Clinical trial results:
A randomized, open-label, multicenter Phase III study to evaluate the efficacy and safety of nilotinib versus imatinib in adult patients with unresectable or metastatic gastrointestinal stromal tumors (GIST)
Due to EudraCT system limitations, which EMA is aware of, results of crossover studies are not accurately represented in this record. Please go to https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Summary

EudraCT number	2008-004758-34
Trial protocol	AT ES SK CZ SE HU NL DE FR IT GB DK GR BG
Global end of trial date	23 October 2014

Results information

Result version number	v1 (current)
This version publication date	15 July 2018
First version publication date	15 July 2018

Trial information

Trial identification

Sponsor protocol code	CAMN107G2301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00785785
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

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	23 October 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to compare the progression free survival (PFS) of nilotinib and imatinib when used as initial therapy in adult patients with unresectable or metastatic gastrointestinal stromal tumors (GIST). This was summarized in the Core clinical study report (CSR) and is not repeated for the final analysis.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 March 2009
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	Argentina: 8
Country: Number of subjects enrolled	Austria: 14
Country: Number of subjects enrolled	Brazil: 17
Country: Number of subjects enrolled	Bulgaria: 2
Country: Number of subjects enrolled	Canada: 22
Country: Number of subjects enrolled	China: 93
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	Denmark: 5
Country: Number of subjects enrolled	Egypt: 13
Country: Number of subjects enrolled	France: 32
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	United Kingdom: 23
Country: Number of subjects enrolled	Hong Kong: 8
Country: Number of subjects enrolled	Hungary: 20
Country: Number of subjects enrolled	Israel: 5
Country: Number of subjects enrolled	Italy: 27
Country: Number of subjects enrolled	Japan: 51
Country: Number of subjects enrolled	Korea, Republic of: 22

Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	Netherlands: 8
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Poland: 18
Country: Number of subjects enrolled	Romania: 13
Country: Number of subjects enrolled	Russian Federation: 33
Country: Number of subjects enrolled	Singapore: 12
Country: Number of subjects enrolled	Slovakia: 5
Country: Number of subjects enrolled	South Africa: 6
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Sweden: 20
Country: Number of subjects enrolled	Taiwan: 18
Country: Number of subjects enrolled	Thailand: 30
Country: Number of subjects enrolled	Turkey: 11
Country: Number of subjects enrolled	United States: 70
Country: Number of subjects enrolled	Venezuela, Bolivarian Republic of: 1
Worldwide total number of subjects	644
EEA total number of subjects	220

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)	453
From 65 to 84 years	189
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients were on either: imatinib 400mg once daily or nilotinib 400 mg twice a day in the core phase and then crossed over to nilotinib 400 mg twice a day or imatinib 400mg once daily in the extension phase.

Period 1

Period 1 title	Core Phase up to 36 months (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Carer, Data analyst, Subject, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Imatinib first, then Nilotinib

Arm description:

patients were on imatinib 400mg once daily in the core phase and then crossed over to nilotinib 400 mg twice a day in the extension phase

Arm type	Experimental
Investigational medicinal product name	Imatinib
Investigational medicinal product code	STI571
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Imatinib 400mg tablet orally once a day

Arm title	Nilotinib first, then Imatinib

Arm description:

patients were on nilotinib 400 mg twice a day in the core phase and then crossed over to in the extension phase imatinib 400mg once daily

Arm type	Experimental
Investigational medicinal product name	Nilotinib
Investigational medicinal product code	AMN107
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Nilotinib 400 mg capsule orally twice daily

Number of subjects in period 1	Imatinib first, then Nilotinib	Nilotinib first, then Imatinib
Started	324	320
Completed	0	0
Not completed	324	320
Patients didn't receive 1st line therapy	3	4
Adverse event, serious fatal	5	8
Consent withdrawn by subject	16	17
Disease progression	139	119
Adverse event, non-fatal	31	21
Protocol deviation	5	6
Administrative problems	3	3
Abnormal laboratory value	1	-
Study terminated by sponsor	116	133
Lost to follow-up	3	7
Abnormal test procedure result	2	2

Baseline characteristics

Reporting groups	
Reporting group title	Imatinib first, then Nilotinib
Reporting group description:	
patients were on imatinib 400mg once daily in the core phase and then crossed over to nilotinib 400 mg twice a day in the extension phase	
Reporting group title	Nilotinib first, then Imatinib
Reporting group description:	
patients were on nilotinib 400 mg twice a day in the core phase and then crossed over to in the extension phase imatinib 400mg once daily	

Reporting group values	Imatinib first, then Nilotinib	Nilotinib first, then Imatinib	Total
Number of subjects	324	320	644
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	225	228	453
From 65-84 years	99	90	189
85 years and over	0	2	2
Age Continuous Units: years			
arithmetic mean	57.4	57.3	
standard deviation	± 12.91	± 12.63	-
Gender, Male/Female Units: participants			
Male	179	187	366
Female	145	133	278

Subject analysis sets	
Subject analysis set title	Nilotinib
Subject analysis set type	Full analysis
Subject analysis set description:	
nilotinib 400 mg twice aday	
Subject analysis set title	Imatinib
Subject analysis set type	Full analysis
Subject analysis set description:	
imatinib 400 mg once daily	

Reporting group values	Nilotinib	Imatinib	
Number of subjects	324	320	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	225	228	
From 65-84 years	99	90	
85 years and over	0	2	
Age Continuous Units: years			
arithmetic mean	57.4	57.3	
standard deviation	± 12.91	± 12.63	
Gender, Male/Female Units: participants			
Male	179	187	
Female	145	133	

End points

End points reporting groups

Reporting group title	Imatinib first, then Nilotinib
Reporting group description:	
patients were on imatinib 400mg once daily in the core phase and then crossed over to nilotinib 400 mg twice a day in the extension phase	
Reporting group title	Nilotinib first, then Imatinib
Reporting group description:	
patients were on nilotinib 400 mg twice a day in the core phase and then crossed over to in the extension phase imatinib 400mg once daily	
Subject analysis set title	Nilotinib
Subject analysis set type	Full analysis
Subject analysis set description:	
nilotinib 400 mg twice aday	
Subject analysis set title	Imatinib
Subject analysis set type	Full analysis
Subject analysis set description:	
imatinib 400 mg once daily	

Primary: Time to Progression Free Survival (PFS)

End point title	Time to Progression Free Survival (PFS)
End point description:	
PFS was defined as the time from the date of start of treatment to the date of the first documented progression or death due to any cause. Progression is defined as a 20% increase in the sum of the longest diameter of target lesions, or a measurable increase in a non-target lesion, or the appearance of new lesions	
End point type	Primary
End point timeframe:	
up to month 37	

End point values	Nilotinib	Imatinib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	324	320		
Units: months				
median (full range (min-max))	25.9 (0 to 32.8)	29.7 (0 to 36.1)		

Statistical analyses

Statistical analysis title	Time to Progression Free Survival (PFS)
Comparison groups	Imatinib v Nilotinib

Number of subjects included in analysis	644
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0081
Method	Hazard Ratio
Parameter estimate	Hazard ratio (HR)
Point estimate	1.466
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.104
upper limit	1.945

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	First-line Nilotinib
Reporting group description:	
First-line Nilotinib	
Reporting group title	First-line Imatinib
Reporting group description:	
First-line Imatinib	
Reporting group title	Crossover Nilotinib
Reporting group description:	
Crossover Nilotinib	
Reporting group title	Crossover Imatinib
Reporting group description:	
Crossover Imatinib	

Serious adverse events	First-line Nilotinib	First-line Imatinib	Crossover Nilotinib
Total subjects affected by serious adverse events			
subjects affected / exposed	80 / 321 (24.92%)	85 / 316 (26.90%)	15 / 39 (38.46%)
number of deaths (all causes)	13	11	1
number of deaths resulting from adverse events	0	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenoma benign			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Bladder cancer			

subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Gastric cancer			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Gastrointestinal stromal tumour			
subjects affected / exposed	2 / 321 (0.62%)	0 / 316 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hodgkin's disease			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic neoplasm			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Infected neoplasm			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Lip and/or oral cavity cancer			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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 neoplasm malignant			

subjects affected / exposed	1 / 321 (0.31%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to liver			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Metastases to peritoneum			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Neoplasm			
subjects affected / exposed	0 / 321 (0.00%)	0 / 316 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma metastatic			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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 intestine carcinoma			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Thyroid cancer			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Tumour haemorrhage			
subjects affected / exposed	3 / 321 (0.93%)	2 / 316 (0.63%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour necrosis			

subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Tumour perforation			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	0 / 321 (0.00%)	0 / 316 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract neoplasm			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 321 (0.31%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral artery occlusion			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Hypotension			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Peripheral arterial occlusive disease			
subjects affected / exposed	2 / 321 (0.62%)	0 / 316 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			

subjects affected / exposed	0 / 321 (0.00%)	0 / 316 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vena cava thrombosis			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Venous thrombosis limb			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Surgical and medical procedures			
Gastrectomy			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Cytoreductive surgery			
subjects affected / exposed	0 / 321 (0.00%)	0 / 316 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour excision			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 321 (0.00%)	0 / 316 (0.00%)	0 / 39 (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

Disease progression			
subjects affected / exposed	0 / 321 (0.00%)	0 / 316 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Face oedema			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Fatigue			
subjects affected / exposed	0 / 321 (0.00%)	2 / 316 (0.63%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 321 (0.00%)	0 / 316 (0.00%)	0 / 39 (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
Generalised oedema			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Multi-organ failure			
subjects affected / exposed	1 / 321 (0.31%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema mucosal			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Oedema peripheral			
subjects affected / exposed	1 / 321 (0.31%)	3 / 316 (0.95%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	1 / 1	3 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			

subjects affected / exposed	0 / 321 (0.00%)	0 / 316 (0.00%)	2 / 39 (5.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Performance status decreased			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Pyrexia			
subjects affected / exposed	2 / 321 (0.62%)	6 / 316 (1.90%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Reproductive system and breast disorders			
Scrotal oedema			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 321 (0.62%)	0 / 316 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			

subjects affected / exposed	1 / 321 (0.31%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	2 / 321 (0.62%)	1 / 316 (0.32%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Laryngeal oedema			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Pneumothorax			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Pulmonary embolism			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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 fibrosis			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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 infarction			

subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Pulmonary oedema			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Respiratory failure			
subjects affected / exposed	2 / 321 (0.62%)	0 / 316 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract congestion			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract haemorrhage			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Confusional state			
subjects affected / exposed	0 / 321 (0.00%)	2 / 316 (0.63%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Aspartate aminotransferase			

increased			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Bilirubin conjugated increased			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood potassium decreased			
subjects affected / exposed	0 / 321 (0.00%)	0 / 316 (0.00%)	0 / 39 (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
Lipase increased			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Haemoglobin decreased			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Weight decreased			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			

Accidental overdose			
subjects affected / exposed	0 / 321 (0.00%)	0 / 316 (0.00%)	0 / 39 (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
Fall			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Femur fracture			
subjects affected / exposed	0 / 321 (0.00%)	0 / 316 (0.00%)	0 / 39 (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
Fracture			
subjects affected / exposed	0 / 321 (0.00%)	2 / 316 (0.63%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple fractures			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Overdose			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural bile leak			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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 pain			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Thermal burn			

subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Transfusion reaction			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Congenital, familial and genetic disorders			
Dermoid cyst			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina unstable			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	2 / 321 (0.62%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	2 / 321 (0.62%)	0 / 316 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Arrhythmia			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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

Atrial fibrillation			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 321 (0.00%)	0 / 316 (0.00%)	0 / 39 (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 congestive			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Cardio-respiratory arrest			
subjects affected / exposed	0 / 321 (0.00%)	2 / 316 (0.63%)	0 / 39 (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
Myocardial infarction			
subjects affected / exposed	1 / 321 (0.31%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve stenosis			
subjects affected / exposed	0 / 321 (0.00%)	0 / 316 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 321 (0.00%)	2 / 316 (0.63%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	2 / 321 (0.62%)	0 / 316 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			

subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Cerebral haemorrhage			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Cerebral infarction			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Cerebral ischaemia			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Cerebrovascular accident			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Cognitive disorder			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Complex partial seizures			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Convulsion			

subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Dizziness			
subjects affected / exposed	0 / 321 (0.00%)	0 / 316 (0.00%)	2 / 39 (5.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Haemorrhage intracranial			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Haemorrhagic stroke			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Hemiparesis			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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	1 / 321 (0.31%)	2 / 316 (0.63%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
IIIrd nerve paralysis			

subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Migraine			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Peripheral motor neuropathy			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Myelitis transverse			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Radiculopathy			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Sciatica			
subjects affected / exposed	2 / 321 (0.62%)	0 / 316 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status epilepticus			

subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Syncope			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 321 (1.87%)	3 / 316 (0.95%)	2 / 39 (5.13%)
occurrences causally related to treatment / all	1 / 7	1 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Neutropenia			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Thrombocytopenia			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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 distension			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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 mass			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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 hernia			

subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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 fissure			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	15 / 321 (4.67%)	12 / 316 (3.80%)	4 / 39 (10.26%)
occurrences causally related to treatment / all	1 / 15	5 / 14	2 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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	2 / 321 (0.62%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fistula			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 321 (0.31%)	4 / 316 (1.27%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic fistula			
subjects affected / exposed	0 / 321 (0.00%)	0 / 316 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			

subjects affected / exposed	3 / 321 (0.93%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Faecaloma			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Gastritis haemorrhagic			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Gastritis			
subjects affected / exposed	2 / 321 (0.62%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Gastrointestinal obstruction			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Gastrointestinal haemorrhage			

subjects affected / exposed	5 / 321 (1.56%)	5 / 316 (1.58%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	1 / 5	5 / 7	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	1 / 321 (0.31%)	2 / 316 (0.63%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Ileus			
subjects affected / exposed	2 / 321 (0.62%)	2 / 316 (0.63%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Intestinal obstruction			
subjects affected / exposed	4 / 321 (1.25%)	2 / 316 (0.63%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	1 / 5	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Intra-abdominal haemorrhage			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Jejunal perforation			

subjects affected / exposed	0 / 321 (0.00%)	2 / 316 (0.63%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Large intestinal stenosis			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Mechanical ileus			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Nausea			
subjects affected / exposed	2 / 321 (0.62%)	2 / 316 (0.63%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	1 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peptic ulcer			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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 haemorrhage			
subjects affected / exposed	0 / 321 (0.00%)	0 / 316 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 321 (0.31%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	2 / 321 (0.62%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	5 / 321 (1.56%)	3 / 316 (0.95%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	2 / 5	2 / 3	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	1 / 321 (0.31%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Cholangitis			
subjects affected / exposed	2 / 321 (0.62%)	2 / 316 (0.63%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic pain			
subjects affected / exposed	0 / 321 (0.00%)	0 / 316 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 321 (0.00%)	0 / 316 (0.00%)	0 / 39 (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
Hepatic function abnormal			
subjects affected / exposed	1 / 321 (0.31%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Jaundice cholestatic			

subjects affected / exposed	1 / 321 (0.31%)	2 / 316 (0.63%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Portal hypertension			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 321 (0.00%)	0 / 316 (0.00%)	0 / 39 (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
Exfoliative rash			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Erythema multiforme			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pityriasis rosea			
subjects affected / exposed	0 / 321 (0.00%)	0 / 316 (0.00%)	0 / 39 (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
Rash			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash generalised			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Anuria			
subjects affected / exposed	0 / 321 (0.00%)	0 / 316 (0.00%)	0 / 39 (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
Haematuria			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 321 (0.00%)	0 / 316 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pollakiuria			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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 impairment			
subjects affected / exposed	0 / 321 (0.00%)	0 / 316 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 321 (0.93%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Fibromyalgia			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint swelling			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Osteoporosis			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Osteoarthritis			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Pain in extremity			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Tenosynovitis			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Infections and infestations			
Abdominal infection			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal wall abscess			
subjects affected / exposed	0 / 321 (0.00%)	0 / 316 (0.00%)	0 / 39 (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
Appendicitis			

subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Bacterial sepsis			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Bronchitis			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 321 (0.31%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear infection			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Eye infection			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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	2 / 321 (0.62%)	0 / 316 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Helicobacter gastritis			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Infection			

subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious pleural effusion			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Lung infection			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Periodontitis			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Peritonitis			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Pneumonia			
subjects affected / exposed	3 / 321 (0.93%)	4 / 316 (1.27%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	1 / 3	1 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Post procedural infection			
subjects affected / exposed	0 / 321 (0.00%)	2 / 316 (0.63%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	0 / 321 (0.00%)	0 / 316 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			

subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (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
Sepsis			
subjects affected / exposed	2 / 321 (0.62%)	2 / 316 (0.63%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Upper respiratory tract infection			
subjects affected / exposed	1 / 321 (0.31%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	4 / 321 (1.25%)	2 / 316 (0.63%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 321 (1.25%)	0 / 316 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 321 (0.00%)	0 / 316 (0.00%)	0 / 39 (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
Diabetes mellitus			

subjects affected / exposed	2 / 321 (0.62%)	0 / 316 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid overload			
subjects affected / exposed	1 / 321 (0.31%)	0 / 316 (0.00%)	0 / 39 (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
Hypokalaemia			
subjects affected / exposed	1 / 321 (0.31%)	3 / 316 (0.95%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 1	1 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	3 / 321 (0.93%)	0 / 316 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomagnesaemia			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 321 (0.00%)	2 / 316 (0.63%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophosphataemia			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemia			
subjects affected / exposed	0 / 321 (0.00%)	1 / 316 (0.32%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Crossover Imatinib		
Total subjects affected by serious			

adverse events				
subjects affected / exposed	26 / 125 (20.80%)			
number of deaths (all causes)	7			
number of deaths resulting from adverse events	0			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Adenoma benign				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bladder cancer				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colon cancer				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric cancer				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal stromal tumour				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hodgkin's disease				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic neoplasm				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infected neoplasm				

subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lip and/or oral cavity cancer			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lung neoplasm malignant			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metastases to liver			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metastases to peritoneum			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neoplasm			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatic carcinoma metastatic			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Small intestine carcinoma			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thyroid cancer			

subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tumour haemorrhage				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tumour necrosis				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tumour perforation				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tumour pain				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract neoplasm				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Deep vein thrombosis				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Femoral artery occlusion				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypotension				

subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peripheral arterial occlusive disease				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thrombosis				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vena cava thrombosis				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Venous thrombosis limb				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				
Gastrectomy				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cytoreductive surgery				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tumour excision				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				

Asthenia			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Disease progression			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Face oedema			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Generalised oedema			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Multi-organ failure			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oedema mucosal			

subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oedema peripheral			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Performance status decreased			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	3 / 125 (2.40%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Scrotal oedema			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Atelectasis			

subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cough				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Interstitial lung disease				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Laryngeal oedema				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				

subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary fibrosis				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary infarction				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract congestion				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory tract haemorrhage				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Mental status changes				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Confusional state				

subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Alanine aminotransferase increased				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bilirubin conjugated increased				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood bilirubin increased				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood creatinine increased				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood potassium decreased				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lipase increased				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemoglobin decreased				

subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Weight decreased				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Accidental overdose				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fracture				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Multiple fractures				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Overdose				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post procedural bile leak				

subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Procedural pain				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thermal burn				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Transfusion reaction				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Congenital, familial and genetic disorders				
Dermoid cyst				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Angina unstable				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Angina pectoris				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Cardiac arrest				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arrhythmia				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardio-respiratory arrest				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mitral valve stenosis				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				

subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pericardial effusion				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Palpitations				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Altered state of consciousness				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral haemorrhage				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral infarction				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral ischaemia				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cognitive disorder				

subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Complex partial seizures			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Convulsion			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhage intracranial			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhagic stroke			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hemiparesis			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Headache			

subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ischaemic stroke			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
IIIrd nerve paralysis			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Loss of consciousness			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Migraine			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral motor neuropathy			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myelitis transverse			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Radiculopathy			

subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sciatica			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Status epilepticus			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 125 (2.40%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Abdominal distension				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal mass				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal hernia				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anal fissure				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	3 / 125 (2.40%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	2 / 125 (1.60%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Anal fistula				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				

subjects affected / exposed	2 / 125 (1.60%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Colonic fistula				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Faecaloma				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastritis haemorrhagic				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer haemorrhage				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrooesophageal reflux disease				

subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal obstruction				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematemesis				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematochezia				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhoids				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	3 / 125 (2.40%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 0			
Intestinal perforation				

subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intra-abdominal haemorrhage				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Jejunal perforation				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large intestinal stenosis				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mechanical ileus				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Peptic ulcer				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Small intestinal haemorrhage				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				

subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subileus				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	4 / 125 (3.20%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Bile duct obstruction				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic failure				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholangitis				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic pain				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperbilirubinaemia				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic function abnormal				

subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Jaundice				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Jaundice cholestatic				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Portal hypertension				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Dermatitis				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Exfoliative rash				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Erythema multiforme				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pityriasis rosea				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Rash				

subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rash generalised				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Anuria				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Haematuria				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pollakiuria				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal failure acute				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal impairment				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract obstruction				

subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fibromyalgia			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Joint swelling			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteoporosis			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tenosynovitis			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			

Abdominal infection				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal wall abscess				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bacterial sepsis				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ear infection				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Eye infection				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				

subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Helicobacter gastritis				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infectious pleural effusion				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Periodontitis				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Post procedural infection				

subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Postoperative wound infection				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Viral infection				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Decreased appetite				

subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	3 / 125 (2.40%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Diabetes mellitus				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fluid overload				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypokalaemia				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoglycaemia				
subjects affected / exposed	1 / 125 (0.80%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypomagnesaemia				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				
subjects affected / exposed	0 / 125 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypophosphataemia				

subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypovolaemia			
subjects affected / exposed	0 / 125 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	First-line Nilotinib	First-line Imatinib	Crossover Nilotinib
Total subjects affected by non-serious adverse events			
subjects affected / exposed	291 / 321 (90.65%)	289 / 316 (91.46%)	28 / 39 (71.79%)
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	27 / 321 (8.41%)	29 / 316 (9.18%)	0 / 39 (0.00%)
occurrences (all)	35	41	0
Face oedema			
subjects affected / exposed	5 / 321 (1.56%)	43 / 316 (13.61%)	0 / 39 (0.00%)
occurrences (all)	9	60	0
Fatigue			
subjects affected / exposed	66 / 321 (20.56%)	65 / 316 (20.57%)	7 / 39 (17.95%)
occurrences (all)	104	99	8
Oedema peripheral			
subjects affected / exposed	29 / 321 (9.03%)	68 / 316 (21.52%)	2 / 39 (5.13%)
occurrences (all)	38	94	2
Pyrexia			
subjects affected / exposed	23 / 321 (7.17%)	30 / 316 (9.49%)	3 / 39 (7.69%)
occurrences (all)	32	40	4
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	28 / 321 (8.72%)	21 / 316 (6.65%)	1 / 39 (2.56%)
occurrences (all)	37	31	3
Dyspnoea			

subjects affected / exposed	17 / 321 (5.30%)	21 / 316 (6.65%)	2 / 39 (5.13%)
occurrences (all)	22	24	2
Psychiatric disorders			
Insomnia			
subjects affected / exposed	21 / 321 (6.54%)	20 / 316 (6.33%)	1 / 39 (2.56%)
occurrences (all)	27	23	2
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	45 / 321 (14.02%)	18 / 316 (5.70%)	5 / 39 (12.82%)
occurrences (all)	63	22	7
Aspartate aminotransferase increased			
subjects affected / exposed	23 / 321 (7.17%)	15 / 316 (4.75%)	2 / 39 (5.13%)
occurrences (all)	30	17	2
Amylase increased			
subjects affected / exposed	8 / 321 (2.49%)	13 / 316 (4.11%)	2 / 39 (5.13%)
occurrences (all)	14	20	4
Blood alkaline phosphatase increased			
subjects affected / exposed	7 / 321 (2.18%)	3 / 316 (0.95%)	3 / 39 (7.69%)
occurrences (all)	8	3	3
Blood bilirubin increased			
subjects affected / exposed	32 / 321 (9.97%)	4 / 316 (1.27%)	2 / 39 (5.13%)
occurrences (all)	48	4	3
Gamma-glutamyltransferase increased			
subjects affected / exposed	9 / 321 (2.80%)	2 / 316 (0.63%)	4 / 39 (10.26%)
occurrences (all)	16	3	6
Haemoglobin decreased			
subjects affected / exposed	10 / 321 (3.12%)	20 / 316 (6.33%)	3 / 39 (7.69%)
occurrences (all)	17	25	3
Lipase increased			
subjects affected / exposed	27 / 321 (8.41%)	23 / 316 (7.28%)	1 / 39 (2.56%)
occurrences (all)	35	34	1
Neutrophil count decreased			
subjects affected / exposed	2 / 321 (0.62%)	24 / 316 (7.59%)	1 / 39 (2.56%)
occurrences (all)	2	40	1
Weight decreased			

subjects affected / exposed	27 / 321 (8.41%)	20 / 316 (6.33%)	3 / 39 (7.69%)
occurrences (all)	38	25	3
White blood cell count decreased			
subjects affected / exposed	3 / 321 (0.93%)	21 / 316 (6.65%)	0 / 39 (0.00%)
occurrences (all)	3	36	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	22 / 321 (6.85%)	19 / 316 (6.01%)	2 / 39 (5.13%)
occurrences (all)	31	28	2
Dysgeusia			
subjects affected / exposed	10 / 321 (3.12%)	9 / 316 (2.85%)	2 / 39 (5.13%)
occurrences (all)	13	12	2
Headache			
subjects affected / exposed	54 / 321 (16.82%)	24 / 316 (7.59%)	5 / 39 (12.82%)
occurrences (all)	76	35	6
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	38 / 321 (11.84%)	61 / 316 (19.30%)	7 / 39 (17.95%)
occurrences (all)	60	92	9
Neutropenia			
subjects affected / exposed	4 / 321 (1.25%)	42 / 316 (13.29%)	1 / 39 (2.56%)
occurrences (all)	7	72	1
Thrombocytopenia			
subjects affected / exposed	2 / 321 (0.62%)	5 / 316 (1.58%)	2 / 39 (5.13%)
occurrences (all)	2	11	2
Leukopenia			
subjects affected / exposed	4 / 321 (1.25%)	35 / 316 (11.08%)	1 / 39 (2.56%)
occurrences (all)	6	70	1
Eye disorders			
Eyelid oedema			
subjects affected / exposed	5 / 321 (1.56%)	55 / 316 (17.41%)	0 / 39 (0.00%)
occurrences (all)	8	87	0
Lacrimation increased			
subjects affected / exposed	3 / 321 (0.93%)	21 / 316 (6.65%)	0 / 39 (0.00%)
occurrences (all)	5	31	0
Periorbital oedema			

subjects affected / exposed	2 / 321 (0.62%)	58 / 316 (18.35%)	0 / 39 (0.00%)
occurrences (all)	2	89	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	17 / 321 (5.30%)	12 / 316 (3.80%)	1 / 39 (2.56%)
occurrences (all)	18	14	1
Abdominal pain			
subjects affected / exposed	63 / 321 (19.63%)	61 / 316 (19.30%)	6 / 39 (15.38%)
occurrences (all)	94	86	11
Constipation			
subjects affected / exposed	49 / 321 (15.26%)	24 / 316 (7.59%)	3 / 39 (7.69%)
occurrences (all)	68	31	4
Abdominal pain upper			
subjects affected / exposed	38 / 321 (11.84%)	15 / 316 (4.75%)	1 / 39 (2.56%)
occurrences (all)	47	16	1
Diarrhoea			
subjects affected / exposed	46 / 321 (14.33%)	106 / 316 (33.54%)	2 / 39 (5.13%)
occurrences (all)	65	170	3
Nausea			
subjects affected / exposed	73 / 321 (22.74%)	105 / 316 (33.23%)	12 / 39 (30.77%)
occurrences (all)	102	163	14
Stomatitis			
subjects affected / exposed	10 / 321 (3.12%)	14 / 316 (4.43%)	2 / 39 (5.13%)
occurrences (all)	11	19	2
Vomiting			
subjects affected / exposed	51 / 321 (15.89%)	65 / 316 (20.57%)	5 / 39 (12.82%)
occurrences (all)	69	105	6
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	63 / 321 (19.63%)	11 / 316 (3.48%)	3 / 39 (7.69%)
occurrences (all)	128	16	5
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	33 / 321 (10.28%)	13 / 316 (4.11%)	1 / 39 (2.56%)
occurrences (all)	40	20	1
Pruritus			

subjects affected / exposed	39 / 321 (12.15%)	25 / 316 (7.91%)	4 / 39 (10.26%)
occurrences (all)	62	42	5
Dry skin			
subjects affected / exposed	19 / 321 (5.92%)	21 / 316 (6.65%)	0 / 39 (0.00%)
occurrences (all)	29	25	0
Rash			
subjects affected / exposed	89 / 321 (27.73%)	46 / 316 (14.56%)	4 / 39 (10.26%)
occurrences (all)	139	85	4
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	20 / 321 (6.23%)	15 / 316 (4.75%)	2 / 39 (5.13%)
occurrences (all)	28	22	2
Back pain			
subjects affected / exposed	32 / 321 (9.97%)	18 / 316 (5.70%)	3 / 39 (7.69%)
occurrences (all)	46	23	5
Pain in extremity			
subjects affected / exposed	22 / 321 (6.85%)	16 / 316 (5.06%)	2 / 39 (5.13%)
occurrences (all)	26	22	4
Myalgia			
subjects affected / exposed	39 / 321 (12.15%)	17 / 316 (5.38%)	2 / 39 (5.13%)
occurrences (all)	49	22	3
Muscle spasms			
subjects affected / exposed	18 / 321 (5.61%)	47 / 316 (14.87%)	1 / 39 (2.56%)
occurrences (all)	25	81	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	25 / 321 (7.79%)	19 / 316 (6.01%)	1 / 39 (2.56%)
occurrences (all)	42	24	1
Upper respiratory tract infection			
subjects affected / exposed	8 / 321 (2.49%)	17 / 316 (5.38%)	0 / 39 (0.00%)
occurrences (all)	15	21	0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	15 / 321 (4.67%)	7 / 316 (2.22%)	2 / 39 (5.13%)
occurrences (all)	23	12	2
Decreased appetite			

subjects affected / exposed	40 / 321 (12.46%)	50 / 316 (15.82%)	5 / 39 (12.82%)
occurrences (all)	53	68	5
Hyperuricaemia			
subjects affected / exposed	2 / 321 (0.62%)	5 / 316 (1.58%)	2 / 39 (5.13%)
occurrences (all)	3	8	2
Hypophosphataemia			
subjects affected / exposed	20 / 321 (6.23%)	53 / 316 (16.77%)	3 / 39 (7.69%)
occurrences (all)	36	85	5
Hypokalaemia			
subjects affected / exposed	9 / 321 (2.80%)	19 / 316 (6.01%)	0 / 39 (0.00%)
occurrences (all)	9	31	0

Non-serious adverse events	Crossover Imatinib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	89 / 125 (71.20%)		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 125 (4.80%)		
occurrences (all)	10		
Face oedema			
subjects affected / exposed	13 / 125 (10.40%)		
occurrences (all)	13		
Fatigue			
subjects affected / exposed	12 / 125 (9.60%)		
occurrences (all)	14		
Oedema peripheral			
subjects affected / exposed	17 / 125 (13.60%)		
occurrences (all)	20		
Pyrexia			
subjects affected / exposed	4 / 125 (3.20%)		
occurrences (all)	8		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 125 (2.40%)		
occurrences (all)	3		
Dyspnoea			

subjects affected / exposed	5 / 125 (4.00%)		
occurrences (all)	5		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 125 (1.60%)		
occurrences (all)	2		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 125 (2.40%)		
occurrences (all)	3		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 125 (1.60%)		
occurrences (all)	5		
Amylase increased			
subjects affected / exposed	2 / 125 (1.60%)		
occurrences (all)	2		
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 125 (1.60%)		
occurrences (all)	2		
Blood bilirubin increased			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences (all)	1		
Haemoglobin decreased			
subjects affected / exposed	5 / 125 (4.00%)		
occurrences (all)	8		
Lipase increased			
subjects affected / exposed	6 / 125 (4.80%)		
occurrences (all)	7		
Neutrophil count decreased			
subjects affected / exposed	7 / 125 (5.60%)		
occurrences (all)	9		
Weight decreased			

subjects affected / exposed occurrences (all) White blood cell count decreased subjects affected / exposed occurrences (all)	3 / 125 (2.40%) 3 11 / 125 (8.80%) 16		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	 4 / 125 (3.20%) 4 3 / 125 (2.40%) 4 2 / 125 (1.60%) 2		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all)	 20 / 125 (16.00%) 22 11 / 125 (8.80%) 12 1 / 125 (0.80%) 1 10 / 125 (8.00%) 11		
Eye disorders Eyelid oedema subjects affected / exposed occurrences (all) Lacrimation increased subjects affected / exposed occurrences (all) Periorbital oedema	 19 / 125 (15.20%) 23 3 / 125 (2.40%) 4		

subjects affected / exposed occurrences (all)	9 / 125 (7.20%) 10		
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Stomatitis subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 1 / 125 (0.80%) 1 18 / 125 (14.40%) 19 3 / 125 (2.40%) 3 5 / 125 (4.00%) 10 17 / 125 (13.60%) 27 20 / 125 (16.00%) 25 1 / 125 (0.80%) 1 10 / 125 (8.00%) 24		
Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all)	 3 / 125 (2.40%) 3		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) Pruritus	 3 / 125 (2.40%) 3		

subjects affected / exposed	2 / 125 (1.60%)		
occurrences (all)	2		
Dry skin			
subjects affected / exposed	3 / 125 (2.40%)		
occurrences (all)	3		
Rash			
subjects affected / exposed	12 / 125 (9.60%)		
occurrences (all)	16		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 125 (2.40%)		
occurrences (all)	3		
Back pain			
subjects affected / exposed	3 / 125 (2.40%)		
occurrences (all)	3		
Pain in extremity			
subjects affected / exposed	3 / 125 (2.40%)		
occurrences (all)	3		
Myalgia			
subjects affected / exposed	2 / 125 (1.60%)		
occurrences (all)	2		
Muscle spasms			
subjects affected / exposed	2 / 125 (1.60%)		
occurrences (all)	2		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences (all)	3		
Upper respiratory tract infection			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	2 / 125 (1.60%)		
occurrences (all)	2		
Decreased appetite			

subjects affected / exposed	5 / 125 (4.00%)		
occurrences (all)	5		
Hyperuricaemia			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences (all)	1		
Hypophosphataemia			
subjects affected / exposed	10 / 125 (8.00%)		
occurrences (all)	12		
Hypokalaemia			
subjects affected / exposed	8 / 125 (6.40%)		
occurrences (all)	9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 April 2009	Amendment 1: To comply with the conduct of Phase III studies at the MD Anderson Cancer Center (MDAAC), an amendment to the current clinical protocol is needed, whereby pharmacokinetic (PK) sampling is not expected from MDACC patients randomized into this study.
18 December 2009	Amend 2: To clarify the inclusion criteria prior anti-neoplastic txmt.To exclude pts with "known symptomatic brain metastasis"To clarify the inclusion criteria for lab parameters(hematology &biochem)To clarify the cardiac & GI exclusion criteria.To remove the exclusion criterion for therapeutic use of coumarin derivatives based on the info in the current Glivec Basic Prescribing Info (BPI) & Tasigna Investigator Brochure (IB Ed. 5, study CAMN107A2123).To remove requirement of male contraception based on the info in the current Glivec Investigator Brochure (IB Edition 10) & Tasigna Basic Prescribing Info (BPI).To update the list of concomitant meds excluded while on study.To provide the most recent nilotinib safety update in the background section.To correct typographical errors in the visit eval schedule.To remove requirements of postbaseline chest CT or MRI scan, unless clinically indicated, & optionally allow follow up with chest Xray.To clarify the method of tumor assessments to be performed by local & central readers. To simplify efficacy & laboratory data collection in the extension study.To allow closing of the core study after the final efficacy analysis & to transition the remaining pts to the extension study.To reflect changes made to the stat analysis specifications which were previously implemented in the stat analysis planTo harmonize the testing approach for superiority & non-inferiority.To clarify the text on the grp sequential monitoring scheme implemented via a flexible alpha spending approach. To provide modifications & additions to the sensitivity analyses & subgrp analyses.In the extension protocol, to clarify the different objectives & specify appropriate stat analyses for pts entering the study after progression in the core versus those transitioning on same txmt following final core efficacy analysis.To provide a list of CYP3A4 inducers & inhibitors in the protocol.
04 March 2010	Amend 3: Clarify ambiguous wording, of the core protocol and post-text supplement 1 Amendment 2, with respect to the specific intent of efficacy assessment in the extension study. Remove reference to central ECG reading by eRT, in the extension study, as per Amendment 2, of Post-text supplement 1.
21 April 2011	Amend 4: The purpose of this amendment is to implement the recommendations of the Data Monitoring Committee (DMC). At a meeting that was held on 4th April 2011 the DMC reviewed the results of an interim futility analysis. The DMC observed that that the futility boundary had been exceeded and therefore concluded that the study was highly unlikely to meet its primary endpoint. The majority of deaths in both arms were associated with progression of GIST. Therefore it was recommended that all patients currently enrolled in the core study who are receiving nilotinib should be offered the opportunity to receive treatment with imatinib. The DMC also recommended that patients who were receiving nilotinib and considered by the investigators to be deriving benefit should also have the option of remaining on the medication. In addition, the DMC recommended that patient recruitment should be stopped immediately (accrual was terminated on 8th April 2011). At a meeting on 7th April 2011 the SC concurred with the recommendation of DMC. The protocol is being amended to offer patients who are on-going in the nilotinib arm, who have not had disease progression, the option to enter the extension study in order to change therapy to imatinib.

28 July 2011	Amend 5: the purpose of this amendment was to define the transition of patients from the Core study to the Extension study due to termination of the Core study. Patients who were on imatinib (study drug) at the time of the closure of the Core study were to be transitioned to an alternative supply of Glivec®/Gleevec® wherever possible. In cases where it was not possible to transfer patients to commercial or other sources of Glivec®/Gleevec®, transition plans were put in place on a country-by-country basis and ensured that patients continued to receive imatinib. Patients who were on nilotinib at the time of the closure of the Core study were to be offered the opportunity to switch to Glivec®/Gleevec®. For those patients who were deriving benefit from nilotinib and the physician/patient preferred to continue nilotinib therapy, the Extension study remained open in order to provide continued access to nilotinib study drug until progression, death or withdrawal of consent unless it was otherwise required by individual HA to switch all nilotinib patients to imatinib (e.g. AFSSAPS-French HA).In addition, changes had been made to the statistical analysis plan. This amendment also included other administrative corrections and clarifications.
25 September 2012	Amend 6: the purpose of this amendment was to specify the close-out of the Extension study, defined as the LPLV (Extension) of 30-Jun-2013 which was inclusive of the 28 days follow-up period. Following the HA/ethics committee approval of amendment 6, every effort was to be made for patients to return to the sites for a scheduled or unscheduled visit (whichever was closest to the HA/ethics committee protocol approval date) to discontinue patients off the Extension study. At the time of this visit, patients on treatment were to complete the Extension end of treatment procedures. Patients deriving benefit from the treatment with imatinib, as determined by the Investigator were to make every effort to switch to commercial Glivec®/Gleevec® or an alternative supply upon discontinuation from the Extension study. In the event that patients were unable to obtain commercial Glivec®/Gleevec® or an alternative supply (i.e. patient access program) despite all efforts, these patients were eligible to enroll into the imatinib rollover protocol [Study STI571A2406]to maintain their current treatment, per the discretion of the Sponsor. Patients on nilotinib who had maintained their originally assigned treatment from the Core to Extension might have switched to commercial Glivec®/Gleevec® or an alternative supply as determined by the Investigator, upon discontinuation from the Extension protocol. Alternatively, patients deriving benefit on nilotinib were eligible to enroll into the nilotinib rollover protocol [Study AMN107A2409] and maintain their current treatment.Patients who consented for the Extension survival follow-up were also to be contacted to discontinue from the Extension study. Those patients in the survival follow-up who did not return by the Extension LPLV date were considered lost to follow-up.
16 December 2013	Amend 7: the purpose of this amendment was to extend the LPLV date of 30-Jun-2013 to allow the remaining three countries to establish viable solutions for the treatment of the ongoing patients prior to the closure of Study CAMN107G2301. In December 2013, patients were still ongoing in Romania (six patients on imatinib), China (26 patients on imatinib; three patients on nilotinib), and Germany (three patients on nilotinib). The new targeted LPLV (inclusive of the 28 days safety follow-up period), was dependent upon the availability of alternative options for the remaining patients to be able to receive drug after discontinuation from the CAMN107G2301 study. Ongoing patients must have maintained their current treatment and remained on the study until an alternative option was available for receipt of drug, or until the occurrence of disease progression, unacceptable toxicities, withdrawal of consent or death. LPLV occurred on 23-Oct-2014.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Due to EudraCT system limitations, which EMA is aware of, results of crossover studies are not accurately represented in this record. Please go to https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Notes: