

**Clinical trial results:**

**A Randomized Two-by-Two, Multicenter, Open-Label Phase III Study of BMS-354825 Administered Orally at a Dose of 50 mg or 70 mg Twice Daily or 100 mg or 140 mg Once Daily in Subjects with Chronic Phase Philadelphia Chromosome or BCR-ABL Positive Chronic Myelogenous Leukemia Who are Resistant or Intolerant to Imatinib Mesylate.**

**Summary**

EudraCT number	2005-001294-99
Trial protocol	AT SE GB HU DK IE CZ FI IT EE ES DE BE
Global end of trial date	14 July 2014

**Results information**

Result version number	v1 (current)
This version publication date	22 April 2016
First version publication date	22 April 2016

**Trial information****Trial identification**

Sponsor protocol code	CA180-034
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00123474
WHO universal trial number (UTN)	-

Notes:

**Sponsors**

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com

Notes:

**Paediatric regulatory details**

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 July 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	14 July 2014
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The main objective of the study was to compare the efficacy of BMS-354825 as defined by major cytogenetic response when administered once daily relative to BMS-354825 administered twice daily in the treatment of chronic phase chronic myelogenous leukemia imatinib-resistant subjects.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 July 2005
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	7 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 36
Country: Number of subjects enrolled	Australia: 18
Country: Number of subjects enrolled	Brazil: 45
Country: Number of subjects enrolled	Canada: 14
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	Israel: 5
Country: Number of subjects enrolled	Korea, Republic of: 46
Country: Number of subjects enrolled	Mexico: 15
Country: Number of subjects enrolled	Netherlands: 8
Country: Number of subjects enrolled	Peru: 2
Country: Number of subjects enrolled	Philippines: 7
Country: Number of subjects enrolled	Poland: 19
Country: Number of subjects enrolled	Russian Federation: 18
Country: Number of subjects enrolled	South Africa: 9
Country: Number of subjects enrolled	Singapore: 7
Country: Number of subjects enrolled	Switzerland: 11
Country: Number of subjects enrolled	Taiwan: 4

Country: Number of subjects enrolled	United States: 224
Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Sweden: 10
Country: Number of subjects enrolled	United Kingdom: 31
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Belgium: 19
Country: Number of subjects enrolled	Czech Republic: 8
Country: Number of subjects enrolled	Denmark: 16
Country: Number of subjects enrolled	France: 69
Country: Number of subjects enrolled	Germany: 42
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Ireland: 11
Country: Number of subjects enrolled	Italy: 19
Worldwide total number of subjects	724
EEA total number of subjects	263

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)	534
From 65 to 84 years	190
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Study initiated July 2005 and completed July 2014.

### Pre-assignment

Screening details:

724 subjects were enrolled, 670 were randomized, and 662 were treated with study drug. Reasons for non-randomization: 38 no longer met criteria, 8 other reasons, 7 withdrew consent, and 1 death. 1 subject was randomized to 100 mg once daily but received 50 mg twice daily; 1 subject was randomized to 50 mg twice daily but received 100 mg once daily.

### Period 1

Period 1 title	As Treated (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Dasatinib 100 mg QD

Arm description:

Subjects received dasatinib 100 mg once daily until progression of disease, development of intolerable toxicity, or the subject's decision to withdraw.

Arm type	Experimental
Investigational medicinal product name	Dasatinib
Investigational medicinal product code	BMS-354825-03
Other name	Sprycel
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2 Dasatinib 50-mg tablets were administered once daily until progression of disease, development of intolerable toxicity, or the subject's decision to withdraw.

<b>Arm title</b>	Dasatinib 140 mg QD
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Arm description:

Subjects received dasatinib 140 mg once daily until progression of disease, development of intolerable toxicity, or the subject's decision to withdraw.

Arm type	Experimental
Investigational medicinal product name	Dasatinib
Investigational medicinal product code	BMS-354825-03
Other name	Sprycel
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2 Dasatinib 20-mg and 50-mg tablets were administered once daily until progression of disease, development of intolerable toxicity, or the subject's decision to withdraw.

<b>Arm title</b>	Dasatinib 50 mg BID
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Arm description:

Subjects received dasatinib 50 mg twice daily until progression of disease, development of intolerable toxicity, or the subject's decision to withdraw. After the 2-year analysis, and with Protocol Amendment 02, subjects on a twice daily dosing schedule were allowed to switch to a once daily dosing schedule.

Arm type	Experimental
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Investigational medicinal product name	Dasatinib
Investigational medicinal product code	BMS-354825-03
Other name	Sprycel
Pharmaceutical forms	Tablet
Routes of administration	Oral use

**Dosage and administration details:**

Dasatinib 50-mg tablet was administered twice daily and switching to once daily was allowed after the 2-year analysis, and with protocol amendment 02, until progression of disease, development of intolerable toxicity, or the subject's decision to withdraw.

<b>Arm title</b>	Dasatinib 70 mg BID
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**Arm description:**

Subjects received dasatinib 70 mg twice daily until progression of disease, development of intolerable toxicity, or the subject's decision to withdraw. After the 2-year analysis, and with Protocol Amendment 02, subjects on a BID dosing schedule were allowed to switch to a QD dosing schedule.

Arm type	Experimental
Investigational medicinal product name	Dasatinib
Investigational medicinal product code	BMS-354825-03
Other name	Sprycel
Pharmaceutical forms	Tablet
Routes of administration	Oral use

**Dosage and administration details:**

Dasatinib 50-mg and 20-mg tablets were administered twice daily and switching to once daily was allowed after the 2-year analysis, and with protocol amendment 02, until progression of disease, development of intolerable toxicity, or the subject's decision to withdraw.

<b>Number of subjects in period 1<sup>[1]</sup></b>	Dasatinib 100 mg QD	Dasatinib 140 mg QD	Dasatinib 50 mg BID
Started	167	167	168
Randomized	167	167	168
Completed	0	0	0
Not completed	167	167	168
Consent withdrawn by subject	14	19	18
Disease progression	35	42	29
Adverse event, non-fatal	10	4	10
Study drug toxicity	39	45	45
Not reported	1	-	-
Randomized, never treated	1	4	2
Treated in 50 mg BID arm	1	-	-
Other reasons	54	47	57
Investigator request	12	6	7

<b>Number of subjects in period 1<sup>[1]</sup></b>	Dasatinib 70 mg BID
Started	168
Randomized	168

Completed	0
Not completed	168
Consent withdrawn by subject	16
Disease progression	27
Adverse event, non-fatal	8
Study drug toxicity	51
Not reported	-
Randomized, never treated	1
Treated in 50 mg BID arm	-
Other reasons	60
Investigator request	5

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Notes:

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

Justification: 724 subjects were enrolled, 670 were randomized. Reasons for non-randomization: 38 no longer met criteria, 8 other reasons, 7 withdrew consent, and 1 death.

## Baseline characteristics

### Reporting groups

Reporting group title	Dasatinib 100 mg QD
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Reporting group description:

Subjects received dasatinib 100 mg once daily until progression of disease, development of intolerable toxicity, or the subject's decision to withdraw.

Reporting group title	Dasatinib 140 mg QD
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Reporting group description:

Subjects received dasatinib 140 mg once daily until progression of disease, development of intolerable toxicity, or the subject's decision to withdraw.

Reporting group title	Dasatinib 50 mg BID
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Reporting group description:

Subjects received dasatinib 50 mg twice daily until progression of disease, development of intolerable toxicity, or the subject's decision to withdraw. After the 2-year analysis, and with Protocol Amendment 02, subjects on a twice daily dosing schedule were allowed to switch to a once daily dosing schedule.

Reporting group title	Dasatinib 70 mg BID
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Reporting group description:

Subjects received dasatinib 70 mg twice daily until progression of disease, development of intolerable toxicity, or the subject's decision to withdraw. After the 2-year analysis, and with Protocol Amendment 02, subjects on a BID dosing schedule were allowed to switch to a QD dosing schedule.

Reporting group values	Dasatinib 100 mg QD	Dasatinib 140 mg QD	Dasatinib 50 mg BID
Number of subjects	167	167	168
Age categorical Units: Subjects			
<=65 years	121	128	130
>65 years	46	39	38
Age continuous Units: years			
arithmetic mean	54.6	53.7	53.3
standard deviation	± 13.6	± 15	± 14.6
Gender categorical Units: Subjects			
Female	83	97	83
Male	84	70	85
Imatinib status			
Primary Resistance: no decrease in white blood cell count after ≥4 weeks imatinib/not achieved a complete hematologic response after 3 months, a major cytogenetic response (MCyR) after 6 months, or a complete cytogenetic response (CCyR) after 12 months. Acquired resistance: achieved MCyR and no longer met the criteria for MCyR. Intolerance: Grade ≥3 toxicity considered at least possibly related to imatinib at a dose of ≤400 mg/day which led to discontinuation of therapy; tolerated the dose of 400 mg but did not achieve a CCyR and subsequently did not tolerate doses ≥600 mg.			
Units: Subjects			
Primary Resistance to Imatinib	75	78	88
Acquired Resistance to Imatinib	49	45	36
Intolerant to Imatinib	43	44	44

Reporting group values	Dasatinib 70 mg BID	Total	
Number of subjects	168	670	

Age categorical Units: Subjects			
<=65 years	125	504	
>65 years	43	166	
Age continuous Units: years			
arithmetic mean	53.7		
standard deviation	± 15	-	
Gender categorical Units: Subjects			
Female	91	354	
Male	77	316	
Imatinib status			
Primary Resistance: no decrease in white blood cell count after ≥4 weeks imatinib/not achieved a complete hematologic response after 3 months, a major cytogenetic response (MCyR) after 6 months, or a complete cytogenetic response (CCyR) after 12 months. Acquired resistance: achieved MCyR and no longer met the criteria for MCyR. Intolerance: Grade ≥3 toxicity considered at least possibly related to imatinib at a dose of ≤400 mg/day which led to discontinuation of therapy; tolerated the dose of 400 mg but did not achieve a CCyR and subsequently did not tolerate doses ≥600 mg.			
Units: Subjects			
Primary Resistance to Imatinib	81	322	
Acquired Resistance to Imatinib	45	175	
Intolerant to Imatinib	42	173	



## End points

### End points reporting groups

Reporting group title	Dasatinib 100 mg QD
Reporting group description: Subjects received dasatinib 100 mg once daily until progression of disease, development of intolerable toxicity, or the subject's decision to withdraw.	
Reporting group title	Dasatinib 140 mg QD
Reporting group description: Subjects received dasatinib 140 mg once daily until progression of disease, development of intolerable toxicity, or the subject's decision to withdraw.	
Reporting group title	Dasatinib 50 mg BID
Reporting group description: Subjects received dasatinib 50 mg twice daily until progression of disease, development of intolerable toxicity, or the subject's decision to withdraw. After the 2-year analysis, and with Protocol Amendment 02, subjects on a twice daily dosing schedule were allowed to switch to a once daily dosing schedule.	
Reporting group title	Dasatinib 70 mg BID
Reporting group description: Subjects received dasatinib 70 mg twice daily until progression of disease, development of intolerable toxicity, or the subject's decision to withdraw. After the 2-year analysis, and with Protocol Amendment 02, subjects on a BID dosing schedule were allowed to switch to a QD dosing schedule.	
Subject analysis set title	QD Dasatinib
Subject analysis set type	Intention-to-treat
Subject analysis set description: Subjects received dasatinib either 100 mg or 140 mg once daily until progression of disease, development of intolerable toxicity, or the subject's decision to withdraw.	
Subject analysis set title	BID Dasatinib
Subject analysis set type	Intention-to-treat
Subject analysis set description: Subjects received dasatinib either 50 mg or 70 mg twice daily until progression of disease, development of intolerable toxicity, or the subject's decision to withdraw.	
Subject analysis set title	Dasatinib 100 mg Total Daily Dose
Subject analysis set type	Intention-to-treat
Subject analysis set description: Subjects received dasatinib 100 mg as a total daily dose (either 50 mg twice daily or 100 mg once daily) until progression of disease, development of intolerable toxicity, or the subject's decision to withdraw.	
Subject analysis set title	Dasatinib 140 mg Total Daily Dose
Subject analysis set type	Intention-to-treat
Subject analysis set description: Subjects received dasatinib 140 mg as a total daily dose (either 70 mg twice daily or 140 mg once daily) until progression of disease, development of intolerable toxicity, or the subject's decision to withdraw.	
Subject analysis set title	Other Treatment Groups
Subject analysis set type	Safety analysis
Subject analysis set description: Subjects participated in all other treatment arms until progression of disease, development of intolerable toxicity, or the subject's decision to withdraw.	
Subject analysis set title	Total
Subject analysis set type	Safety analysis
Subject analysis set description: Subjects received study drug in any schedule or total daily dose until progression of disease, development of intolerable toxicity, or the subject's decision to withdraw.	

**Primary: Percentage of Subjects With Major Cytogenetic Response (MCyR) After at Least 6 Months Follow-Up - Imatinib-Resistant Subjects**

End point title	Percentage of Subjects With Major Cytogenetic Response (MCyR) After at Least 6 Months Follow-Up - Imatinib-Resistant Subjects
End point description: Cytogenetic response (CyR) was based on the number of Philadelphia chromosome positive (Ph+) metaphases among cells in metaphase on a Bone Marrow (BM) sample. The criteria for CyR were as follows: Complete cytogenetic response (CCyR): 0% Ph+ cells in metaphase in BM; Partial CyR (PCyR): >0 to 35% Ph+ cells in metaphase in BM; Minor cytogenetic response: >35 to 65% Ph+ cells in metaphase in BM; Minimal cytogenetic response: >65 to 95% Ph+ cells in metaphase in BM; No cytogenetic response: >95 to 100% Ph+ cells in metaphase in BM; Best CyR was defined as the best response obtained at any time during the study; MCyR was defined as a best CyR of CCyR or PCyR. Baseline=closest to, but no later than, the first day of study drug for treated subjects and closest to, but no later than, the date of randomization, for those who were randomized but who never received treatment, unless otherwise specified. All randomized imatinib-resistant subjects with available data were summarized	
End point type	Primary
End point timeframe: Baseline up to at Least 6 Months follow-up	

End point values	QD Dasatinib	BID Dasatinib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	247	251		
Units: Percentage of subjects				
number (confidence interval 95%)	51.8 (45.4 to 58.2)	49 (42.7 to 55.4)		

**Statistical analyses**

<b>Statistical analysis title</b>	MCyR: 6 month follow-up analysis
Comparison groups	QD Dasatinib v BID Dasatinib
Number of subjects included in analysis	498
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[1]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	11.6

Notes:

[1] - Non-inferiority of the QD schedule relative to the BID schedule was deduced if the lower bound of the 95% confidence interval (CI) for the MCyR QD minus MCyR BID difference was greater than or equal to -15%.

**Secondary: Percentage of Subjects With Major Cytogenetic Response (MCyR) at or Prior to 24 Months Follow-Up - Imatinib-Resistant Subjects**

End point title	Percentage of Subjects With Major Cytogenetic Response (MCyR) at or Prior to 24 Months Follow-Up - Imatinib-Resistant
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## End point description:

Cytogenetic response (CyR) was based on the number of Philadelphia chromosome positive (Ph+) metaphases among cells in metaphase on a Bone Marrow (BM) sample. The criteria for CyR were as follows: Complete cytogenetic response (CCyR): 0% Ph+ cells in metaphase in BM; Partial CyR (PCyR): >0 to 35% Ph+ cells in metaphase in BM; Minor cytogenetic response: >35 to 65% Ph+ cells in metaphase in BM; Minimal cytogenetic response: >65 to 95% Ph+ cells in metaphase in BM; No cytogenetic response: >95 to 100% Ph+ cells in metaphase in BM; Best CyR was defined as the best response obtained at any time during the study; MCyR was defined as a best CyR of CCyR or PCyR. Baseline=closest to, but no later than, the first day of study drug for treated subjects and closest to, but no later than, the date of randomization, for those who were randomized but who never received treatment, unless otherwise specified. All randomized imatinib-resistant subjects with available data were summarized.

End point type	Secondary
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End point timeframe:

Baseline up to 24 Months Follow-Up

End point values	QD Dasatinib	BID Dasatinib	Dasatinib 100 mg Total Daily Dose	Dasatinib 140 mg Total Daily Dose
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	247	250	248	249
Units: Percentage of subjects				
number (confidence interval 95%)	58.3 (51.9 to 64.5)	56.4 (50 to 62.6)	57.3 (50.8 to 63.5)	57.4 (51 to 63.7)

## Statistical analyses

<b>Statistical analysis title</b>	MCyR: At or Prior to 24 Months Follow-Up
Comparison groups	QD Dasatinib v BID Dasatinib
Number of subjects included in analysis	497
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[2]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.8
upper limit	10.6

Notes:

[2] - Non-inferiority of the QD schedule relative to the BID schedule was deduced if the lower bound of the 95% CI for the MCyRRQD minus MCyRRBID difference was greater than or equal to -15%.

<b>Statistical analysis title</b>	MCyR: At or Prior to 24 Months Follow-Up
Comparison groups	Dasatinib 100 mg Total Daily Dose v Dasatinib 140 mg Total Daily Dose

Number of subjects included in analysis	497
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[3]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.9
upper limit	8.5

Notes:

[3] - Non-inferiority of 100 mg total daily dose relative to 140 mg total daily dose was deduced if the lower bound of the 95% CI for the difference was greater than or equal to -15%.

### Secondary: Percentage of Subjects With Complete Hematologic Response (CHR) After at Least 6 and 24 Months Follow-Up - Imatinib-Resistant Subjects

End point title	Percentage of Subjects With Complete Hematologic Response (CHR) After at Least 6 and 24 Months Follow-Up - Imatinib-Resistant Subjects
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End point description:

CHR was obtained when all the following criteria were met: White Blood Cells  $\leq$  institutional upper limit of normal (ULN); Platelets  $< 450,000/\text{mm}^3$ ; No blasts or promyelocytes in peripheral blood (PB);  $< 5\%$  myelocytes plus metamyelocytes in PB; Basophils in PB  $< 20\%$ ; No extramedullary involvement (including no splenomegaly or hepatomegaly). Hematologic responses were counted anytime following 14 days after the dosing start date. All randomized imatinib-resistant subjects with available data were summarized. Here, 'n' signifies evaluable subjects for specified categories in respective treatment arms.

End point type	Secondary
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End point timeframe:

Baseline up to at Least 6 and 24 Months Follow-Up

End point values	Dasatinib 100 mg QD	Dasatinib 140 mg QD	Dasatinib 50 mg BID	Dasatinib 70 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	124	123	124	126
Units: Percentage of subjects				
number (confidence interval 95%)				
6 Months (n=124, 123, 124, 126)	86.3 (79 to 91.8)	85.4 (77.9 to 91.1)	91.1 (84.7 to 95.5)	87.4 (80.3 to 92.6)
24 Months (n=124, 123, 124, 126)	88.7 (81.8 to 93.7)	86.2 (78.8 to 91.7)	91.9 (85.7 to 96.1)	88.9 (82.1 to 93.8)

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Major Cytogenetic Response (MCyR) in Subjects With MCyR After At Least 24 Months Follow-Up - Imatinib-Resistant Subjects

End point title	Time to Major Cytogenetic Response (MCyR) in Subjects With MCyR After At Least 24 Months Follow-Up - Imatinib-Resistant Subjects
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**End point description:**

Time to MCyR was defined as the time from the first dosing date until criteria were first met for complete cytogenetic response or partial cytogenetic response, whichever occurred first. Non-responders were censored at the maximum time of all subjects in their respective group (that is, maximum between time to MCyR response for responders and time to last cytogenetic assessment for non-responders). All randomized imatinib-resistant subjects with MCyR and available data were summarized.

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End point type	Secondary
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End point timeframe:

Baseline up to at Least 24 Months Follow-Up

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End point values	Dasatinib 100 mg QD	Dasatinib 140 mg QD	Dasatinib 50 mg BID	Dasatinib 70 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	73	71	69	72
Units: Months				
median (confidence interval 95%)	2.9 (2.8 to 3.4)	2.8 (2.8 to 3)	2.9 (2.8 to 3.3)	2.9 (2.8 to 3)

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**Statistical analyses**

No statistical analyses for this end point

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**Secondary: Time to Complete Hematologic Response (CHR) in Subjects With CHR After at Least 24 Months Follow-Up - Imatinib-Resistant Subjects**

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End point title	Time to Complete Hematologic Response (CHR) in Subjects With CHR After at Least 24 Months Follow-Up - Imatinib-Resistant Subjects
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End point description:

Time to CHR was defined as the time from the first dosing date until criteria are first met for the response. Non-responders were censored at the maximum time of all subjects in their respective group (that is, maximum between time to CHR response for responders and time to last hematologic assessment for non-responders). Cytogenetic assessments were not done after the 2 Year Follow-up. All randomized imatinib-resistant subjects with CHR were summarized.

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End point type	Secondary
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End point timeframe:

Baseline up to at Least 24 Months Follow-up

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End point values	Dasatinib 100 mg QD	Dasatinib 140 mg QD	Dasatinib 50 mg BID	Dasatinib 70 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	110	106	114	112
Units: Months				
median (confidence interval 95%)	0.5 (0.5 to 0.6)	0.5 (0.5 to 0.7)	0.6 (0.5 to 0.9)	0.7 (0.5 to 0.9)

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects With Major Cytogenetic Response (MCyR) Whose Disease Progressed - Imatinib-Resistant Subjects

End point title	Number of Subjects With Major Cytogenetic Response (MCyR) Whose Disease Progressed - Imatinib-Resistant Subjects
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End point description:

Progression in a subject=subject achieved a complete hematologic response (CHR) and no longer met the criteria consistently over consecutive 2-weeks after starting their maximum dose; had no CHR after receiving their maximum dose and had a doubling of the white blood cell count from the lowest value to  $>20,000/\text{mm}^3$  or an increase by  $>50,000/\text{mm}^3$  on two assessments performed at least 2 weeks apart; subject met criteria of accelerated or blast phase chronic myelogenous leukemia at any time; had a MCyR and subsequently no longer met the criteria for MCyR after starting their maximum dose; had a  $\geq 30\%$  absolute increase in the number of Philadelphia chromosome positive metaphases. Medium duration of MCyR could not be estimated because the majority of subjects with MCyR continued to respond, or could not be reliably estimated because of the large number of censored subjects. All imatinib-resistant subjects who had achieved MCyR and experienced disease progression were summarized.

End point type	Secondary
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End point timeframe:

Baseline up to at Least 24 Months Follow-Up

End point values	Dasatinib 100 mg QD	Dasatinib 140 mg QD	Dasatinib 50 mg BID	Dasatinib 70 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	73	71	69	72
Units: Subjects	5	17	6	9

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects With Complete Hematologic Response (CHR) Whose Disease Progressed - Imatinib-Resistant Subjects

End point title	Number of Subjects With Complete Hematologic Response (CHR) Whose Disease Progressed - Imatinib-Resistant Subjects
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End point description:

Progression in a subject=achieved a CHR and subsequently no longer met the criteria consistently over a consecutive 2-week period after starting their maximum dose; had no CHR after receiving their maximum dose and had a doubling of the white blood cell count from the lowest value to  $>20,000/\text{mm}^3$  or an increase by  $>50,000/\text{mm}^3$  on two assessments performed at least 2 weeks apart; met the criteria of accelerated or blast phase chronic myelogenous leukemia at any time; had a major cytogenetic response (MCyR) and subsequently no longer met the criteria for MCyR after starting their maximum dose; had a  $\geq 30\%$  absolute increase in the number of Philadelphia chromosome positive metaphases. Medium duration of CHR could not be estimated because the majority of subjects with CHR continued to respond, or could not be reliably estimated because of the large number of censored subjects. All imatinib-resistant subjects who achieved CHR and then experienced disease progression were summarized.

End point type	Secondary
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End point timeframe:

Baseline up to at Least 24 Months Follow-Up

End point values	Dasatinib 100 mg QD	Dasatinib 140 mg QD	Dasatinib 50 mg BID	Dasatinib 70 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	110	106	114	112
Units: Subjects	18	28	22	24

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects With Major Cytogenetic Response (MCyR) and Baseline BCR-ABL Gene Mutation - All Treated Subjects

End point title	Number of Subjects With Major Cytogenetic Response (MCyR) and Baseline BCR-ABL Gene Mutation - All Treated Subjects
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End point description:

BCR-ABL mutations were assessed in subjects prior to the start of study drug (baseline) and at the time of disease progression or at end of therapy. Quantification of BCR-ABL transcripts in peripheral blood was evaluated using quantitative reverse transcriptase polymerase chain reaction (Q-RT-PCR, RT-PCR). All randomized, treated subjects with available mutation data were summarized.

End point type	Secondary
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End point timeframe:

Baseline up to 2 Years

End point values	Dasatinib 100 mg QD	Dasatinib 140 mg QD	Dasatinib 50 mg BID	Dasatinib 70 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	147	139	149	146
Units: Subjects				
Imatinib-resistant mutations	49	49	62	48
Mutations with unknown Imatinib-resistance status	0	1	1	2
Imatinib resistant or unknown mutations	49	50	63	50
Polymorphisms	0	2	0	0
No mutations	98	87	96	96

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Imatinib-Resistant Subjects With Progression Free Survival (PFS) After at Least 24, 36, 48, 60, 72, and 84 Months Follow-Up

End point title	Percentage of Imatinib-Resistant Subjects With Progression
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## End point description:

PFS=time from randomization until: complete hematologic response (CHR) achieved and subject subsequently no longer met criteria for CHR over 2 weeks; no CHR after receiving maximum dose and had a doubling of the white blood cell count from the lowest value to  $>20,000/\text{mm}^3$  or an increase by  $> 50,000/\text{mm}^3$  on 2 assessments performed 2 weeks apart); subject met criteria of accelerated phase or blast phase chronic myelogenous leukemia; had MCyR and subsequently no longer met criteria for MCyR after starting maximum dose;  $\geq 30\%$  absolute increase in number of Philadelphia chromosome positive metaphases. Deaths without a reported prior progression were considered to have progressed on the date of death; those who neither progressed nor died were censored on the date of their last cytogenetic or hematologic assessment. If the first progression reported during follow-up was death, subject considered to have progressed at date of death. All randomized imatinib-resistant subjects were summarized.

End point type	Secondary
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End point timeframe:

Baseline up to 84 months follow up

End point values	Dasatinib 100 mg QD	Dasatinib 140 mg QD	Dasatinib 50 mg BID	Dasatinib 70 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	124	123	124	126
Units: Percentage of subjects				
number (confidence interval 95%)				
24 Months (n=124, 123, 124, 126)	75.2 (66.3 to 82.1)	61.3 (52.7 to 69.6)	70.3 (60.8 to 77.9)	70.8 (61.6 to 78.2)
36 Months (n=124, 123, 124, 126)	64.8 (55.2 to 72.9)	47.4 (37.7 to 56.5)	67.1 (57.3 to 75.1)	58.2 (48.4 to 66.8)
48 Months (n=124, 123, 124, 126)	57.8 (48 to 66.5)	40 (30.6 to 49.3)	63.8 (53.7 to 72.2)	55.1 (45.2 to 64.8)
60 Months (n=124, 123, 124, 126)	50.2 (40.2 to 59.3)	36.4 (27.1 to 45.8)	57.4 (46.9 to 66.5)	50.2 (40.2 to 59.4)
72 Months (n=124, 123, 124, 126)	44 (34 to 53.6)	31.4 (22.4 to 40.8)	50.7 (40 to 60.4)	45.3 (35.2 to 54.8)
84 Months (n=124, 123, 124, 126)	39 (29.2 to 48.7)	30.2 (21.2 to 39.6)	42.1 (31.5 to 52.4)	41.3 (31.3 to 51)

## Statistical analyses

No statistical analyses for this end point

**Secondary: Percentage of Imatinib-Resistant Subjects With Overall Survival (OS) After at Least 24, 36, 48, 60, 72, and 84 Months Follow-Up**

End point title	Percentage of Imatinib-Resistant Subjects With Overall Survival (OS) After at Least 24, 36, 48, 60, 72, and 84 Months Follow-Up
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## End point description:

OS was defined as the time from randomization until death. Survival data were collected for up to 5 years on subjects who had discontinued dasatinib treatment. Subjects who did not die or who were lost to follow-up were censored on the last date the subject was known to be alive. All randomized imatinib-resistant subjects were summarized. Here, 'n' signifies evaluable subjects for specified categories in respective treatment arms.

End point type	Secondary
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End point timeframe:

Baseline up to 84 months follow up

End point values	Dasatinib 100 mg QD	Dasatinib 140 mg QD	Dasatinib 50 mg BID	Dasatinib 70 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	124	123	124	126
Units: Percentage of Subjects				
number (confidence interval 95%)				
24 Months (n=124, 123, 124, 126)	90.1 (83.2 to 94.2)	93.9 (87.6 to 97)	88.9 (81.6 to 93.4)	85.1 (77.3 to 90.3)
36 Months (n=124, 123, 124, 126)	87.5 (80.2 to 92.3)	83.8 (75.6 to 89.5)	83.5 (75.3 to 89.1)	76.5 (67.7 to 83.1)
48 Months (n=124, 123, 124, 126)	79.7 (71.3 to 85.9)	82 (73.4 to 88)	80.7 (72.1 to 86.9)	71.1 (61.9 to 78.4)
60 Months (n=124, 123, 124, 126)	75.1 (66.1 to 82)	78 (68.9 to 84.7)	73.6 (64.1 to 80.9)	69.1 (59.8 to 76.7)
72 Months (n=124, 123, 124, 126)	67.9 (58.3 to 75.8)	72.6 (62.9 to 80.1)	71.4 (61.8 to 79)	67.1 (57.6 to 74.9)
84 Months (n=124, 123, 124, 126)	62.6 (52.6 to 71)	68.1 (58 to 76.2)	67.9 (57.9 to 76)	65 (55.3 to 73)

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects Intolerant to Imatinib With Major Cytogenetic Response (MCyR) After at Least 6 Months and After at Least 24 Months Follow-Up, by QD and BID Schedules and by Total Daily Dose

End point title	Percentage of Subjects Intolerant to Imatinib With Major Cytogenetic Response (MCyR) After at Least 6 Months and After at Least 24 Months Follow-Up, by QD and BID Schedules and by Total Daily Dose
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End point description:

Cytogenetic response (CyR) was based on the number of Philadelphia chromosome positive (Ph+) metaphases among cells in metaphase on a Bone Marrow (BM) sample. The criteria for CyR were as follows: complete cytogenetic response (CCyR): 0% Ph+ cells in metaphase in BM; PCyR: >0 to 35% Ph+ cells in metaphase in BM; Minor cytogenetic response: >35 to 65% Ph+ cells in metaphase in BM; Minimal cytogenetic response: >65 to 95% Ph+ cells in metaphase in BM; No CyR: >95 to 100% Ph+ cells in metaphase in BM; Best CyR was defined as the best response obtained at any time during the study; MCyR was defined as a best CyR of CCyR or PCyR. All randomized imatinib-intolerant subjects with available data were summarized.

End point type	Secondary
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End point timeframe:

Baseline up to at least 6 months and 24 months follow-up

End point values	QD Dasatinib	BID Dasatinib	Dasatinib 100 mg Total Daily Dose	Dasatinib 140 mg Total Daily Dose
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	87	85	87	86
Units: Percentage of Subjects				
number (confidence interval 95%)				
6 Month	72.4 (61.8 to 81.5)	70.6 (59.7 to 80)	73.6 (63 to 82.4)	69.4 (58.5 to 79)
24 Month	77 (66.8 to 85.4)	75.6 (65.1 to 84.2)	77 (66.8 to 85.4)	75.6 (65.1 to 84.2)

## Statistical analyses

Statistical analysis title	Risk difference: QD Dasatinib and BID Dasatinib
Statistical analysis description: 6 month analysis.	
Comparison groups	QD Dasatinib v BID Dasatinib
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[4]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.7
upper limit	15.3

Notes:

[4] - Non-inferiority of the QD schedule relative to the BID schedule was deduced if the lower bound of the 95% CI for the MCyR QD minus MCyR BID difference was greater than or equal to -15%.

Statistical analysis title	Risk difference: Total Daily Dose 100 mg and 140 mg
Statistical analysis description: 6 month analysis.	
Comparison groups	Dasatinib 100 mg Total Daily Dose v Dasatinib 140 mg Total Daily Dose
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[5]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.3
upper limit	17.6

Notes:

[5] - Non-inferiority of 100 mg QD Total Daily Dose relative to 140 mg QD Total Daily Dose was deduced if the lower bound of the 95% CI difference was greater than or equal to -15%.

Statistical analysis title	Risk difference: QD Dasatinib and BID Dasatinib
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Statistical analysis description:

24 month analysis.

Comparison groups	QD Dasatinib v BID Dasatinib
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[6]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.2
upper limit	14.1

Notes:

[6] - Non-inferiority of the QD schedule relative to the BID schedule was deduced if the lower bound of the 95% CI for the MCyR QD minus MCyR BID difference was greater than or equal to -15%.

<b>Statistical analysis title</b>	Risk difference:Total Daily Dose 100 mg and 140 mg
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Statistical analysis description:

24 month analysis.

Comparison groups	Dasatinib 100 mg Total Daily Dose v Dasatinib 140 mg Total Daily Dose
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[7]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.2
upper limit	14.1

Notes:

[7] - Non-inferiority of 100 mg QD Total Daily Dose relative to 140 mg QD Total Daily Dose was deduced if the lower bound of the 95% CI difference was greater than or equal to -15%.

### **Secondary: Percentage of Subjects Intolerant to Imatinib With Complete Hematologic Response (CHR) After at Least 6 Months and After at Least 24 Months Follow-Up**

End point title	Percentage of Subjects Intolerant to Imatinib With Complete Hematologic Response (CHR) After at Least 6 Months and After at Least 24 Months Follow-Up
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End point description:

A CHR was obtained when all the following criteria were met: white blood cells  $\leq$  institutional upper limit of normal (ULN); Platelets  $< 450,000/\text{mm}^3$ ; No blasts or promyelocytes in peripheral blood (PB);  $< 5\%$  myelocytes plus metamyelocytes in PB; Basophils in PB  $< 20\%$ ; No extramedullary involvement (including no splenomegaly or hepatomegaly). Hematologic responses were counted anytime following 14 days after the dosing start date. All randomized imatinib-intolerant subjects were summarized. Here, 'n' signifies evaluable subjects for specified categories in respective treatment arms.

End point type	Secondary
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End point timeframe:

Baseline up to at Least 6 months and 24 months follow up

End point values	Dasatinib 100 mg QD	Dasatinib 140 mg QD	Dasatinib 50 mg BID	Dasatinib 70 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43	44	44	42
Units: Percentage of Subjects				
number (not applicable)				
6 Months (n=43, 44, 44, 41)	100	86	93	85
24 Months (n=43, 44, 44, 42)	100	89	93	86

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Imatinib Intolerant Subjects With Progression Free Survival (PFS) After 24, 36, 48, 60, 72, and 84 Months of Follow-Up

End point title	Percentage of Imatinib Intolerant Subjects With Progression Free Survival (PFS) After 24, 36, 48, 60, 72, and 84 Months of Follow-Up
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End point description:

PFS= From randomization until: complete hematologic response (CHR) achieved and subject subsequently no longer met criteria for CHR over 2 weeks; no CHR after receiving maximum dose and doubling of the white blood cells count from the lowest value to  $> 20,000/\text{mm}^3$  or an increase by  $> 50,000/\text{mm}^3$  on 2 assessments performed 2 weeks apart; subject met criteria of accelerated phase or blast phase chronic myelogenous leukemia; subject had Major Cytogenetic Response (MCyR) and subsequently no longer met criteria for MCyR after starting maximum dose;  $\geq 30\%$  absolute increase in number of Ph+ metaphases. Deaths without a reported prior progression were considered to have progressed on the date of death; those who neither progressed nor died were censored on the date of their last cytogenetic or hematologic assessment. All randomized imatinib-intolerant subjects with available data were summarized. Here, 'n' signifies evaluable subjects for specified categories in respective treatment arms.

End point type	Secondary
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End point timeframe:

Baseline up to 84 months follow-up

End point values	Dasatinib 100 mg QD	Dasatinib 140 mg QD	Dasatinib 50 mg BID	Dasatinib 70 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43	44	44	42
Units: Percentage of Subjects				
number (confidence interval 95%)				
24 Months (n=43, 44, 44, 42)	83.6 (67 to 92.3)	87.7 (72.8 to 94.7)	77.4 (61 to 87.6)	83.7 (67.1 to 92.4)
36 Months (n=43, 44, 44, 42)	71.7 (53.6 to 83.7)	76 (58.7 to 86.8)	68.6 (51.1 to 80.9)	77.4 (59.6 to 88.1)
48 Months (n=43, 44, 44, 42)	62.7 (44.5 to 76.5)	76 (58.7 to 86.8)	62 (44.1 to 75.7)	66.9 (47.8 to 80.4)
60 Months (n=43, 44, 44, 42)	59.2 (40.8 to 73.6)	71.2 (52.1 to 83.8)	62 (44.1 to 75.7)	59.5 (40.1 to 74.4)

72 Months (n=43, 44, 44, 42)	59.2 (40.8 to 73.6)	66.5 (46.3 to 80.6)	58.2 (39.8 to 72.7)	55.2 (35.7 to 71.1)
84 Months (n=43, 44, 44, 42)	50.9 (32.1 to 67)	66.5 (46.3 to 80.6)	47.5 (27.4 to 65.2)	50.2 (30.4 to 67.1)

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Imatinib Intolerant Subjects With Overall Survival (OS) After 24, 36, 48, 60, 72, and 84 Months of Follow-up

End point title	Percentage of Imatinib Intolerant Subjects With Overall Survival (OS) After 24, 36, 48, 60, 72, and 84 Months of Follow-up
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End point description:

OS was defined as the time from randomization until death. Survival data were collected for up to 5 years on subjects who had discontinued dasatinib treatment. Subjects who did not die or who were lost to follow-up were censored on the last date the subject was known to be alive. All randomized imatinib-intolerant subjects were summarized. Here, 'n' signifies evaluable subjects for specified categories in respective treatment arms.

End point type	Secondary
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End point timeframe:

Baseline up to 84 months follow-up

End point values	Dasatinib 100 mg QD	Dasatinib 140 mg QD	Dasatinib 50 mg BID	Dasatinib 70 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43	44	44	42
Units: Percentage of subjects				
number (confidence interval 95%)				
24 Months (n=43, 44, 44, 42)	94.9 (81.2 to 98.7)	92.8 (79.2 to 97.6)	95.3 (82.5 to 98.8)	97.4 (82.8 to 99.6)
36 Months (n=43, 44, 44, 42)	89.7 (74.9 to 96)	92.8 (79.2 to 97.6)	90.4 (76.4 to 96.3)	94.7 (80.6 to 98.7)
48 Months (n=43, 44, 44, 42)	84.5 (68.6 to 92.7)	87.5 (72.4 to 94.6)	85.1 (69.7 to 93)	86.8 (71.2 to 94.3)
60 Months (n=43, 44, 44, 42)	81.8 (65.6 to 90.9)	87.5 (72.4 to 94.6)	82.4 (66.6 to 91.2)	81.1 (64.3 to 90.5)
72 Months (n=43, 44, 44, 42)	79 (62.3 to 88.9)	87.5 (72.4 to 94.6)	79.6 (63.2 to 89.3)	81.1 (64.3 to 90.5)
84 Months (n=43, 44, 44, 42)	70 (52.2 to 82.2)	87.5 (72.4 to 94.6)	76.9 (59.7 to 87.2)	77.7 (60.1 to 88.2)

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of All Randomized Subjects With Cytogenic and Hematologic Response by Dosing Schedule (QD or BID) and by Total Daily Dose (100 mg or 140

**mg) After at Least 6 Months Follow-Up**

End point title	Percentage of All Randomized Subjects With Cytogenic and Hematologic Response by Dosing Schedule (QD or BID) and by Total Daily Dose (100 mg or 140 mg) After at Least 6 Months Follow-Up
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## End point description:

Complete cytogenetic response (CCyR): 0% Philadelphia chromosome positive cells in metaphase in Bone Marrow (BM). Partial cytogenetic response (PCyR) >0 to 35% Ph+ cells in metaphase in BM. MCyR: best cytogenetic response of CCyR or PCyR. A complete hematologic response (CHR) was obtained when all the following criteria were met: White Blood Cells ≤ institutional upper limit of normal (ULN); Platelets <450,000/mm<sup>3</sup>; No blasts or promyelocytes in peripheral blood (PB); <5% myelocytes plus metamyelocytes in PB; Basophils in PB <20%; No extramedullary involvement (including no splenomegaly or hepatomegaly). Hematologic responses were counted anytime following 14 days after the dosing start date. All randomized subjects were summarized. Here, 'n' signifies evaluable subjects for specified categories in respective treatment arms.

End point type	Secondary
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## End point timeframe:

Baseline up to at least 6 months follow-up

End point values	QD Dasatinib	BID Dasatinib	Dasatinib 100 mg Total Daily Dose	Dasatinib 140 mg Total Daily Dose
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	334	336	335	335
Units: Percentage of Subjects				
number (confidence interval 95%)				
MCyR (n=334, 336, 335, 335)	57.2 (51.7 to 62.6)	54.5 (49 to 59.9)	56.1 (50.6 to 61.5)	55.5 (50 to 60.9)
CHR (n=334, 336, 335, 335)	87.7 (83.7 to 91)	89.3 (85.5 to 92.4)	90.7 (87.1 to 93.6)	86.3 (82.1 to 89.8)

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Percentage of All Randomized Subjects With Cytogenic and Hematologic Response by Dosing Schedule (QD or BID) and by Total Daily Dose (100 mg or 140 mg) After at Least 24 Months Follow-Up**

End point title	Percentage of All Randomized Subjects With Cytogenic and Hematologic Response by Dosing Schedule (QD or BID) and by Total Daily Dose (100 mg or 140 mg) After at Least 24 Months Follow-Up
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## End point description:

Complete cytogenetic response (CCyR): 0% Philadelphia chromosome positive cells in metaphase in Bone Marrow (BM). Partial cytogenetic response (PCyR) : >0 to 35% Ph+ cells in metaphase in BM. Major cytogenetic response: best cytogenetic response of CCyR or PCyR. A complete hematologic response was obtained when all the following criteria were met: White Blood Cells ≤ institutional upper limit of normal (ULN); Platelets <450,000/mm<sup>3</sup>; No blasts or promyelocytes in peripheral blood (PB); <5% myelocytes plus metamyelocytes in PB; Basophils in PB <20%; No extramedullary involvement (including no splenomegaly or hepatomegaly). Hematologic responses were counted anytime following 14 days after the dosing start date. No cytogenic assessments were made after 2 years of follow-up. All randomized subjects were summarized. Here, 'n' signifies evaluable subjects for specified categories in respective treatment arms.

End point type	Secondary
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End point timeframe:

Baseline up to at least 24 months follow-up

End point values	QD Dasatinib	BID Dasatinib	Dasatinib 100 mg Total Daily Dose	Dasatinib 140 mg Total Daily Dose
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	334	336	335	335
Units: Percentage of Subjects				
number (confidence interval 95%)				
MCyR (n=334, 336, 335, 335)	63.2 (57.8 to 68.4)	61.3 (55.9 to 66.5)	62.4 (57 to 67.6)	62.1 (56.7 to 67.3)
CHR (n=334, 336, 335, 335)	89.2 (85.4 to 92.3)	90.2 (86.5 to 93.1)	91.9 (88.5 to 94.6)	87.5 (83.4 to 90.8)

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With Progression Free Survival (PFS) at 24, 36, 48, 60, 72, and 84 Months Follow-Up by Dose Schedule and Total Daily Dose - All Randomized Subjects

End point title	Percentage of Subjects With Progression Free Survival (PFS) at 24, 36, 48, 60, 72, and 84 Months Follow-Up by Dose Schedule and Total Daily Dose - All Randomized Subjects
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End point description:

PFS= time from randomization until: complete hematologic response (CHR) achieved and subject subsequently no longer met criteria for CHR over 2 weeks; no CHR after receiving maximum dose and doubling of the white blood cells count from the lowest value to  $> 20,000/\text{mm}^3$  or an increase by  $> 50,000/\text{mm}^3$  on 2 assessments performed 2 weeks apart; subject met criteria of accelerated phase or blast phase chronic myelogenous leukemia; subject had major cytogenetic response (MCyR) and subsequently no longer met criteria for MCyR after starting maximum dose;  $\geq 30\%$  absolute increase in number of Ph+ metaphases. Deaths without a reported prior progression were considered to have progressed on the date of death; those who neither progressed nor died were censored on the date of their last cytogenetic or hematologic assessment. All subjects who were randomized to a treatment arm were summarized. Here, 'n' signifies evaluable subjects for specified categories in respective treatment arms.

End point type	Secondary
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End point timeframe:

Baseline up to 84 months follow-up

End point values	Dasatinib 100 mg QD	Dasatinib 140 mg QD	Dasatinib 50 mg BID	Dasatinib 70 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	167	167	168	168
Units: Percentage of Subjects				
number (confidence interval 95%)				
24 Months (n=167, 167, 168, 168)	77.4 (69.9 to 83.2)	67.7 (59.6 to 74.5)	72.2 (64.3 to 78.7)	73.9 (66.1 to 80.1)

36 Months (n=167, 167, 168, 168)	66.6 (58.3 to 73.6)	54 (45.4 to 61.8)	67.5 (59.2 to 74.5)	62.8 (54.3 to 70.1)
48 Months (n=167, 167, 168, 168)	59.1 (50.6 to 66.6)	48 (39.4 to 56.2)	63.3 (54.8 to 70.7)	58.7 (50.1 to 66.3)
60 Months (n=167, 167, 168, 168)	52.5 (43.8 to 60.5)	44.2 (35.5 to 52.5)	58.7 (49.8 to 66.5)	52.5 (43.7 to 60.5)
72 Months (n=167, 167, 168, 168)	48 (39.2 to 56.2)	39.2 (30.6 to 47.7)	52.8 (43.7 to 61.1)	47.7 (38.7 to 56)
84 Months (n=167, 167, 168, 168)	42.1 (33.4 to 50.6)	38.2 (29.6 to 46.7)	43.9 (34.5 to 52.9)	43.5 (34.5 to 52.1)

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With Overall Survival (OS) at 24, 36, 48, 60, 72, and 84 Months Follow-Up - All Randomized Subjects

End point title	Percentage of Subjects With Overall Survival (OS) at 24, 36, 48, 60, 72, and 84 Months Follow-Up - All Randomized Subjects
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End point description:

OS was defined as the time from randomization until death. Survival data were collected for up to 5 years on subjects who had discontinued dasatinib treatment. Subjects who did not die or who were lost to follow-up were censored on the last date the subject was known to be alive. All subjects who were randomized to a treatment arm were summarized. Here, 'n' signifies evaluable subjects for specified categories in respective treatment arms.

End point type	Secondary
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End point timeframe:

Baseline up to 84 months follow-up

End point values	Dasatinib 100 mg QD	Dasatinib 140 mg QD	Dasatinib 50 mg BID	Dasatinib 70 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	167	167	168	168
Units: Percentage of Subjects				
number (confidence interval 95%)				
24 Months (n=167, 167, 168, 168)	91.3 (85.8 to 94.8)	93.6 (88.4 to 96.5)	90.6 (84.9 to 94.2)	88.1 (81.9 to 92.2)
36 Months (n=167, 167, 168, 168)	88.1 (82 to 92.3)	86.2 (79.6 to 90.8)	85.3 (78.7 to 90)	80.9 (73.9 to 86.3)
48 Months (n=167, 167, 168, 168)	81 (73.9 to 86.3)	83.4 (76.4 to 88.5)	81.8 (74.7 to 87.1)	74.9 (67.3 to 81)
60 Months (n=167, 167, 168, 168)	76.8 (69.4 to 82.7)	80.5 (73.1 to 86)	75.9 (68.2 to 82)	72 (64.1 to 78.4)
72 Months (n=167, 167, 168, 168)	70.9 (62.9 to 77.5)	76.6 (68.7 to 82.7)	73.6 (65.6 to 80)	70.5 (62.5 to 77.1)
84 Months (n=167, 167, 168, 168)	64.6 (56.1 to 71.8)	73.4 (65.2 to 79.9)	70.3 (62 to 77.1)	68.1 (59.8 to 74.9)



## Statistical analyses

No statistical analyses for this end point

### Secondary: After 2 Years Follow-Up: Number of Subjects With Death, Serious Adverse Events (SAEs), Adverse Events (AEs) That Led to Treatment Discontinuation

End point title	After 2 Years Follow-Up: Number of Subjects With Death, Serious Adverse Events (SAEs), Adverse Events (AEs) That Led to Treatment Discontinuation
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End point description:

AE=any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that may not have a causal relationship with treatment. SAE=a medical event that at any dose results in death, persistent or significant disability/incapacity, or drug dependency/abuse; is life-threatening, an important medical event, or a congenital anomaly/birth defect; or requires or prolongs hospitalization. Treatment-related=having certain, probable, possible, or missing relationship to study drug. Baseline=closest to, but no later than, the first day of study drug for treated subjects. All randomized subjects who received at least 1 dose of study drug were summarized.

End point type	Secondary
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End point timeframe:

Baseline up to 2 years follow-up

End point values	Dasatinib 100 mg QD	Dasatinib 140 mg QD	Dasatinib 50 mg BID	Dasatinib 70 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	165	163	167	167
Units: Subjects				
Any SAEs	58	67	73	78
Drug-Related SAEs	32	40	47	55
Drug-Related AEs that led to discontinuation	14	24	20	25
Death within 30 days of last dose of study drug	3	2	6	5

## Statistical analyses

No statistical analyses for this end point

### Secondary: After 7 Years Follow-Up and Study Closure: Number of Subjects With Death, Serious Adverse Events (SAEs), Adverse Events (AEs) That Led to Treatment Discontinuation

End point title	After 7 Years Follow-Up and Study Closure: Number of Subjects With Death, Serious Adverse Events (SAEs), Adverse Events (AEs) That Led to Treatment Discontinuation <sup>[8]</sup>
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End point description:

AE=any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that may not have a causal relationship with treatment. SAE=a medical event that at any dose results in death, persistent or significant disability/incapacity, or drug dependency/abuse; is life-threatening, an important medical event, or a congenital anomaly/birth defect; or requires or prolongs hospitalization. Treatment-related=having certain, probable, possible, or missing relationship to study drug. After the 2-year analysis those on a twice daily dosing schedule were allowed to switch to a once daily dosing schedule. Due to the large number of subjects switching from twice daily dosing to once daily dosing, the overall safety data are presented for the 100 mg once daily group and combined for the other

treatment groups. All randomized subjects who received at least 1 dose of study drug were summarized.

End point type	Secondary
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End point timeframe:

Baseline to 30 days post last dose; 7 years follow up; study closure July 2014

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint was to be evaluated for the specified arms only.

End point values	Dasatinib 100 mg QD	Other Treatment Groups	Total	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	165	497	662	
Units: Subjects				
All Deaths	51	133	184	
Deaths on-study or within 30 days post dose	11	15	26	
SAEs	75	259	334	
AEs Leading to Discontinuation of Treatment	43	153	196	

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline to 30 days post last dose; 7 years follow up

Adverse event reporting additional description:

Study closure July 2014.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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### Reporting groups

Reporting group title	Dasatinib 100 mg QD
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Reporting group description:

Subjects received dasatinib 100 mg once a day (QD) until progression of disease, development of intolerable toxicity, or the subject's decision to withdraw.

Reporting group title	Dasatinib 140 mg QD
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Reporting group description:

Subjects received dasatinib 140 mg QD until progression of disease, development of intolerable toxicity, or the subject's decision to withdraw.

Reporting group title	Dasatinib 50 mg BID
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Reporting group description:

Subjects received 50 mg twice a day (BID) until progression of disease, development of intolerable toxicity, or the subject's decision to withdraw. After the 2-year analysis, and with Protocol Amendment 02, subjects on a BID dosing schedule were allowed to switch to a QD dosing schedule.

Reporting group title	Dasatinib 70 mg BID
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Reporting group description:

Subjects received 70 mg BID until progression of disease, development of intolerable toxicity, or the subject's decision to withdraw. After the 2-year analysis, and with Protocol Amendment 02, subjects on a BID dosing schedule were allowed to switch to a QD dosing schedule.

Serious adverse events	Dasatinib 100 mg QD	Dasatinib 140 mg QD	Dasatinib 50 mg BID
Total subjects affected by serious adverse events			
subjects affected / exposed	75 / 165 (45.45%)	78 / 163 (47.85%)	89 / 167 (53.29%)
number of deaths (all causes)	15	11	17
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenoma benign			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Basal cell carcinoma			

subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blast cell crisis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	3 / 167 (1.80%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Blast cell proliferation			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Blast crisis in myelogenous leukaemia			
subjects affected / exposed	0 / 165 (0.00%)	2 / 163 (1.23%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Breast cancer			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic lymphocytic leukaemia			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic myeloid leukaemia			
subjects affected / exposed	1 / 165 (0.61%)	1 / 163 (0.61%)	0 / 167 (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
Chronic myeloid leukaemia transformation			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	2 / 167 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Intraductal proliferative breast lesion			

subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukaemia			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lip neoplasm malignant stage unspecified			
subjects affected / exposed	1 / 165 (0.61%)	1 / 163 (0.61%)	0 / 167 (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
Pituitary tumour			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Prostate cancer			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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
Renal cell carcinoma			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin cancer			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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 cancer metastatic			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Squamous cell carcinoma			

subjects affected / exposed	3 / 165 (1.82%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 165 (0.61%)	1 / 163 (0.61%)	0 / 167 (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
Thyroid adenoma			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Tongue neoplasm malignant stage unspecified			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vulval cancer			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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
Extremity necrosis			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Haematoma			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Haemorrhage			

subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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 artery thrombosis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Poor peripheral circulation			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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			
Chest discomfort			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			

subjects affected / exposed	4 / 165 (2.42%)	2 / 163 (1.23%)	3 / 167 (1.80%)
occurrences causally related to treatment / all	2 / 4	3 / 3	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	2 / 165 (1.21%)	0 / 163 (0.00%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Device failure			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device malfunction			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Fatigue			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Malaise			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Medical device pain			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Multi-organ failure			



subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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
Non-cardiac chest pain			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Oedema peripheral			
subjects affected / exposed	2 / 165 (1.21%)	1 / 163 (0.61%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	3 / 165 (1.82%)	11 / 163 (6.75%)	6 / 167 (3.59%)
occurrences causally related to treatment / all	2 / 3	6 / 13	4 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Serositis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Sudden death			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Thrombosis in device			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			

subjects affected / exposed	1 / 165 (0.61%)	2 / 163 (1.23%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Allergy to arthropod sting			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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
Anaphylactoid reaction			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Menorrhagia			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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
Menstrual disorder			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine haemorrhage			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	7 / 165 (4.24%)	15 / 163 (9.20%)	14 / 167 (8.38%)
occurrences causally related to treatment / all	16 / 16	30 / 30	23 / 23
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	4 / 165 (2.42%)	6 / 163 (3.68%)	7 / 167 (4.19%)
occurrences causally related to treatment / all	8 / 8	4 / 7	11 / 12
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Pneumonitis			
subjects affected / exposed	2 / 165 (1.21%)	1 / 163 (0.61%)	0 / 167 (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
Asthma			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	2 / 167 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infiltration			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	1 / 1	3 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Alveolar proteinosis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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

Bronchospasm			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	1 / 165 (0.61%)	1 / 163 (0.61%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea exertional			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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
Interstitial lung disease			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal oedema			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Obstructive airways disorder			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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
Oropharyngeal pain			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Pleurisy			

subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Pneumothorax			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary arterial hypertension			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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 congestion			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Pulmonary hypertension			
subjects affected / exposed	2 / 165 (1.21%)	2 / 163 (1.23%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Confusional state			
subjects affected / exposed	3 / 165 (1.82%)	1 / 163 (0.61%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	0 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressed mood			

subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Depression			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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
Mental status changes			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Psychotic disorder			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Blast cell count increased			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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 creatinine increased			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Clostridium test positive			

subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Haemoglobin			
subjects affected / exposed	3 / 165 (1.82%)	0 / 163 (0.00%)	0 / 167 (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
Haemoglobin decreased			
subjects affected / exposed	3 / 165 (1.82%)	0 / 163 (0.00%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count increased			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
White blood cell count decreased			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental overdose			

subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Brain contusion			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Fibula fracture			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Incisional hernia, obstructive			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Jaw fracture			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint injury			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laceration			



subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Ligament sprain			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle strain			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Postoperative thoracic procedure complication			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Procedural intestinal perforation			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Rib fracture			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Road traffic accident			

subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Spinal compression fracture			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	1 / 165 (0.61%)	1 / 163 (0.61%)	0 / 167 (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
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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
Angina pectoris			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Arrhythmia supraventricular			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	4 / 167 (2.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bradycardia			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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 congestive			
subjects affected / exposed	0 / 165 (0.00%)	3 / 163 (1.84%)	2 / 167 (1.20%)
occurrences causally related to treatment / all	0 / 0	3 / 3	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac valve disease			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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
Cor pulmonale			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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
Left ventricular dysfunction			

subjects affected / exposed	0 / 165 (0.00%)	2 / 163 (1.23%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	2 / 165 (1.21%)	1 / 163 (0.61%)	2 / 167 (1.20%)
occurrences causally related to treatment / all	0 / 2	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Myocardial ischaemia			
subjects affected / exposed	1 / 165 (0.61%)	2 / 163 (1.23%)	2 / 167 (1.20%)
occurrences causally related to treatment / all	1 / 1	2 / 2	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Pericardial effusion			
subjects affected / exposed	2 / 165 (1.21%)	3 / 163 (1.84%)	3 / 167 (1.80%)
occurrences causally related to treatment / all	2 / 2	3 / 3	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	1 / 165 (0.61%)	2 / 163 (1.23%)	2 / 167 (1.20%)
occurrences causally related to treatment / all	1 / 1	2 / 2	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Restrictive cardiomyopathy			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Stress cardiomyopathy			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			

subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Ventricular arrhythmia			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nervous system disorders			
Central nervous system haemorrhage			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cerebellar infarction			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haematoma			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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 ischaemia			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Cerebrovascular accident			
subjects affected / exposed	2 / 165 (1.21%)	0 / 163 (0.00%)	0 / 167 (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
Cognitive disorder			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			

subjects affected / exposed	2 / 165 (1.21%)	2 / 163 (1.23%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	0 / 2	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 165 (0.00%)	2 / 163 (1.23%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoaesthesia			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myasthenia gravis			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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
Neuropathy peripheral			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Paraesthesia			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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
Syncope			

subjects affected / exposed	1 / 165 (0.61%)	2 / 163 (1.23%)	0 / 167 (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
Transient ischaemic attack			
subjects affected / exposed	2 / 165 (1.21%)	1 / 163 (0.61%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VIIth nerve paralysis			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 165 (0.61%)	3 / 163 (1.84%)	3 / 167 (1.80%)
occurrences causally related to treatment / all	1 / 1	4 / 4	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	2 / 165 (1.21%)	2 / 163 (1.23%)	3 / 167 (1.80%)
occurrences causally related to treatment / all	4 / 4	3 / 3	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenopathy			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Neutropenia			
subjects affected / exposed	2 / 165 (1.21%)	2 / 163 (1.23%)	2 / 167 (1.20%)
occurrences causally related to treatment / all	2 / 2	1 / 2	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			

subjects affected / exposed	2 / 165 (1.21%)	4 / 163 (2.45%)	6 / 167 (3.59%)
occurrences causally related to treatment / all	1 / 2	4 / 5	8 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Eye disorders</b>			
Amaurosis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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
Diplopia			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal haemorrhage			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous haemorrhage			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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
<b>Gastrointestinal disorders</b>			
Abdominal pain			
subjects affected / exposed	2 / 165 (1.21%)	2 / 163 (1.23%)	4 / 167 (2.40%)
occurrences causally related to treatment / all	1 / 2	1 / 2	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 165 (0.00%)	2 / 163 (1.23%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fistula			



subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Colitis			
subjects affected / exposed	0 / 165 (0.00%)	2 / 163 (1.23%)	0 / 167 (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
Constipation			
subjects affected / exposed	2 / 165 (1.21%)	1 / 163 (0.61%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dental caries			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Diarrhoea			
subjects affected / exposed	5 / 165 (3.03%)	12 / 163 (7.36%)	5 / 167 (2.99%)
occurrences causally related to treatment / all	3 / 5	10 / 15	6 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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
Gastritis			
subjects affected / exposed	1 / 165 (0.61%)	2 / 163 (1.23%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 1	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis erosive			

subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 165 (0.61%)	1 / 163 (0.61%)	4 / 167 (2.40%)
occurrences causally related to treatment / all	0 / 1	0 / 1	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal necrosis			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Gingival bleeding			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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
Ileus			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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
Inguinal hernia			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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
Intestinal obstruction			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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
Irritable bowel syndrome			

subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Loose tooth			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	2 / 165 (1.21%)	3 / 163 (1.84%)	2 / 167 (1.20%)
occurrences causally related to treatment / all	2 / 2	2 / 3	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal pain			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Rectal haemorrhage			

subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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
Toothache			
subjects affected / exposed	0 / 165 (0.00%)	2 / 163 (1.23%)	0 / 167 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 165 (1.21%)	5 / 163 (3.07%)	6 / 167 (3.59%)
occurrences causally related to treatment / all	2 / 2	3 / 6	5 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	1 / 165 (0.61%)	3 / 163 (1.84%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 1	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Acute febrile neutrophilic dermatosis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angioedema			

subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Decubitus ulcer			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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
Dermatosis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythema nodosum			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Exfoliative rash			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Pruritus			
subjects affected / exposed	2 / 165 (1.21%)	0 / 163 (0.00%)	0 / 167 (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
Pyoderma gangrenosum			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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	3 / 165 (1.82%)	1 / 163 (0.61%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	1 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash generalised			

subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin lesion			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
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 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Renal failure acute			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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
Hypothyroidism			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	2 / 167 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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
Arthritis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	1 / 165 (0.61%)	1 / 163 (0.61%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flank pain			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Lumbar spinal stenosis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle spasms			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Myalgia			
subjects affected / exposed	1 / 165 (0.61%)	1 / 163 (0.61%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myositis			

subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 165 (0.00%)	2 / 163 (1.23%)	0 / 167 (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
Osteonecrosis			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal infection			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Anal abscess			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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 / 165 (0.00%)	2 / 163 (1.23%)	0 / 167 (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
Bacteraemia			



subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Campylobacter gastroenteritis			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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
Campylobacter infection			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	5 / 165 (3.03%)	2 / 163 (1.23%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Clostridium difficile infection			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Endocarditis			

subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	2 / 167 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis bacterial			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Endocarditis enterococcal			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Enteritis infectious			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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
Erysipelas			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	2 / 167 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 165 (0.00%)	2 / 163 (1.23%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis clostridial			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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 viral			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			

subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Gastrointestinal viral infection			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Haematoma infection			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Herpes zoster			
subjects affected / exposed	1 / 165 (0.61%)	1 / 163 (0.61%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	5 / 165 (3.03%)	0 / 163 (0.00%)	2 / 167 (1.20%)
occurrences causally related to treatment / all	3 / 9	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious colitis			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lobar pneumonia			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			

subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	3 / 165 (1.82%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nasopharyngitis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Neutropenic sepsis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periodontitis			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Pharyngitis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Pharyngotonsillitis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	4 / 165 (2.42%)	15 / 163 (9.20%)	10 / 167 (5.99%)
occurrences causally related to treatment / all	2 / 5	6 / 21	9 / 15
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			

subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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
Pseudomembranous colitis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 165 (0.61%)	1 / 163 (0.61%)	3 / 167 (1.80%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 3
deaths causally related to treatment / all	1 / 1	0 / 1	0 / 0
Septic shock			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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
Sinusitis			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	0 / 167 (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
Skin bacterial infection			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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 infection			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	2 / 165 (1.21%)	0 / 163 (0.00%)	0 / 167 (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
Tuberculosis			

subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 165 (0.00%)	2 / 163 (1.23%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Viral infection			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	2 / 167 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Fluid overload			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Fluid retention			

subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Hyperkalaemia			
subjects affected / exposed	0 / 165 (0.00%)	1 / 163 (0.61%)	0 / 167 (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
Hypokalaemia			
subjects affected / exposed	0 / 165 (0.00%)	0 / 163 (0.00%)	0 / 167 (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
Hyponatraemia			
subjects affected / exposed	1 / 165 (0.61%)	0 / 163 (0.00%)	1 / 167 (0.60%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

<b>Serious adverse events</b>	Dasatinib 70 mg BID		
Total subjects affected by serious adverse events			
subjects affected / exposed	92 / 167 (55.09%)		
number of deaths (all causes)	22		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenoma benign			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blast cell crisis			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Blast cell proliferation				
subjects affected / exposed	1 / 167 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Blast crisis in myelogenous leukaemia				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Breast cancer				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chronic lymphocytic leukaemia				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chronic myeloid leukaemia				
subjects affected / exposed	2 / 167 (1.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Chronic myeloid leukaemia transformation				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intraductal proliferative breast lesion				
subjects affected / exposed	1 / 167 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Leukaemia				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lip neoplasm malignant stage				



unspecified				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pituitary tumour				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Prostate cancer				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal cell carcinoma				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin cancer				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin cancer metastatic				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma				
subjects affected / exposed	1 / 167 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of skin				
subjects affected / exposed	1 / 167 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thyroid adenoma				

subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tongue neoplasm malignant stage unspecified			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vulval cancer			
subjects affected / exposed	0 / 167 (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 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Extremity necrosis			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematoma			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhage			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypotension			

subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral artery thrombosis			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral ischaemia			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Poor peripheral circulation			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombosis			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	3 / 167 (1.80%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Chills			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Death			

subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Device failure			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Device malfunction			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malaise			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Medical device pain			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Multi-organ failure			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oedema peripheral			

subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	9 / 167 (5.39%)		
occurrences causally related to treatment / all	4 / 13		
deaths causally related to treatment / all	0 / 0		
Serositis			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sudden death			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombosis in device			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholangitis			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis acute			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Allergy to arthropod sting			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anaphylactoid reaction			

subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypersensitivity			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Menorrhagia			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Menstrual disorder			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Uterine haemorrhage			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	20 / 167 (11.98%)		
occurrences causally related to treatment / all	32 / 35		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	9 / 167 (5.39%)		
occurrences causally related to treatment / all	10 / 14		
deaths causally related to treatment / all	0 / 0		

Pneumonitis				
subjects affected / exposed	1 / 167 (0.60%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Asthma				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	2 / 167 (1.20%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Lung infiltration				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute respiratory distress syndrome				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Alveolar proteinosis				
subjects affected / exposed	1 / 167 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchospasm				
subjects affected / exposed	0 / 167 (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 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cough				

subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea exertional			
subjects affected / exposed	0 / 167 (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 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Laryngeal oedema			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Obstructive airways disorder			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oropharyngeal pain			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleurisy			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary arterial hypertension			



subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary congestion			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary hypertension			
subjects affected / exposed	2 / 167 (1.20%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Confusional state			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Depressed mood			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mental status changes			

subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychotic disorder			
subjects affected / exposed	0 / 167 (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	1 / 167 (0.60%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blast cell count increased			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood creatinine increased			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Clostridium test positive			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haemoglobin			

subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemoglobin decreased			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neutrophil count decreased			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Platelet count decreased			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Platelet count increased			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
White blood cell count decreased			
subjects affected / exposed	0 / 167 (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 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Brain contusion			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fibula fracture			

subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fracture			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Incisional hernia, obstructive			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Jaw fracture			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Joint injury			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Laceration			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ligament sprain			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lumbar vertebral fracture			

subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Muscle strain			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Overdose			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Postoperative thoracic procedure complication			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Procedural intestinal perforation			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rib fracture			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Spinal compression fracture			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			

Atrial septal defect			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	2 / 167 (1.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Angina pectoris			
subjects affected / exposed	2 / 167 (1.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Arrhythmia supraventricular			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	3 / 167 (1.80%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Bradycardia			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			

subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure acute			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			
subjects affected / exposed	5 / 167 (2.99%)		
occurrences causally related to treatment / all	4 / 7		
deaths causally related to treatment / all	0 / 0		
Cardiac valve disease			
subjects affected / exposed	0 / 167 (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 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cor pulmonale			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Left ventricular dysfunction			
subjects affected / exposed	2 / 167 (1.20%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial ischaemia			

subjects affected / exposed	2 / 167 (1.20%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Palpitations			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pericardial effusion			
subjects affected / exposed	3 / 167 (1.80%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Pericarditis			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Restrictive cardiomyopathy			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stress cardiomyopathy			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tachycardia			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ventricular arrhythmia			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Central nervous system haemorrhage			



subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebellar infarction			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebral haematoma			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebral ischaemia			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cognitive disorder			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoaesthesia			

subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Migraine			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myasthenia gravis			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neuropathy peripheral			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Paraesthesia			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	2 / 167 (1.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
VIIth nerve paralysis			

subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Blood and lymphatic system disorders</b>			
Anaemia			
subjects affected / exposed	5 / 167 (2.99%)		
occurrences causally related to treatment / all	3 / 5		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	6 / 167 (3.59%)		
occurrences causally related to treatment / all	6 / 6		
deaths causally related to treatment / all	1 / 1		
Lymphadenopathy			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	3 / 167 (1.80%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	9 / 167 (5.39%)		
occurrences causally related to treatment / all	9 / 10		
deaths causally related to treatment / all	0 / 0		
<b>Eye disorders</b>			
Amaurosis			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cataract			

subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diplopia			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Retinal haemorrhage			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vitreous haemorrhage			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 167 (1.80%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anal fistula			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	2 / 167 (1.20%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Constipation			

subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dental caries				
subjects affected / exposed	1 / 167 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	4 / 167 (2.40%)			
occurrences causally related to treatment / all	3 / 5			
deaths causally related to treatment / all	0 / 0			
Enteritis				
subjects affected / exposed	1 / 167 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterocolitis				
subjects affected / exposed	1 / 167 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	1 / 167 (0.60%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastritis erosive				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	3 / 167 (1.80%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal necrosis				

subjects affected / exposed	1 / 167 (0.60%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 1			
Gingival bleeding				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhoids				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Inguinal hernia				
subjects affected / exposed	1 / 167 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Irritable bowel syndrome				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large intestine polyp				
subjects affected / exposed	1 / 167 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Loose tooth				

subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower gastrointestinal haemorrhage				
subjects affected / exposed	1 / 167 (0.60%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophageal pain				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophagitis				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	1 / 167 (0.60%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	2 / 167 (1.20%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Toothache				

subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	2 / 167 (1.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Acute febrile neutrophilic dermatosis			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Angioedema			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Decubitus ulcer			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dermatosis			



subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Erythema nodosum			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Exfoliative rash			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pruritus			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyoderma gangrenosum			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Rash			
subjects affected / exposed	3 / 167 (1.80%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Rash generalised			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin lesion			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			

subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pollakiuria			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure acute			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypothyroidism			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Arthritis			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Back pain				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Flank pain				
subjects affected / exposed	1 / 167 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lumbar spinal stenosis				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Muscle spasms				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal chest pain				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myalgia				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myositis				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neck pain				
subjects affected / exposed	1 / 167 (0.60%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Osteoarthritis				

subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteonecrosis			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	0 / 167 (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 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anal abscess			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bacteraemia			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchopneumonia			

subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Campylobacter gastroenteritis				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Campylobacter infection				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	4 / 167 (2.40%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile colitis				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile infection				
subjects affected / exposed	1 / 167 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Endocarditis				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Endocarditis bacterial				
subjects affected / exposed	1 / 167 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Endocarditis enterococcal				

subjects affected / exposed	1 / 167 (0.60%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Enteritis infectious				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Erysipelas				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	2 / 167 (1.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis clostridial				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis viral				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal infection				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal viral infection				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematoma infection				

subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	2 / 167 (1.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infectious colitis			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Influenza			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lobar pneumonia			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nasopharyngitis			

subjects affected / exposed	1 / 167 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenic sepsis				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Periodontitis				
subjects affected / exposed	1 / 167 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pharyngitis				
subjects affected / exposed	1 / 167 (0.60%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pharyngotonsillitis				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	8 / 167 (4.79%)			
occurrences causally related to treatment / all	3 / 8			
deaths causally related to treatment / all	0 / 0			
Postoperative wound infection				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pseudomembranous colitis				
subjects affected / exposed	0 / 167 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				



subjects affected / exposed	4 / 167 (2.40%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	1 / 1		
Septic shock			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sinusitis			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin bacterial infection			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin infection			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Soft tissue infection			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tuberculosis			
subjects affected / exposed	0 / 167 (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 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			

subjects affected / exposed	2 / 167 (1.20%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wound infection			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	3 / 167 (1.80%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fluid overload			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fluid retention			
subjects affected / exposed	0 / 167 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			

subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	Dasatinib 100 mg QD	Dasatinib 140 mg QD	Dasatinib 50 mg BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	160 / 165 (96.97%)	155 / 163 (95.09%)	160 / 167 (95.81%)
Vascular disorders			
Flushing			
subjects affected / exposed	9 / 165 (5.45%)	5 / 163 (3.07%)	5 / 167 (2.99%)
occurrences (all)	11	11	6
Hypertension			
subjects affected / exposed	15 / 165 (9.09%)	12 / 163 (7.36%)	13 / 167 (7.78%)
occurrences (all)	17	14	15
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	15 / 165 (9.09%)	16 / 163 (9.82%)	23 / 167 (13.77%)
occurrences (all)	20	18	32
Chest pain			
subjects affected / exposed	21 / 165 (12.73%)	16 / 163 (9.82%)	19 / 167 (11.38%)
occurrences (all)	27	19	21
Chills			
subjects affected / exposed	11 / 165 (6.67%)	11 / 163 (6.75%)	16 / 167 (9.58%)
occurrences (all)	15	15	21
Fatigue			
subjects affected / exposed	62 / 165 (37.58%)	62 / 163 (38.04%)	56 / 167 (33.53%)
occurrences (all)	80	77	71
Influenza like illness			

subjects affected / exposed occurrences (all)	14 / 165 (8.48%) 21	17 / 163 (10.43%) 29	9 / 167 (5.39%) 14
Oedema peripheral subjects affected / exposed occurrences (all)	30 / 165 (18.18%) 41	29 / 163 (17.79%) 39	30 / 167 (17.96%) 39
Pain subjects affected / exposed occurrences (all)	19 / 165 (11.52%) 28	10 / 163 (6.13%) 11	12 / 167 (7.19%) 14
Pyrexia subjects affected / exposed occurrences (all)	32 / 165 (19.39%) 52	40 / 163 (24.54%) 88	43 / 167 (25.75%) 68
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	53 / 165 (32.12%) 68	42 / 163 (25.77%) 64	57 / 167 (34.13%) 84
Dyspnoea subjects affected / exposed occurrences (all)	49 / 165 (29.70%) 63	51 / 163 (31.29%) 71	53 / 167 (31.74%) 76
Dyspnoea exertional subjects affected / exposed occurrences (all)	11 / 165 (6.67%) 11	8 / 163 (4.91%) 9	9 / 167 (5.39%) 9
Epistaxis subjects affected / exposed occurrences (all)	15 / 165 (9.09%) 17	15 / 163 (9.20%) 28	7 / 167 (4.19%) 9
Oropharyngeal pain subjects affected / exposed occurrences (all)	20 / 165 (12.12%) 24	16 / 163 (9.82%) 20	19 / 167 (11.38%) 27
Pleural effusion subjects affected / exposed occurrences (all)	41 / 165 (24.85%) 56	51 / 163 (31.29%) 68	54 / 167 (32.34%) 71
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	6 / 165 (3.64%) 6	9 / 163 (5.52%) 11	15 / 167 (8.98%) 19
Depression			

subjects affected / exposed occurrences (all)	16 / 165 (9.70%) 17	12 / 163 (7.36%) 12	14 / 167 (8.38%) 17
Insomnia subjects affected / exposed occurrences (all)	19 / 165 (11.52%) 19	20 / 163 (12.27%) 21	14 / 167 (8.38%) 16
Investigations Weight decreased subjects affected / exposed occurrences (all)	14 / 165 (8.48%) 14	19 / 163 (11.66%) 22	18 / 167 (10.78%) 18
Weight increased subjects affected / exposed occurrences (all)	18 / 165 (10.91%) 20	8 / 163 (4.91%) 10	13 / 167 (7.78%) 14
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	4 / 165 (2.42%) 4	10 / 163 (6.13%) 11	12 / 167 (7.19%) 12
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	13 / 165 (7.88%) 16	7 / 163 (4.29%) 8	8 / 167 (4.79%) 9
Pericardial effusion subjects affected / exposed occurrences (all)	3 / 165 (1.82%) 3	9 / 163 (5.52%) 9	10 / 167 (5.99%) 11
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	24 / 165 (14.55%) 30	26 / 163 (15.95%) 35	25 / 167 (14.97%) 33
Headache subjects affected / exposed occurrences (all)	75 / 165 (45.45%) 142	73 / 163 (44.79%) 146	60 / 167 (35.93%) 95
Paraesthesia subjects affected / exposed occurrences (all)	12 / 165 (7.27%) 12	11 / 163 (6.75%) 14	10 / 167 (5.99%) 13
Blood and lymphatic system disorders Anaemia			

subjects affected / exposed occurrences (all)	23 / 165 (13.94%) 28	14 / 163 (8.59%) 13	26 / 167 (15.57%) 38
Neutropenia subjects affected / exposed occurrences (all)	23 / 165 (13.94%) 71	28 / 163 (17.18%) 70	29 / 167 (17.37%) 68
Thrombocytopenia subjects affected / exposed occurrences (all)	22 / 165 (13.33%) 43	38 / 163 (23.31%) 80	29 / 167 (17.37%) 85
Eye disorders			
Periorbital oedema subjects affected / exposed occurrences (all)	8 / 165 (4.85%) 9	4 / 163 (2.45%) 4	17 / 167 (10.18%) 21
Vision blurred subjects affected / exposed occurrences (all)	11 / 165 (6.67%) 12	8 / 163 (4.91%) 9	5 / 167 (2.99%) 6
Gastrointestinal disorders			
Abdominal distension subjects affected / exposed occurrences (all)	13 / 165 (7.88%) 16	8 / 163 (4.91%) 9	9 / 167 (5.39%) 11
Abdominal pain subjects affected / exposed occurrences (all)	25 / 165 (15.15%) 31	26 / 163 (15.95%) 39	24 / 167 (14.37%) 36
Abdominal pain upper subjects affected / exposed occurrences (all)	13 / 165 (7.88%) 15	24 / 163 (14.72%) 30	17 / 167 (10.18%) 18
Constipation subjects affected / exposed occurrences (all)	31 / 165 (18.79%) 33	20 / 163 (12.27%) 29	25 / 167 (14.97%) 31
Diarrhoea subjects affected / exposed occurrences (all)	67 / 165 (40.61%) 114	70 / 163 (42.94%) 139	73 / 167 (43.71%) 152
Dyspepsia subjects affected / exposed occurrences (all)	13 / 165 (7.88%) 14	25 / 163 (15.34%) 33	13 / 167 (7.78%) 15
Flatulence			

subjects affected / exposed occurrences (all)	9 / 165 (5.45%) 10	5 / 163 (3.07%) 5	6 / 167 (3.59%) 6
Gastritis			
subjects affected / exposed occurrences (all)	4 / 165 (2.42%) 4	11 / 163 (6.75%) 13	7 / 167 (4.19%) 7
Nausea			
subjects affected / exposed occurrences (all)	37 / 165 (22.42%) 63	54 / 163 (33.13%) 74	52 / 167 (31.14%) 83
Stomatitis			
subjects affected / exposed occurrences (all)	5 / 165 (3.03%) 6	7 / 163 (4.29%) 9	12 / 167 (7.19%) 16
Toothache			
subjects affected / exposed occurrences (all)	10 / 165 (6.06%) 15	15 / 163 (9.20%) 17	8 / 167 (4.79%) 13
Vomiting			
subjects affected / exposed occurrences (all)	23 / 165 (13.94%) 33	29 / 163 (17.79%) 37	32 / 167 (19.16%) 54
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed occurrences (all)	5 / 165 (3.03%) 5	7 / 163 (4.29%) 9	7 / 167 (4.19%) 9
Alopecia			
subjects affected / exposed occurrences (all)	13 / 165 (7.88%) 14	8 / 163 (4.91%) 9	7 / 167 (4.19%) 7
Dermatitis acneiform			
subjects affected / exposed occurrences (all)	4 / 165 (2.42%) 4	8 / 163 (4.91%) 10	8 / 167 (4.79%) 9
Dry skin			
subjects affected / exposed occurrences (all)	10 / 165 (6.06%) 11	8 / 163 (4.91%) 9	8 / 167 (4.79%) 8
Erythema			
subjects affected / exposed occurrences (all)	5 / 165 (3.03%) 5	7 / 163 (4.29%) 9	9 / 167 (5.39%) 13
Hyperhidrosis			
subjects affected / exposed occurrences (all)	11 / 165 (6.67%) 12	4 / 163 (2.45%) 4	9 / 167 (5.39%) 10

Night sweats			
subjects affected / exposed	7 / 165 (4.24%)	10 / 163 (6.13%)	12 / 167 (7.19%)
occurrences (all)	10	12	14
Petechiae			
subjects affected / exposed	1 / 165 (0.61%)	11 / 163 (6.75%)	4 / 167 (2.40%)
occurrences (all)	1	11	4
Pruritus			
subjects affected / exposed	24 / 165 (14.55%)	22 / 163 (13.50%)	17 / 167 (10.18%)
occurrences (all)	27	27	29
Rash			
subjects affected / exposed	37 / 165 (22.42%)	52 / 163 (31.90%)	43 / 167 (25.75%)
occurrences (all)	50	83	59
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	47 / 165 (28.48%)	39 / 163 (23.93%)	36 / 167 (21.56%)
occurrences (all)	59	51	47
Back pain			
subjects affected / exposed	26 / 165 (15.76%)	29 / 163 (17.79%)	28 / 167 (16.77%)
occurrences (all)	30	36	34
Bone pain			
subjects affected / exposed	20 / 165 (12.12%)	25 / 163 (15.34%)	15 / 167 (8.98%)
occurrences (all)	26	31	18
Muscle spasms			
subjects affected / exposed	10 / 165 (6.06%)	4 / 163 (2.45%)	14 / 167 (8.38%)
occurrences (all)	14	4	20
Musculoskeletal pain			
subjects affected / exposed	24 / 165 (14.55%)	13 / 163 (7.98%)	15 / 167 (8.98%)
occurrences (all)	31	14	16
Myalgia			
subjects affected / exposed	27 / 165 (16.36%)	26 / 163 (15.95%)	24 / 167 (14.37%)
occurrences (all)	40	36	27
Neck pain			
subjects affected / exposed	10 / 165 (6.06%)	6 / 163 (3.68%)	5 / 167 (2.99%)
occurrences (all)	9	9	5
Pain in extremity			



subjects affected / exposed occurrences (all)	33 / 165 (20.00%) 37	29 / 163 (17.79%) 35	24 / 167 (14.37%) 30
Infections and infestations			
Bronchitis			
subjects affected / exposed	14 / 165 (8.48%)	5 / 163 (3.07%)	16 / 167 (9.58%)
occurrences (all)	16	9	21
Conjunctivitis			
subjects affected / exposed	3 / 165 (1.82%)	11 / 163 (6.75%)	7 / 167 (4.19%)
occurrences (all)	3	12	8
Infection			
subjects affected / exposed	9 / 165 (5.45%)	4 / 163 (2.45%)	8 / 167 (4.79%)
occurrences (all)	11	6	6
Influenza			
subjects affected / exposed	13 / 165 (7.88%)	4 / 163 (2.45%)	17 / 167 (10.18%)
occurrences (all)	20	4	20
Nasopharyngitis			
subjects affected / exposed	23 / 165 (13.94%)	13 / 163 (7.98%)	22 / 167 (13.17%)
occurrences (all)	26	21	37
Oral herpes			
subjects affected / exposed	13 / 165 (7.88%)	5 / 163 (3.07%)	9 / 167 (5.39%)
occurrences (all)	16	5	14
Pneumonia			
subjects affected / exposed	5 / 165 (3.03%)	5 / 163 (3.07%)	10 / 167 (5.99%)
occurrences (all)	7	5	7
Sinusitis			
subjects affected / exposed	19 / 165 (11.52%)	8 / 163 (4.91%)	17 / 167 (10.18%)
occurrences (all)	29	11	22
Upper respiratory tract infection			
subjects affected / exposed	28 / 165 (16.97%)	26 / 163 (15.95%)	35 / 167 (20.96%)
occurrences (all)	46	43	52
Urinary tract infection			
subjects affected / exposed	15 / 165 (9.09%)	13 / 163 (7.98%)	12 / 167 (7.19%)
occurrences (all)	23	17	25
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	16 / 165 (9.70%)	21 / 163 (12.88%)	21 / 167 (12.57%)
occurrences (all)	20	24	28

<b>Non-serious adverse events</b>	Dasatinib 70 mg BID		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	165 / 167 (98.80%)		
Vascular disorders			
Flushing			
subjects affected / exposed	7 / 167 (4.19%)		
occurrences (all)	10		
Hypertension			
subjects affected / exposed	20 / 167 (11.98%)		
occurrences (all)	20		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	27 / 167 (16.17%)		
occurrences (all)	34		
Chest pain			
subjects affected / exposed	17 / 167 (10.18%)		
occurrences (all)	31		
Chills			
subjects affected / exposed	14 / 167 (8.38%)		
occurrences (all)	14		
Fatigue			
subjects affected / exposed	49 / 167 (29.34%)		
occurrences (all)	74		
Influenza like illness			
subjects affected / exposed	13 / 167 (7.78%)		
occurrences (all)	16		
Oedema peripheral			
subjects affected / exposed	36 / 167 (21.56%)		
occurrences (all)	43		
Pain			
subjects affected / exposed	10 / 167 (5.99%)		
occurrences (all)	12		
Pyrexia			

subjects affected / exposed	44 / 167 (26.35%)		
occurrences (all)	69		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	54 / 167 (32.34%)		
occurrences (all)	81		
Dyspnoea			
subjects affected / exposed	43 / 167 (25.75%)		
occurrences (all)	58		
Dyspnoea exertional			
subjects affected / exposed	2 / 167 (1.20%)		
occurrences (all)	2		
Epistaxis			
subjects affected / exposed	12 / 167 (7.19%)		
occurrences (all)	13		
Oropharyngeal pain			
subjects affected / exposed	17 / 167 (10.18%)		
occurrences (all)	16		
Pleural effusion			
subjects affected / exposed	51 / 167 (30.54%)		
occurrences (all)	73		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	12 / 167 (7.19%)		
occurrences (all)	16		
Depression			
subjects affected / exposed	11 / 167 (6.59%)		
occurrences (all)	13		
Insomnia			
subjects affected / exposed	12 / 167 (7.19%)		
occurrences (all)	14		
Investigations			
Weight decreased			
subjects affected / exposed	27 / 167 (16.17%)		
occurrences (all)	32		
Weight increased			

subjects affected / exposed occurrences (all)	11 / 167 (6.59%) 12		
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	3 / 167 (1.80%) 13		
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)  Pericardial effusion subjects affected / exposed occurrences (all)	11 / 167 (6.59%) 12  7 / 167 (4.19%) 7		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)  Headache subjects affected / exposed occurrences (all)  Paraesthesia subjects affected / exposed occurrences (all)	25 / 167 (14.97%) 28  76 / 167 (45.51%) 131  7 / 167 (4.19%) 8		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)  Neutropenia subjects affected / exposed occurrences (all)  Thrombocytopenia subjects affected / exposed occurrences (all)	23 / 167 (13.77%) 35  28 / 167 (16.77%) 61  27 / 167 (16.17%) 83		
Eye disorders Periorbital oedema			

subjects affected / exposed	5 / 167 (2.99%)		
occurrences (all)	6		
Vision blurred			
subjects affected / exposed	5 / 167 (2.99%)		
occurrences (all)	5		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	7 / 167 (4.19%)		
occurrences (all)	10		
Abdominal pain			
subjects affected / exposed	20 / 167 (11.98%)		
occurrences (all)	24		
Abdominal pain upper			
subjects affected / exposed	18 / 167 (10.78%)		
occurrences (all)	21		
Constipation			
subjects affected / exposed	20 / 167 (11.98%)		
occurrences (all)	22		
Diarrhoea			
subjects affected / exposed	82 / 167 (49.10%)		
occurrences (all)	151		
Dyspepsia			
subjects affected / exposed	16 / 167 (9.58%)		
occurrences (all)	17		
Flatulence			
subjects affected / exposed	3 / 167 (1.80%)		
occurrences (all)	3		
Gastritis			
subjects affected / exposed	7 / 167 (4.19%)		
occurrences (all)	8		
Nausea			
subjects affected / exposed	69 / 167 (41.32%)		
occurrences (all)	109		
Stomatitis			
subjects affected / exposed	7 / 167 (4.19%)		
occurrences (all)	10		

Toothache			
subjects affected / exposed	8 / 167 (4.79%)		
occurrences (all)	10		
Vomiting			
subjects affected / exposed	52 / 167 (31.14%)		
occurrences (all)	89		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	9 / 167 (5.39%)		
occurrences (all)	12		
Alopecia			
subjects affected / exposed	13 / 167 (7.78%)		
occurrences (all)	13		
Dermatitis acneiform			
subjects affected / exposed	11 / 167 (6.59%)		
occurrences (all)	12		
Dry skin			
subjects affected / exposed	6 / 167 (3.59%)		
occurrences (all)	6		
Erythema			
subjects affected / exposed	5 / 167 (2.99%)		
occurrences (all)	7		
Hyperhidrosis			
subjects affected / exposed	1 / 167 (0.60%)		
occurrences (all)	1		
Night sweats			
subjects affected / exposed	10 / 167 (5.99%)		
occurrences (all)	10		
Petechiae			
subjects affected / exposed	6 / 167 (3.59%)		
occurrences (all)	6		
Pruritus			
subjects affected / exposed	23 / 167 (13.77%)		
occurrences (all)	31		
Rash			

subjects affected / exposed	43 / 167 (25.75%)		
occurrences (all)	63		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	30 / 167 (17.96%)		
occurrences (all)	39		
Back pain			
subjects affected / exposed	24 / 167 (14.37%)		
occurrences (all)	37		
Bone pain			
subjects affected / exposed	15 / 167 (8.98%)		
occurrences (all)	19		
Muscle spasms			
subjects affected / exposed	8 / 167 (4.79%)		
occurrences (all)	8		
Musculoskeletal pain			
subjects affected / exposed	18 / 167 (10.78%)		
occurrences (all)	20		
Myalgia			
subjects affected / exposed	22 / 167 (13.17%)		
occurrences (all)	26		
Neck pain			
subjects affected / exposed	6 / 167 (3.59%)		
occurrences (all)	6		
Pain in extremity			
subjects affected / exposed	22 / 167 (13.17%)		
occurrences (all)	27		
Infections and infestations			
Bronchitis			
subjects affected / exposed	11 / 167 (6.59%)		
occurrences (all)	12		
Conjunctivitis			
subjects affected / exposed	6 / 167 (3.59%)		
occurrences (all)	6		
Infection			

subjects affected / exposed	2 / 167 (1.20%)		
occurrences (all)	2		
Influenza			
subjects affected / exposed	11 / 167 (6.59%)		
occurrences (all)	13		
Nasopharyngitis			
subjects affected / exposed	13 / 167 (7.78%)		
occurrences (all)	16		
Oral herpes			
subjects affected / exposed	8 / 167 (4.79%)		
occurrences (all)	10		
Pneumonia			
subjects affected / exposed	13 / 167 (7.78%)		
occurrences (all)	12		
Sinusitis			
subjects affected / exposed	12 / 167 (7.19%)		
occurrences (all)	15		
Upper respiratory tract infection			
subjects affected / exposed	23 / 167 (13.77%)		
occurrences (all)	43		
Urinary tract infection			
subjects affected / exposed	9 / 167 (5.39%)		
occurrences (all)	9		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	24 / 167 (14.37%)		
occurrences (all)	39		



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 April 2006	The purpose of this amendment was to make minor modifications to the hematologic response criteria and to remove the restriction of concurrent medications that inhibit platelet function.
08 March 2007	The purpose of this amendment was to allow subjects on the twice daily dosing schedule to switch to once daily dosing, in specific circumstances, to optimize the safety of dasatinib.
28 February 2008	The purpose of this amendment was to describe the participation requirements and study conduct for subjects who completed 2 years on study: The study will continue until all subjects have discontinued due to death, withdrawn consent or lost to follow up or until all subjects are followed for at least 5 years after study start, whichever occurs first.
19 December 2008	The purpose of this amendment was to clarify language surrounding study conduct for all enrolled subjects after two years on study in terms of data collection and submission of adverse events.
14 September 2010	The purpose of this amendment was to extend the duration of the study to subjects who continued to have clinical benefit.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported