 35 (2.86%)	1 / 36 (2.78%)	
occurrences (all)	1	1	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	2 / 35 (5.71%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 35 (8.57%)	1 / 36 (2.78%)	
occurrences (all)	3	1	
Back Pain			
subjects affected / exposed	0 / 35 (0.00%)	3 / 36 (8.33%)	
occurrences (all)	0	3	
Bone Pain			
subjects affected / exposed	0 / 35 (0.00%)	1 / 36 (2.78%)	
occurrences (all)	0	1	
Muscle Spasms			
subjects affected / exposed	2 / 35 (5.71%)	3 / 36 (8.33%)	
occurrences (all)	3	4	
Pain In Extremity			

subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	1 / 36 (2.78%) 1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 35 (11.43%)	2 / 36 (5.56%)	
occurrences (all)	4	2	
Conjunctivitis			
subjects affected / exposed	3 / 35 (8.57%)	1 / 36 (2.78%)	
occurrences (all)	3	1	
Gastroenteritis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 36 (0.00%)	
occurrences (all)	0	0	
Nasopharyngitis			
subjects affected / exposed	1 / 35 (2.86%)	1 / 36 (2.78%)	
occurrences (all)	1	1	
Tooth Abscess			
subjects affected / exposed	0 / 35 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Upper Respiratory Tract Infection			
subjects affected / exposed	5 / 35 (14.29%)	1 / 36 (2.78%)	
occurrences (all)	5	1	
Urinary Tract Infection			
subjects affected / exposed	1 / 35 (2.86%)	2 / 36 (5.56%)	
occurrences (all)	3	2	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	2 / 35 (5.71%)	4 / 36 (11.11%)	
occurrences (all)	2	4	
Hyperglycaemia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 36 (2.78%)	
occurrences (all)	0	1	
Hyperkalaemia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences (all)	1	0	
Hyperuricaemia			

subjects affected / exposed	0 / 35 (0.00%)	1 / 36 (2.78%)	
occurrences (all)	0	1	
Hypocalcaemia			
subjects affected / exposed	0 / 35 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 July 2011	<ul style="list-style-type: none">- The secondary endpoint of symptom response rate was changed from 40% to 50% reduction from baseline to end of Cycle 6 in the total symptom score.- Additional ECG assessments added to schedule.- An alert to the use of strong inhibitors of CYP2C19 with SAR302503 was added.- Wording for the modified MFSAF diary was clarified.- The assessment schedule was corrected.
17 February 2012	<ul style="list-style-type: none">- Updated the inclusion and exclusion criteria of subjects who may be at risk for aspartate aminotransferase (AST), alanine aminotransferase (ALT), and/or bilirubin abnormalities.- Added more frequent monitoring of ALT, AST and bilirubin (total and direct). Following the occurrence of an episode of reversible hepatic failure in a subject treated with SAR302503 in a clinical trial, the entire SAR302503 development program was amended to add more frequent monitoring of ALT, AST and bilirubin (total and direct) during the first 3 cycles of treatment and in case severe liver enzyme elevations occurred at any time during study treatment.- Explicit instructions given for dose modifications in the case that elevations of transaminases and/or bilirubin were detected.- Added clarification to the concomitant medications section regarding the recommendation to not use oral contraceptives and hormonal replacement therapies that include estrogen (ie, ethinyl estradiol) and progesterone (ie, levonorgestrel) during study treatment.- Added study name JAKARTA.
20 November 2012	<ul style="list-style-type: none">- Included use of a central pathology review of bone marrow biopsy samples.- Based on the preliminary data from study INT12497, SAR302503 was likely a moderate-to-potent inhibitor of CYP3A4 and based on this information, the concomitant medications section was adapted accordingly.- Dose modification for toxicity was clarified.- Guidance on dose reduction in case of Grade 3, 4 AEs and transfusion dependency was added.- The list of adverse event(s) of special interest (AESI) was updated.- Exploratory endpoint analyses were updated in the statistical section.- Administrative changes.
27 November 2013	<ul style="list-style-type: none">- All subjects were permanently discontinued from further SAR302503 treatment, and all subjects, including those previously discontinued from the study, were asked to participate in the Thiamine Supplementation Period.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported