



Clinical trial results:

A Phase 3, Randomized, Open-Label Study of Bosutinib Versus Imatinib in Subjects With Newly Diagnosed Chronic Phase Philadelphia Chromosome Positive Chronic Myelogenous Leukemia

Summary

EudraCT number	2007-003780-50
Trial protocol	DE HU GB BE ES LV LT FR IT SI
Global end of trial date	27 May 2015

Results information

Result version number	v1 (current)
This version publication date	12 June 2016
First version publication date	12 June 2016

Trial information

Trial identification

Sponsor protocol code	3160A4-3000
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00574873
WHO universal trial number (UTN)	-
Other trial identifiers	Alias identification: B1871008

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 May 2015
Is this the analysis of the primary completion data?	No

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

Notes:

General information about the trial

Main objective of the trial:

This was a multinational, multicentre, randomized, open-label, parallel-arm Phase 3 study to compare the efficacy and safety of bosutinib alone to that of imatinib alone in subjects with newly diagnosed chronic phase chronic myelogenous leukemia.

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonisation Clinical Practice. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial participants. The final protocol and any amendments were reviewed and approved by the Institutional Review Board(s)/or Independent Ethics Committee(s) each of the investigational centres participating in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 February 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 4
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Canada: 15
Country: Number of subjects enrolled	Chile: 3
Country: Number of subjects enrolled	Colombia: 7
Country: Number of subjects enrolled	Germany: 20
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Hong Kong: 9
Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	India: 54
Country: Number of subjects enrolled	Italy: 18
Country: Number of subjects enrolled	Japan: 27
Country: Number of subjects enrolled	Korea, Republic of: 19

Country: Number of subjects enrolled	Lithuania: 17
Country: Number of subjects enrolled	Latvia: 4
Country: Number of subjects enrolled	Mexico: 3
Country: Number of subjects enrolled	Poland: 30
Country: Number of subjects enrolled	Russian Federation: 54
Country: Number of subjects enrolled	Singapore: 15
Country: Number of subjects enrolled	South Africa: 2
Country: Number of subjects enrolled	Thailand: 10
Country: Number of subjects enrolled	Turkey: 7
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	Ukraine: 58
Country: Number of subjects enrolled	United States: 41
Country: Number of subjects enrolled	Brazil: 12
Country: Number of subjects enrolled	China: 18
Worldwide total number of subjects	502
EEA total number of subjects	141

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)	446
From 65 to 84 years	54
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening included the following assessments: Sokal score calculation; Eastern Cooperative Oncology Group assessment; extramedullary assessment; bone marrow aspirate; peripheral blood sampling; electrocardiogram; chest x-ray; echocardiogram or multiple gated acquisition scan.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Bosutinib

Arm description:

Bosutinib 500 milligram (mg) tablet orally once daily up to 5 years or until treatment failure, unacceptable toxicity, death, withdrawal of consent. Dose adjustments, if needed, included an escalation to bosutinib 600 mg tablet orally once daily or a reduction to bosutinib 300 mg tablet orally once daily.

Arm type	Experimental
Investigational medicinal product name	Bosutinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Film-coated bosutinib tablets administered once daily at a dose of 500 mg with food (preferably in the morning) for up to 5 years or until treatment failure, unacceptable toxicity, death, withdrawal of consent. Dose adjustments, if needed, included an escalation to bosutinib 600 mg tablet orally once daily or a reduction to bosutinib 300 mg (<300 mg if deemed appropriate by the investigator and sponsor) tablet orally once daily.

Arm title	Imatinib
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Arm description:

Imatinib 400 mg tablet orally once daily up to 5 years or until treatment failure, unacceptable toxicity, death, withdrawal of consent. Dose adjustments, if needed, included an escalation to imatinib 600 mg tablet orally once daily or a reduction to imatinib 300 mg tablet orally once daily.

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

Dosage and administration details:

Imatinib tablets administered once daily at a dose of 400 mg with food and a large glass of water for up to 5 years or until treatment failure, unacceptable toxicity, death, withdrawal of consent. Dose adjustments, if needed, included an escalation to imatinib 600 mg tablet orally once daily or a reduction to imatinib 300 mg tablet orally once daily.

Number of subjects in period 1	Bosutinib	Imatinib
Started	250	252
Completed	12	1
Not completed	238	251
Adverse event, serious fatal	15	14
Consent withdrawn by subject	18	19
Extension study	126	-
Unspecified	40	4
Discontinuation of study by sponsor	5	199
Blank, site closed per local regulations	2	2
Lost to follow-up	14	5
Investigator request	18	8

Baseline characteristics

Reporting groups

Reporting group title	Bosutinib
Reporting group description: Bosutinib 500 milligram (mg) tablet orally once daily up to 5 years or until treatment failure, unacceptable toxicity, death, withdrawal of consent. Dose adjustments, if needed, included an escalation to bosutinib 600 mg tablet orally once daily or a reduction to bosutinib 300 mg tablet orally once daily.	
Reporting group title	Imatinib
Reporting group description: Imatinib 400 mg tablet orally once daily up to 5 years or until treatment failure, unacceptable toxicity, death, withdrawal of consent. Dose adjustments, if needed, included an escalation to imatinib 600 mg tablet orally once daily or a reduction to imatinib 300 mg tablet orally once daily.	

Reporting group values	Bosutinib	Imatinib	Total
Number of subjects	250	252	502
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	221	225	446
From 65-84 years	28	26	54
85 years and over	1	1	2
Age Continuous Units: years			
arithmetic mean	47.4	45.6	
standard deviation	± 14.39	± 14.8	-
Gender, Male/Female Units: participants			
Female	101	117	218
Male	149	135	284

End points

End points reporting groups

Reporting group title	Bosutinib
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Reporting group description:

Bosutinib 500 milligram (mg) tablet orally once daily up to 5 years or until treatment failure, unacceptable toxicity, death, withdrawal of consent. Dose adjustments, if needed, included an escalation to bosutinib 600 mg tablet orally once daily or a reduction to bosutinib 300 mg tablet orally once daily.

Reporting group title	Imatinib
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Reporting group description:

Imatinib 400 mg tablet orally once daily up to 5 years or until treatment failure, unacceptable toxicity, death, withdrawal of consent. Dose adjustments, if needed, included an escalation to imatinib 600 mg tablet orally once daily or a reduction to imatinib 300 mg tablet orally once daily.

Subject analysis set title	Bosutinib
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

Bosutinib 500 milligram (mg) tablet orally once daily up to 5 years or until treatment failure, unacceptable toxicity, death, withdrawal of consent. Dose adjustments, if needed, included an escalation to bosutinib 600 mg tablet orally once daily or a reduction to bosutinib 300 mg tablet orally once daily.

Subject analysis set title	Imatinib
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

Imatinib 400 mg tablet orally once daily up to 5 years or until treatment failure, unacceptable toxicity, death, withdrawal of consent. Dose adjustments, if needed, included an escalation to imatinib 600 mg tablet orally once daily or a reduction to imatinib 300 mg tablet orally once daily.

Primary: Percentage of Participants with Complete Cytogenetic Response (CCyR) at Year 1

End point title	Percentage of Participants with Complete Cytogenetic Response (CCyR) at Year 1
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End point description:

Cytogenetic Response (CyR) is based on the prevalence of Philadelphia chromosome positive (Ph+) metaphases among cells in metaphase on a bone marrow (BM) aspirate. CCyR was achieved when there was 0 percent (%) Ph+ metaphases among cells in a BM sample when at least 20 metaphases from a BM sample were analyzed, or less than (<) 1% breakpoint cluster region Abelson protooncogene (Bcr-Abl) fusion product among cells in a BM sample or peripheral blood sample when at least 200 cells were analyzed.

End point type	Primary
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End point timeframe:

Year 1 (48 weeks)

End point values	Bosutinib	Imatinib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	250	252		
Units: Percentage of Participants				
number (confidence interval 95%)	70 (64.3 to 75.7)	68.3 (62.5 to 74)		

Statistical analyses

Statistical analysis title	Analysis of CCyR at Year 1
Comparison groups	Bosutinib v Imatinib
Number of subjects included in analysis	502
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.667 ^[1]
Method	Stratified Cochran-Mantel-Haenszel

Notes:

[1] - p-value was based on a Cochran Mantel Haenszel test for general association between treatment and responder stratification by Sokal risk group (low, intermediate, high) and region (1 to 3) as determined at time of randomization.

Secondary: Percentage of Participants with Major Molecular Response (MMR) at Year 1

End point title	Percentage of Participants with Major Molecular Response (MMR) at Year 1
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End point description:

Molecular response was assessed using Bcr-Abl transcript levels measured by reverse transcriptase polymerase chain reaction (RT-PCR) from peripheral blood. A MMR was defined as a ratio Bcr-Abl/Abl less than or equal to (\leq) 0.1% on the international scale (greater than or equal to [\geq] 3 log reduction from standardized baseline in ratio of Bcr-Abl to Abl transcripts) with at least 3000 Abl analyzed.

End point type	Secondary
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End point timeframe:

Year 1 (48 weeks)

End point values	Bosutinib	Imatinib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	250	252		
Units: Percentage of Participants				
number (confidence interval 95%)	38 (32 to 44)	25.4 (20 to 30.8)		

Statistical analyses

Statistical analysis title	Analysis of MMR at Year 1
Comparison groups	Bosutinib v Imatinib
Number of subjects included in analysis	502
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.002 ^[2]
Method	Stratified Cochran-Mantel-Haenszel

Notes:

[2] - p-value was based on a Cochran Mantel Haenszel test for general association between treatment and responder stratification by Sokal risk group (low, intermediate, high) and region (1 to 3) as determined at time of randomization.

Secondary: Kaplan-Meier Estimate of Probability of Retaining CCyR at 192 Weeks

End point title	Kaplan-Meier Estimate of Probability of Retaining CCyR at 192 Weeks
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End point description:

Duration of CCyR was measured from the first date of response until the first date of loss of response, objectively documented. Duration of response was calculated using only participants who responded to study medication. CyR is based on the prevalence of Ph+ metaphases among cells in metaphase on a bone marrow sample. CCyR was achieved when there was 0% Ph+ metaphases among cells in a bone marrow sample when at least 20 metaphases from a BM sample were analyzed, or <1% Bcr-Abl fusion product among cells in a BM sample or peripheral blood sample when at least 200 cells were analyzed. The medians have not been reached in either arm, as such, the premature estimated hazard ratio is provided. 4 year rates displayed since the majority of participants had first CCyR by Year 1.

End point type	Secondary
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End point timeframe:

Every 12 weeks in Year 1, every 24 weeks in Years 2 and 3 and every 48 weeks for Year 4 through 5

End point values	Bosutinib	Imatinib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	197	204		
Units: weeks				
number (confidence interval 95%)	92.9 (87.8 to 95.9)	88.9 (83.2 to 92.7)		

Statistical analyses

Statistical analysis title	Analysis of Retainment of CCyR at 192 Weeks
Comparison groups	Bosutinib v Imatinib
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	1.31

Secondary: Kaplan-Meier Estimate of Probability of Retaining Complete Hematologic Response (CHR) at 192 Weeks

End point title	Kaplan-Meier Estimate of Probability of Retaining Complete Hematologic Response (CHR) at 192 Weeks
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End point description:

Duration of CHR was measured from the first date of response until the first date of loss of response, objectively documented. Duration of response was calculated using only participants who responded to study medication. CHR must have been of at least 4 weeks in duration confirmed by 2 assessments at least 4 weeks apart and was defined as follows: white blood cells \leq institutional upper limit of normal [20×10^9 per liter (/L)], no peripheral blasts or promyelocytes, myelocytes + metamyelocytes <5% in blood, absolute neutrophil count $\geq 1.0 \times 10^9$ /L, platelets ≥ 100 but $< 450 \times 10^9$ /L unless related to therapy, <20% basophils in blood and no extramedullary involvement (including hepato- or splenomegaly). The medians have not been reached in either arm; as such, the premature estimated

hazard ratio is provided. 4 year rates displayed since the majority of participants had first CHR by Year 1.

End point type	Secondary
End point timeframe:	
Every 4 weeks up to Week 20 thereafter every 12 weeks until 7 to 28 days after last dose of study medication	

End point values	Bosutinib	Imatinib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	219	242		
Units: weeks				
number (confidence interval 95%)	91.6 (86.5 to 94.9)	86 (80.7 to 90)		

Statistical analyses

Statistical analysis title	Analysis of Retainment of CHR at 192 Weeks
Comparison groups	Bosutinib v Imatinib
Number of subjects included in analysis	461
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	1.08

Secondary: Kaplan-Meier Estimate of Probability of Retaining Derived MMR at 144 Weeks

End point title	Kaplan-Meier Estimate of Probability of Retaining Derived MMR at 144 Weeks
End point description:	
Duration of MMR was measured from the first date of response until the first date loss of response, objectively documented. Duration of response was calculated using only participants who responded to study medication. Molecular response was assessed using Bcr-Abl transcript levels measured by RT-PCR from peripheral blood. MMR is defined as a ratio Bcr-Abl/Abl \leq 0.1% on the international scale (\geq 3 log reduction from standardized baseline in ratio of Bcr-Abl to Abl transcripts) with at least 3000 Abl analyzed. The medians have not been reached in either arm; as such, the premature estimated hazard ratio is provided. 3 year rates displayed since the majority of imatinb participants had first MMR by Year 2.	
End point type	Secondary
End point timeframe:	
Every 12 weeks for Years 1 and 2 and every 24 weeks for Year 3 through 5	

End point values	Bosutinib	Imatinib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	168	170		
Units: weeks				
number (confidence interval 95%)	94.7 (89.6 to 97.3)	98 (93.8 to 99.3)		

Statistical analyses

Statistical analysis title	Analysis of Retainment of Derived MMR at 144 Weeks
Comparison groups	Bosutinib v Imatinib
Number of subjects included in analysis	338
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	3.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	11.72

Secondary: Cumulative Incidence of On-Treatment Transformation to Accelerated Phase (AP) or Blast Phase (BP) at 192 Weeks

End point title	Cumulative Incidence of On-Treatment Transformation to Accelerated Phase (AP) or Blast Phase (BP) at 192 Weeks
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End point description:

Time to transformation to AP/BP was defined as the time from randomization to the first date of transformation to AP or BP while on study treatment adjusting for the competing risk of treatment discontinuation without transformation. Criteria for transformation to AP: 15 to 29% blasts; ≥30% blasts + promyelocytes; ≥20% basophils in blood or bone marrow; platelets <100*10⁹/L (not related to therapy), in blood. Criteria for transformation to BP: ≥30% blasts in blood or bone marrow and extramedullary involvement other than liver or spleen (example: chloromas). Time to transformation was calculated as weeks = ([date of first documented occurrence of the event - date of randomization] + 1)/7. If transformation was not obtained, censoring was at the last hematologic assessment or death (whichever was earliest). Participants who were not treated contributed time=1 day/7. 95% confidence interval for the cumulative incidence is from Gray's method.

End point type	Secondary
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End point timeframe:

From date of randomization (Week 0) up to first transformation to AP/BP phase or 7 to 28 days after last dose of study medication

End point values	Bosutinib	Imatinib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	250	252		
Units: weeks				
number (confidence interval 95%)	1.6 (0.6 to 4.3)	4.4 (2.5 to 7.8)		

Statistical analyses

Statistical analysis title	Analysis of Transformation to AP/ BP at 192 Weeks
Comparison groups	Bosutinib v Imatinib
Number of subjects included in analysis	502
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.13
upper limit	1.29

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were recorded from first dose of study treatment through last subject visit. Serious adverse events (SAE) were recorded from informed consent through and including 28 calendar days after last administration of study treatment.

Adverse event reporting additional description:

The same event may appear as both an AE and SAE. However, what is presented are distinct events. An event may be categorized as serious in one subject and as nonserious in another subject, or one subject may have experienced both a serious and nonserious event during the study.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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Reporting groups

Reporting group title	Imatinib
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Reporting group description:

Imatinib 400 mg tablet orally once daily up to 5 years or until treatment failure, unacceptable toxicity, death, withdrawal of consent. Dose adjustments, if needed, included an escalation to imatinib 600 mg tablet orally once daily or a reduction to imatinib 300 mg tablet orally once daily.

Reporting group title	Bosutinib
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Reporting group description:

Bosutinib 500 milligram (mg) tablet orally once daily up to 5 years or until treatment failure, unacceptable toxicity, death, withdrawal of consent. Dose adjustments, if needed, included an escalation to bosutinib 600 mg tablet orally once daily or a reduction to bosutinib 300 mg tablet orally once daily.

Serious adverse events	Imatinib	Bosutinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	57 / 251 (22.71%)	90 / 248 (36.29%)	
number of deaths (all causes)	5	3	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Blast cell crisis			
subjects affected / exposed	1 / 251 (0.40%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic myeloid leukaemia transformation			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malignant melanoma			

subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma gastric			
subjects affected / exposed	0 / 251 (0.00%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	1 / 251 (0.40%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder squamous cell carcinoma stage unspecified			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blast crisis in myelogenous leukaemia			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic lymphocytic leukaemia			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer recurrent			

subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haemorrhage			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypertension			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cyst removal			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	1 / 251 (0.40%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 251 (0.80%)	7 / 248 (2.82%)	
occurrences causally related to treatment / all	0 / 3	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			

subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sudden death			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	0 / 251 (0.00%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Pregnancy of partner			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast			

disorders			
Menstruation irregular			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metrorrhagia			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease			
subjects affected / exposed	0 / 251 (0.00%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 251 (0.00%)	11 / 248 (4.44%)	
occurrences causally related to treatment / all	0 / 0	10 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	0 / 251 (0.00%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiectasis			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bronchitis chronic			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord polyp			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	0 / 251 (0.00%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 251 (0.40%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Dissociative disorder			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 251 (0.40%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Allergic hepatitis			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			

subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder polyp			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 251 (0.00%)	7 / 248 (2.82%)	
occurrences causally related to treatment / all	0 / 0	12 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 251 (0.00%)	4 / 248 (1.61%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatitis C antibody positive subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion subjects affected / exposed	1 / 251 (0.40%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exposure via father subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gun shot wound subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Laceration			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	0 / 251 (0.00%)	3 / 248 (1.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 251 (0.40%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 251 (0.00%)	5 / 248 (2.02%)	
occurrences causally related to treatment / all	0 / 0	3 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			

subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block right			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 251 (0.00%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pericarditis			
subjects affected / exposed	0 / 251 (0.00%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery aneurysm			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carpal tunnel syndrome			

subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar radiculopathy			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system haemorrhage			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 251 (0.00%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 251 (0.40%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	7 / 251 (2.79%)	5 / 248 (2.02%)	
occurrences causally related to treatment / all	20 / 22	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			

subjects affected / exposed	8 / 251 (3.19%)	6 / 248 (2.42%)	
occurrences causally related to treatment / all	9 / 10	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	5 / 251 (1.99%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	5 / 6	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness unilateral			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Vitreous haemorrhage			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual impairment			

subjects affected / exposed	1 / 251 (0.40%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	1 / 251 (0.40%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glaucoma			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinopathy			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 251 (0.00%)	9 / 248 (3.63%)	
occurrences causally related to treatment / all	0 / 0	11 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	3 / 251 (1.20%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 251 (0.80%)	3 / 248 (1.21%)	
occurrences causally related to treatment / all	1 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 251 (0.00%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			

subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 251 (0.00%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal necrosis			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Mesenteric artery embolism			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nausea			

subjects affected / exposed	2 / 251 (0.80%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal haemorrhage			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 251 (0.40%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcoholic pancreatitis			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			

subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal polyp			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis haemorrhagic			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 251 (0.40%)	3 / 248 (1.21%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			

subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	0 / 251 (0.00%)	5 / 248 (2.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus bladder			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Myalgia			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	2 / 251 (0.80%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc disorder			
subjects affected / exposed	0 / 251 (0.00%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 251 (0.40%)	8 / 248 (3.23%)	
occurrences causally related to treatment / all	0 / 1	2 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 251 (0.40%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	1 / 251 (0.40%)	3 / 248 (1.21%)	
occurrences causally related to treatment / all	1 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected dermal cyst			
subjects affected / exposed	1 / 251 (0.40%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 251 (0.00%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			

subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonella bacteraemia			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salpingo-oophoritis			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			

subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis of male external genital organ			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis infected			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eczema infected			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis A			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis E			

subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious colitis			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intrauterine infection			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malaria			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngotonsillitis			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 251 (0.00%)	2 / 248 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cell death			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	1 / 251 (0.40%)	0 / 248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	0 / 251 (0.00%)	1 / 248 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Imatinib	Bosutinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	238 / 251 (94.82%)	235 / 248 (94.76%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	14 / 251 (5.58%)	20 / 248 (8.06%)	
occurrences (all)	15	24	
General disorders and administration			

site conditions			
Fatigue			
subjects affected / exposed	33 / 251 (13.15%)	38 / 248 (15.32%)	
occurrences (all)	43	68	
Pyrexia			
subjects affected / exposed	34 / 251 (13.55%)	44 / 248 (17.74%)	
occurrences (all)	44	62	
Oedema peripheral			
subjects affected / exposed	32 / 251 (12.75%)	14 / 248 (5.65%)	
occurrences (all)	43	22	
Asthenia			
subjects affected / exposed	23 / 251 (9.16%)	23 / 248 (9.27%)	
occurrences (all)	40	48	
Oedema			
subjects affected / exposed	16 / 251 (6.37%)	14 / 248 (5.65%)	
occurrences (all)	20	20	
Face oedema			
subjects affected / exposed	15 / 251 (5.98%)	5 / 248 (2.02%)	
occurrences (all)	19	5	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	31 / 251 (12.35%)	30 / 248 (12.10%)	
occurrences (all)	39	46	
Dyspnoea			
subjects affected / exposed	9 / 251 (3.59%)	24 / 248 (9.68%)	
occurrences (all)	13	47	
Oropharyngeal pain			
subjects affected / exposed	15 / 251 (5.98%)	12 / 248 (4.84%)	
occurrences (all)	23	14	
Pleural effusion			
subjects affected / exposed	1 / 251 (0.40%)	14 / 248 (5.65%)	
occurrences (all)	1	31	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	13 / 251 (5.18%)	10 / 248 (4.03%)	
occurrences (all)	17	13	

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	27 / 251 (10.76%)	85 / 248 (34.27%)	
occurrences (all)	58	297	
Aspartate aminotransferase increased			
subjects affected / exposed	28 / 251 (11.16%)	70 / 248 (28.23%)	
occurrences (all)	55	176	
Lipase increased			
subjects affected / exposed	29 / 251 (11.55%)	47 / 248 (18.95%)	
occurrences (all)	97	108	
Blood creatine phosphokinase increased			
subjects affected / exposed	58 / 251 (23.11%)	23 / 248 (9.27%)	
occurrences (all)	152	40	
Blood alkaline phosphatase increased			
subjects affected / exposed	11 / 251 (4.38%)	18 / 248 (7.26%)	
occurrences (all)	20	30	
Blood creatinine increased			
subjects affected / exposed	16 / 251 (6.37%)	14 / 248 (5.65%)	
occurrences (all)	22	34	
Weight increased			
subjects affected / exposed	24 / 251 (9.56%)	6 / 248 (2.42%)	
occurrences (all)	33	10	
Gamma-glutamyltransferase increased			
subjects affected / exposed	5 / 251 (1.99%)	16 / 248 (6.45%)	
occurrences (all)	8	42	
Amylase increased			
subjects affected / exposed	16 / 251 (6.37%)	27 / 248 (10.89%)	
occurrences (all)	57	59	
Haemoglobin decreased			
subjects affected / exposed	14 / 251 (5.58%)	5 / 248 (2.02%)	
occurrences (all)	50	10	
Weight decreased			
subjects affected / exposed	3 / 251 (1.20%)	16 / 248 (6.45%)	
occurrences (all)	4	22	
Nervous system disorders			

Headache			
subjects affected / exposed	34 / 251 (13.55%)	33 / 248 (13.31%)	
occurrences (all)	55	56	
Dizziness			
subjects affected / exposed	28 / 251 (11.16%)	23 / 248 (9.27%)	
occurrences (all)	46	35	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	72 / 251 (28.69%)	70 / 248 (28.23%)	
occurrences (all)	232	201	
Anaemia			
subjects affected / exposed	58 / 251 (23.11%)	63 / 248 (25.40%)	
occurrences (all)	156	150	
Neutropenia			
subjects affected / exposed	78 / 251 (31.08%)	35 / 248 (14.11%)	
occurrences (all)	270	85	
Leukopenia			
subjects affected / exposed	57 / 251 (22.71%)	24 / 248 (9.68%)	
occurrences (all)	178	46	
Lymphopenia			
subjects affected / exposed	16 / 251 (6.37%)	8 / 248 (3.23%)	
occurrences (all)	27	20	
Eye disorders			
Eyelid oedema			
subjects affected / exposed	20 / 251 (7.97%)	3 / 248 (1.21%)	
occurrences (all)	29	4	
Periorbital oedema			
subjects affected / exposed	38 / 251 (15.14%)	4 / 248 (1.61%)	
occurrences (all)	52	7	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	69 / 251 (27.49%)	174 / 248 (70.16%)	
occurrences (all)	155	668	
Nausea			
subjects affected / exposed	93 / 251 (37.05%)	87 / 248 (35.08%)	
occurrences (all)	173	165	
Vomiting			

subjects affected / exposed	42 / 251 (16.73%)	86 / 248 (34.68%)	
occurrences (all)	73	160	
Abdominal pain upper			
subjects affected / exposed	21 / 251 (8.37%)	38 / 248 (15.32%)	
occurrences (all)	39	53	
Abdominal pain			
subjects affected / exposed	19 / 251 (7.57%)	34 / 248 (13.71%)	
occurrences (all)	30	59	
Dyspepsia			
subjects affected / exposed	17 / 251 (6.77%)	22 / 248 (8.87%)	
occurrences (all)	25	26	
Abdominal distension			
subjects affected / exposed	13 / 251 (5.18%)	8 / 248 (3.23%)	
occurrences (all)	16	15	
Constipation			
subjects affected / exposed	12 / 251 (4.78%)	13 / 248 (5.24%)	
occurrences (all)	17	18	
Toothache			
subjects affected / exposed	4 / 251 (1.59%)	13 / 248 (5.24%)	
occurrences (all)	5	16	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	49 / 251 (19.52%)	64 / 248 (25.81%)	
occurrences (all)	80	130	
Pruritus			
subjects affected / exposed	16 / 251 (6.37%)	16 / 248 (6.45%)	
occurrences (all)	22	21	
Alopecia			
subjects affected / exposed	9 / 251 (3.59%)	13 / 248 (5.24%)	
occurrences (all)	11	19	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	61 / 251 (24.30%)	13 / 248 (5.24%)	
occurrences (all)	114	14	
Arthralgia			

subjects affected / exposed	34 / 251 (13.55%)	24 / 248 (9.68%)	
occurrences (all)	44	33	
Bone pain			
subjects affected / exposed	25 / 251 (9.96%)	10 / 248 (4.03%)	
occurrences (all)	44	13	
Myalgia			
subjects affected / exposed	31 / 251 (12.35%)	16 / 248 (6.45%)	
occurrences (all)	41	19	
Pain in extremity			
subjects affected / exposed	24 / 251 (9.56%)	18 / 248 (7.26%)	
occurrences (all)	36	24	
Back pain			
subjects affected / exposed	21 / 251 (8.37%)	20 / 248 (8.06%)	
occurrences (all)	28	25	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	24 / 251 (9.56%)	33 / 248 (13.31%)	
occurrences (all)	43	48	
Nasopharyngitis			
subjects affected / exposed	28 / 251 (11.16%)	26 / 248 (10.48%)	
occurrences (all)	44	53	
Bronchitis			
subjects affected / exposed	14 / 251 (5.58%)	14 / 248 (5.65%)	
occurrences (all)	17	22	
Influenza			
subjects affected / exposed	11 / 251 (4.38%)	23 / 248 (9.27%)	
occurrences (all)	16	33	
Pharyngitis			
subjects affected / exposed	4 / 251 (1.59%)	13 / 248 (5.24%)	
occurrences (all)	7	16	
Metabolism and nutrition disorders			
Hypophosphataemia			
subjects affected / exposed	55 / 251 (21.91%)	26 / 248 (10.48%)	
occurrences (all)	166	64	
Decreased appetite			

subjects affected / exposed	8 / 251 (3.19%)	22 / 248 (8.87%)	
occurrences (all)	9	31	
Hypokalaemia			
subjects affected / exposed	22 / 251 (8.76%)	8 / 248 (3.23%)	
occurrences (all)	60	15	
Hyperglycaemia			
subjects affected / exposed	16 / 251 (6.37%)	6 / 248 (2.42%)	
occurrences (all)	34	10	
Hypocalcaemia			
subjects affected / exposed	17 / 251 (6.77%)	11 / 248 (4.44%)	
occurrences (all)	35	27	
Hypomagnesaemia			
subjects affected / exposed	16 / 251 (6.37%)	5 / 248 (2.02%)	
occurrences (all)	43	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 November 2007	Addition of mutation testing at screening and treatment completion visit, study length increased from 5 to 8 years, any prior imatinib treatment deleted, added suggested text around magnesium and potassium supplements.
21 November 2007	A specific statement referring to suspected unexpected serious adverse reactions and the European Directive was added to the protocol.
21 November 2008	Additional clarity regarding inclusion/exclusion criteria, informed consent process at Japanese centers, monetary compensation practices in Japan and records retention policy for Japan were included according to Japanese regulations.
01 September 2009	Clarifications in relation to Amendment 1 with regard to protocol consistency. Also included all previous country-specific amendments for United Kingdom and Japan (Amendments 2 and 3, respectively) for worldwide alignment.
11 October 2011	Updated with current information on ongoing studies, changes made to dose escalation, dose reduction, toxicities, discontinuation, storage and stability of tablets, AE reporting, pre-study documentation, and lists of prohibited medications (those that prolong QT and those that inhibit cytochrome P450 2A). Independent data monitoring committee disbanded after interim analysis. Study period shortened to 5 years.
15 April 2012	Sponsor contact information updated, safety profile updated with current information. Changes made to total volume of blood collected, dose escalation, AE and SAE definitions and reporting periods, potential drug-induced liver injury cases, causality assessment. Addition of medication errors section.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported