



Clinical trial results:

An Open-Label, Randomized, Multicenter Phase III Trial of Dasatinib (SPRYCEL®) vs. Standard Dose Imatinib (400 mg) in the Treatment of Subjects with Newly Diagnosed Chronic Phase Philadelphia Chromosome Positive Chronic Myeloid Leukemia

Summary

EudraCT number	2006-005712-27
Trial protocol	FR CZ GR BE NL DE AT HU ES IT DK PL
Global end of trial date	22 December 2015

Results information

Result version number	v1 (current)
This version publication date	03 February 2017
First version publication date	03 February 2017

Trial information

Trial identification

Sponsor protocol code	CA180-056
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00481247
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb International Corporation
Sponsor organisation address	Chausse de la Hulpe 185, Brussels, Belgium, 1170
Public contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb Study Director, 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	22 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 December 2009
Global end of trial reached?	Yes
Global end of trial date	22 December 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this clinical research study is to compare the confirmed complete cytogenetic response of dasatinib with that of imatinib within 12 months after randomization in patients with newly diagnosed chronic-phase Philadelphia positive chronic myeloid leukemia. The safety of this treatment will also be studied.

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	24 September 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Poland: 21
Country: Number of subjects enrolled	Spain: 30
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Czech Republic: 22
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	France: 42
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	Argentina: 28
Country: Number of subjects enrolled	Australia: 11
Country: Number of subjects enrolled	Brazil: 24
Country: Number of subjects enrolled	Chile: 11
Country: Number of subjects enrolled	China: 37

Country: Number of subjects enrolled	Colombia: 5
Country: Number of subjects enrolled	India: 111
Country: Number of subjects enrolled	Japan: 49
Country: Number of subjects enrolled	Korea, Republic of: 14
Country: Number of subjects enrolled	Mexico: 40
Country: Number of subjects enrolled	Peru: 18
Country: Number of subjects enrolled	Russian Federation: 10
Country: Number of subjects enrolled	Singapore: 11
Country: Number of subjects enrolled	Turkey: 6
Worldwide total number of subjects	547
EEA total number of subjects	172

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)	488
From 65 to 84 years	59
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 108 sites in 26 countries.

Pre-assignment

Screening details:

Of the 547 subjects enrolled, 519 were randomized and 516 received treatment. Of the 28 who were enrolled but not randomized, 20 no longer met study criteria, 3 withdrew consent, 1 was lost to follow-up, and 4 withdrew for other reasons.

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	Dasatinib

Arm description:

Dasatinib 100 mg once daily (QD)

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

Dosage and administration details:

Dasatinib: 100 mg orally once daily

Arm title	Imatinib
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Arm description:

Imatinib 400 mg once daily (QD)

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: 400 mg orally once daily

Number of subjects in period 1^[1]	Dasatinib	Imatinib
Started	259	260
Received treatment	258	258
Completed	0	0
Not completed	259	260
Adverse event, serious fatal	-	1
Consent withdrawn by subject	8	13
Disease progression	18	22
Treatment failure	10	14
Varied	6	15
Poor compliance/noncompliance	1	7
Pregnancy	2	1
AE unrelated to study drug	13	4
Intolerance	42	17
Lost to follow-up	1	2
Did not receive treatment	1	2
Administrative reason by sponsor	157	162

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: Of the 547 patients enrolled, 519 were randomized and 516 received treatment. Of the 28 who were enrolled but not randomized, 20 no longer met study criteria, 3 withdrew consent, 1 was lost to follow-up, and 4 withdrew for other reasons.

Baseline characteristics

Reporting groups

Reporting group title	Dasatinib
Reporting group description: Dasatinib 100 mg once daily (QD)	
Reporting group title	Imatinib
Reporting group description: Imatinib 400 mg once daily (QD)	

Reporting group values	Dasatinib	Imatinib	Total
Number of subjects	259	260	519
Age, Customized Units: Subjects			
<20 years	5	9	14
Between 21 and 45 years	123	102	225
Between 46 and 65 years	111	125	236
Between 66 and 75 years	13	20	33
>75 years	7	4	11
Age Continuous Units: Years			
arithmetic mean	46.4	47.1	-
standard deviation	± 14.6	± 13.9	-
Gender, Male/Female Units: Subjects			
Female	115	97	212
Male	144	163	307
Race/Ethnicity, Customized Units: Subjects			
White	132	143	275
Black/African American	2	1	3
Asian	108	95	203
Other	17	21	38
Eastern Cooperative Oncology Group (ECOG) Performance Status			
ECOG is a 6-item scale used to assess disease progression, daily functioning, and appropriate treatment and prognosis. Performance status is scored on a scale ranging from 0-5, with (best score) 0=fully active and able to carry on all predisease performance without restriction and (worst score) 5=death.			
Units: Subjects			
ECOG score=0	213	205	418
ECOG score=1	46	53	99
ECOG score=2	0	2	2

End points

End points reporting groups

Reporting group title	Dasatinib
Reporting group description:	
Dasatinib 100 mg once daily (QD)	
Reporting group title	Imatinib
Reporting group description:	
Imatinib 400 mg once daily (QD)	

Primary: Number of Subjects with Best Confirmed Complete Cytogenetic Response (cCCyR) Within 12 Months

End point title	Number of Subjects with Best Confirmed Complete Cytogenetic Response (cCCyR) Within 12 Months
End point description:	
Cytogenetic response (CyR) is based on the prevalence of Philadelphia positive (Ph+) cells in metaphase from bone marrow (BM) sample. (Ideally, 25 metaphases but at least 20 metaphases from a BM sample were evaluated). Complete Cytogenetic Response (CCyR)=0% Ph+ cells in metaphase in BM. A cCCyR=those in which all measurements up to at least 28 days after the initial response show an equivalent or better CCyR. The analysis population included all randomized subjects.	
End point type	Primary
End point timeframe:	
Pretreatment, every 3 months up to 12 months	

End point values	Dasatinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259	260		
Units: Subjects				
number (not applicable)	204	177		

Statistical analyses

Statistical analysis title	Comparison of Dasatinib and Imatinib
Comparison groups	Dasatinib v Imatinib
Number of subjects included in analysis	519
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0056 ^[1]
Method	Cochran-Mantel-Haenszel

Notes:

[1] - A priori threshold for statistical significance=0.05.

Secondary: Percentage of Subjects Remaining in Confirmed Complete Cytogenetic Response (cCCyR)

End point title	Percentage of Subjects Remaining in Confirmed Complete Cytogenetic Response (cCCyR)
End point description:	
Cytogenetic response (CyR) is based on the prevalence of Philadelphia positive (Ph+) cells in metaphase from bone marrow (BM) sample. (Ideally, 25 metaphases but at least 20 metaphases from a BM sample were evaluated). Complete Cytogenetic Response (CCyR)=0% Ph+ cells in metaphase in BM. A cCCyR=those in which all measurements up to at least 28 days after the initial response show an equivalent or better CCyR.	
Percentage of subjects in cCCyR at years 2, 3, 4 and 5 was computed for all randomized subjects who achieved cCCyR as measured from the time of first confirmation until the date of progression or death. Subjects with cCCyR who neither progress nor die are censored on the date of their last cytogenetic assessment. Subjects without cCCyR are considered to have progressed on Day 1.	
The analysis population included all randomized subjects who achieved cCCyR.	
End point type	Secondary
End point timeframe:	
Years 2, 3, 4 and 5	

End point values	Dasatinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	215	204		
Units: percentage of subjects				
number (confidence interval 95%)				
At Year 2	98 (94.7 to 99.2)	96.9 (93.2 to 98.6)		
At Year 3	96.9 (93.3 to 98.6)	95.7 (91.6 to 97.8)		
At Year 4	95.6 (91.4 to 97.8)	95.7 (91.6 to 97.8)		
At Year 5	93.1 (86.5 to 96.5)	91 (83.6 to 95.2)		

Statistical analyses

Statistical analysis title	Comparison of Dasatinib and Imatinib
Comparison groups	Dasatinib v Imatinib
Number of subjects included in analysis	419
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.13

Secondary: Percentage of Subjects with Major Molecular Response (MMR) at Any Time

End point title	Percentage of Subjects with Major Molecular Response (MMR) at Any Time
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End point description:

Molecular response was assessed using BCR-ABL transcript levels measured by realtime quantitative polymerase chain reaction. MMR is defined as a ratio BCR-ABL/ABL $\leq 0.1\%$ on the international scale (ie, at least 3 log reduction from a standardized baseline value). The analysis population included all randomized subjects.

End point type	Secondary
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End point timeframe:

Planned total follow-up duration of 5 years

End point values	Dasatinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259	260		
Units: Percentage of subjects				
number (not applicable)	76.4	64.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Confirmed Complete Cytogenic Response (cCCyR) Overall

End point title	Time to Confirmed Complete Cytogenic Response (cCCyR) Overall
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End point description:

The time to cCCyR for all randomized subjects is defined as the time from the randomization date until criteria are first met for complete cytogenic response (provided it is confirmed later). The time to cCCyR analysis censors nonresponders who do not progress at their last cytogenetic assessments and nonresponders who progress at the maximum time of all randomized subjects. The analysis population included all randomized subjects.

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End point type	Secondary
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End point timeframe:

Day 1 to 5 years

End point values	Dasatinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	215	204		
Units: Months				
median (confidence interval 95%)	3.1 (3 to 3.1)	5.8 (5.6 to 6)		

Statistical analyses

Statistical analysis title	Comparison of Dasatinib and Imatinib
Statistical analysis description:	
Hazard Ratio and Confidence Interval were based on analyses on all randomized subjects	
Comparison groups	Dasatinib v Imatinib
Number of subjects included in analysis	419
Analysis specification	Pre-specified
Analysis type	superiority
Method	Stratified Log-rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	1.77

Secondary: Time to Major Molecular Response (MMR) Overall

End point title	Time to Major Molecular Response (MMR) Overall
End point description:	
The time to MMR for all randomized subjects is defined as the time from randomization date until measurement criteria are first met for MMR. The time to MMR analysis censors nonresponders who do not progress at their last molecular assessments and nonresponders who progress at the maximum time of all randomized subjects. The analysis population included all randomized subjects.	
End point type	Secondary
End point timeframe:	
Day 1 to 5 years	

End point values	Dasatinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	198	167		
Units: Months				
median (confidence interval 95%)	9.3 (8.8 to 11.8)	15 (12.2 to 18.2)		

Statistical analyses

Statistical analysis title	Comparison of Dasatinib and Imatinib
Statistical analysis description:	
Hazard Ratio, and Confidence Interval were based on analyses on all randomized subjects	
Comparison groups	Dasatinib v Imatinib

Number of subjects included in analysis	365
Analysis specification	Pre-specified
Analysis type	superiority
Method	Stratified Log-rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.25
upper limit	1.89

Secondary: Percentage of Subjects with Progression-free Survival (PFS)

End point title	Percentage of Subjects with Progression-free Survival (PFS)
End point description:	
PFS was defined as the time from randomization until progression (any progression/death within 30 days of last dosing date, or between 30-60 days of last dosing prior to start of secondary therapy). Those who did not progress/die or who progressed/died after 60 days of last dose were censored at last on-study hematologic/cytogenetic assessment; those with progression/death 30-60 days of last dosing date and after start date of secondary therapy censored at last on-study hematologic/cytogenetic assessment prior to start of secondary therapy; those who had not received study treatment censored on date randomized. The analysis population included all randomized subjects.	
End point type	Secondary
End point timeframe:	
Subjects were followed-up for at least 5 years	

End point values	Dasatinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259	260		
Units: Percentage of subjects				
number (not applicable)	88.9	89.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Overall Survival (OS)

End point title	Percentage of Subjects With Overall Survival (OS)
End point description:	
OS was defined as the time from randomization to the date of death. If the subject had not died, survival was censored on last date the subject was known to be alive. The analysis population included all randomized subjects.	
End point type	Secondary
End point timeframe:	
Subjects were followed-up for at least 5 years	

End point values	Dasatinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259	260		
Units: Percentage of subjects				
number (not applicable)	90.9	89.6		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects with Adverse Events (AEs), Drug-related AEs, Drug-related Serious Adverse Events (SAEs), Drug-related AEs Leading to Discontinuation, and All Deaths

End point title	Number of Subjects with Adverse Events (AEs), Drug-related AEs, Drug-related Serious Adverse Events (SAEs), Drug-related AEs Leading to Discontinuation, and All Deaths
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End point description:

AE=any new untoward medical occurrence or worsening of a pre-existing medical condition in a subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. SAE=any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or causes prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is an important medical event. The analysis population included all treated subjects.

End point type	Other pre-specified
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End point timeframe:

From date of last person, first visit to date of last person, last visit (approximately 8 years)

End point values	Dasatinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	258	258		
Units: Subjects				
number (not applicable)				
All AEs	251	251		
All Drug-related AEs	224	231		
Diarrhea	100	91		
Pleural effusion	74	3		
Nausea	40	74		
Cough	68	28		
Muscle spasms	14	63		
Thrombocytopenia	61	50		
Neutropenia	60	49		
Headache	59	46		
Pyrexia	58	51		
Vomiting	43	54		

SAEs	90	70		
Drug-related SAEs	43	22		
AEs leading to discontinuation	51	26		
All deaths	26	26		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Grade 3/4 Abnormalities in On-study Laboratory Test Results

End point title	Number of Subjects With Grade 3/4 Abnormalities in On-study Laboratory Test Results
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End point description:

ULN=upper limit of normal. Grade 3=Severe AE; Grade 4=Life-threatening or disabling AE. Absolute neutrophil count: Grade 3 <1000-500/mm³; Grade 4 <500/mm³. Hemoglobin: Grade 3 <8.0-6.5 g/dL; Grade 4 <6.5 g/dL. Platelets: Grade 3 <50,000-25,000/mm³; Grade 4 <25,000/mm³. ALT/AST: Grade 3 >5.0-20*ULN; Grade 4 >20*ULN. Total bilirubin: Grade 3 >3-10*ULN; Grade 4 >10*ULN. Sample normal ranges (may vary by institution): ALT, Female: 7-30 U/L, Male: 10-55 U/L; AST, Female: 9-25 U/L, Male 10-40 U/L; Total bilirubin: 0.0-1.0 mg/dL. Creatinine: Grade 3 >3.0-6.0*ULN; Grade 4 >6.0*ULN. Phosphate: Grade 3 <2.0-1.0 mg/dL; Grade 4 <1.0 mg/dL. Calcium: Grade 3 <7.0-6.0 mg/dL; Grade 4 <6.0 mg/dL. Potassium: Grade 3 <3.0-2.5 mmol/L; Grade 4 <2.5 mmol/L. The analysis population included all subjects with laboratory assessments.

End point type	Other pre-specified
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End point timeframe:

From date of last person, first visit to date of last person, last visit (approximately 8 years)

End point values	Dasatinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	257		
Units: Subjects				
number (not applicable)				
Grade 3/4 Absolute neutrophil count	74	61		
Grade 3/4 Hemoglobin	35	23		
Grade 3/4 Platelets	56	37		
Grade 3/4 Alanine aminotransferase (ALT)	2	4		
Grade 3/4 Aspartate aminotransferase (AST)	2	3		
Grade 3/4 Total bilirubin	3	0		
Grade 3/4 Creatinine	3	2		
Grade 3/4 Phosphate	19	79		
Grade 3/4 Calcium	9	7		
Grade 3/4 Potassium	0	8		

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug until the last dose of study drug plus 30 days

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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Reporting groups

Reporting group title	Imatinib
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Reporting group description:

Imatinib

Reporting group title	Dasatinib
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Reporting group description:

Dasatinib

Serious adverse events	Imatinib	Dasatinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	70 / 258 (27.13%)	90 / 258 (34.88%)	
number of deaths (all causes)	5	8	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder neoplasm			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
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	4 / 258 (1.55%)	3 / 258 (1.16%)	
occurrences causally related to treatment / all	1 / 4	2 / 3	
deaths causally related to treatment / all	1 / 2	1 / 1	
Blast cell proliferation			
subjects affected / exposed	2 / 258 (0.78%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraductal proliferative breast lesion			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoma			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nodal marginal zone b-cell lymphoma			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	3 / 258 (1.16%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal adenocarcinoma			

subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectosigmoid cancer			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 258 (0.39%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Device occlusion			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 258 (0.00%)	2 / 258 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Oedema			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pain			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 258 (0.78%)	3 / 258 (1.16%)	
occurrences causally related to treatment / all	1 / 2	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Prostatitis			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal oedema			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine haemorrhage			
subjects affected / exposed	2 / 258 (0.78%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 258 (0.00%)	2 / 258 (0.78%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lung infiltration			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 258 (0.39%)	13 / 258 (5.04%)	
occurrences causally related to treatment / all	1 / 1	22 / 23	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	0 / 258 (0.00%)	7 / 258 (2.71%)	
occurrences causally related to treatment / all	0 / 0	10 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
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	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood glucose increased			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella test positive			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Heat stroke			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle rupture			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	2 / 258 (0.78%)	2 / 258 (0.78%)	
occurrences causally related to treatment / all	0 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax traumatic			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin injury			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			

subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 258 (0.39%)	3 / 258 (1.16%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 2	
Angina unstable			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
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	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			

subjects affected / exposed	2 / 258 (0.78%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 258 (0.39%)	3 / 258 (1.16%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive cardiomegaly			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 258 (0.39%)	3 / 258 (1.16%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinoatrial block			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			

subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carpal tunnel syndrome			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic neuritis			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	0 / 258 (0.00%)	2 / 258 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 258 (0.39%)	4 / 258 (1.55%)	
occurrences causally related to treatment / all	0 / 1	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bicytopenia			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	3 / 258 (1.16%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			

subjects affected / exposed	4 / 258 (1.55%)	4 / 258 (1.55%)	
occurrences causally related to treatment / all	4 / 5	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytosis			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	2 / 258 (0.78%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glaucoma			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scleral haemorrhage			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual impairment			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			

subjects affected / exposed	1 / 258 (0.39%)	5 / 258 (1.94%)	
occurrences causally related to treatment / all	0 / 1	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fissure			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic gastritis			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 258 (0.00%)	2 / 258 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 258 (1.16%)	5 / 258 (1.94%)	
occurrences causally related to treatment / all	2 / 3	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 258 (0.78%)	2 / 258 (0.78%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Haemorrhoids			

subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 258 (0.00%)	2 / 258 (0.78%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal ulcer			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic disorder			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Protein-Losing gastroenteropathy			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toothache			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 258 (1.16%)	2 / 258 (0.78%)	
occurrences causally related to treatment / all	2 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	2 / 258 (0.78%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 258 (0.00%)	2 / 258 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis toxic			

subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus ureteric			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 258 (0.00%)	2 / 258 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder polyp			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urogenital haemorrhage			

subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (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			
Arthralgia			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibromyalgia			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gouty arthritis			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin pain			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaw cyst			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			

subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in jaw			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	1 / 258 (0.39%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 258 (0.00%)	2 / 258 (0.78%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 258 (0.00%)	3 / 258 (1.16%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis infectious			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			

subjects affected / exposed	0 / 258 (0.00%)	2 / 258 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 258 (0.39%)	2 / 258 (0.78%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1n1 influenza			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis viral			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 258 (0.00%)	3 / 258 (1.16%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Lower respiratory tract infection			
subjects affected / exposed	2 / 258 (0.78%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis viral			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningoencephalitis bacterial			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neutropenic sepsis			

subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal abscess			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 258 (1.16%)	3 / 258 (1.16%)	
occurrences causally related to treatment / all	2 / 4	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyelonephritis			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Subcutaneous abscess			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 258 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	2 / 258 (0.78%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 258 (0.39%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Imatinib	Dasatinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	243 / 258 (94.19%)	238 / 258 (92.25%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	20 / 258 (7.75%)	26 / 258 (10.08%)	
occurrences (all)	22	32	
Pallor			
subjects affected / exposed	13 / 258 (5.04%)	7 / 258 (2.71%)	
occurrences (all)	21	10	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	37 / 258 (14.34%)	42 / 258 (16.28%)	
occurrences (all)	51	49	
Chest pain			
subjects affected / exposed	13 / 258 (5.04%)	24 / 258 (9.30%)	
occurrences (all)	14	32	
Face oedema			
subjects affected / exposed	27 / 258 (10.47%)	14 / 258 (5.43%)	
occurrences (all)	38	15	
Fatigue			
subjects affected / exposed	40 / 258 (15.50%)	40 / 258 (15.50%)	
occurrences (all)	54	66	
Influenza like illness			

subjects affected / exposed occurrences (all)	17 / 258 (6.59%) 26	23 / 258 (8.91%) 44	
Oedema subjects affected / exposed occurrences (all)	24 / 258 (9.30%) 38	10 / 258 (3.88%) 11	
Oedema peripheral subjects affected / exposed occurrences (all)	32 / 258 (12.40%) 38	25 / 258 (9.69%) 47	
Pyrexia subjects affected / exposed occurrences (all)	50 / 258 (19.38%) 72	58 / 258 (22.48%) 119	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	28 / 258 (10.85%) 40	68 / 258 (26.36%) 102	
Dyspnoea subjects affected / exposed occurrences (all)	10 / 258 (3.88%) 11	36 / 258 (13.95%) 60	
Oropharyngeal pain subjects affected / exposed occurrences (all)	11 / 258 (4.26%) 15	14 / 258 (5.43%) 14	
Pleural effusion subjects affected / exposed occurrences (all)	3 / 258 (1.16%) 4	69 / 258 (26.74%) 119	
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	13 / 258 (5.04%) 18	5 / 258 (1.94%) 8	
Insomnia subjects affected / exposed occurrences (all)	16 / 258 (6.20%) 20	20 / 258 (7.75%) 28	
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	7 / 258 (2.71%) 16	13 / 258 (5.04%) 13	
Haemoglobin decreased			

subjects affected / exposed occurrences (all)	17 / 258 (6.59%) 32	30 / 258 (11.63%) 76	
Weight increased subjects affected / exposed occurrences (all)	33 / 258 (12.79%) 47	25 / 258 (9.69%) 38	
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	18 / 258 (6.98%) 33	28 / 258 (10.85%) 37	
Headache subjects affected / exposed occurrences (all)	46 / 258 (17.83%) 73	59 / 258 (22.87%) 99	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	31 / 258 (12.02%) 38	38 / 258 (14.73%) 53	
Leukopenia subjects affected / exposed occurrences (all)	28 / 258 (10.85%) 45	21 / 258 (8.14%) 48	
Neutropenia subjects affected / exposed occurrences (all)	49 / 258 (18.99%) 101	60 / 258 (23.26%) 124	
Thrombocytopenia subjects affected / exposed occurrences (all)	48 / 258 (18.60%) 78	59 / 258 (22.87%) 117	
Eye disorders			
Eyelid oedema subjects affected / exposed occurrences (all)	40 / 258 (15.50%) 61	7 / 258 (2.71%) 8	
Periorbital oedema subjects affected / exposed occurrences (all)	20 / 258 (7.75%) 42	4 / 258 (1.55%) 5	
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	28 / 258 (10.85%) 37	36 / 258 (13.95%) 60	
Abdominal pain upper			

subjects affected / exposed	18 / 258 (6.98%)	22 / 258 (8.53%)	
occurrences (all)	19	30	
Constipation			
subjects affected / exposed	7 / 258 (2.71%)	21 / 258 (8.14%)	
occurrences (all)	10	26	
Diarrhoea			
subjects affected / exposed	89 / 258 (34.50%)	99 / 258 (38.37%)	
occurrences (all)	196	223	
Dyspepsia			
subjects affected / exposed	22 / 258 (8.53%)	17 / 258 (6.59%)	
occurrences (all)	25	31	
Gastritis			
subjects affected / exposed	18 / 258 (6.98%)	23 / 258 (8.91%)	
occurrences (all)	21	25	
Nausea			
subjects affected / exposed	74 / 258 (28.68%)	40 / 258 (15.50%)	
occurrences (all)	106	54	
Toothache			
subjects affected / exposed	10 / 258 (3.88%)	17 / 258 (6.59%)	
occurrences (all)	10	26	
Vomiting			
subjects affected / exposed	52 / 258 (20.16%)	41 / 258 (15.89%)	
occurrences (all)	159	62	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 258 (0.39%)	14 / 258 (5.43%)	
occurrences (all)	1	19	
Pruritus			
subjects affected / exposed	19 / 258 (7.36%)	15 / 258 (5.81%)	
occurrences (all)	22	19	
Rash			
subjects affected / exposed	44 / 258 (17.05%)	45 / 258 (17.44%)	
occurrences (all)	59	74	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	38 / 258 (14.73%)	34 / 258 (13.18%)	
occurrences (all)	59	46	
Back pain			
subjects affected / exposed	44 / 258 (17.05%)	35 / 258 (13.57%)	
occurrences (all)	57	59	
Muscle spasms			
subjects affected / exposed	63 / 258 (24.42%)	14 / 258 (5.43%)	
occurrences (all)	119	15	
Musculoskeletal pain			
subjects affected / exposed	19 / 258 (7.36%)	22 / 258 (8.53%)	
occurrences (all)	23	26	
Myalgia			
subjects affected / exposed	39 / 258 (15.12%)	36 / 258 (13.95%)	
occurrences (all)	53	52	
Pain in extremity			
subjects affected / exposed	39 / 258 (15.12%)	28 / 258 (10.85%)	
occurrences (all)	50	39	
Infections and infestations			
Bronchitis			
subjects affected / exposed	14 / 258 (5.43%)	20 / 258 (7.75%)	
occurrences (all)	18	28	
Conjunctivitis			
subjects affected / exposed	17 / 258 (6.59%)	10 / 258 (3.88%)	
occurrences (all)	21	13	
Gastroenteritis			
subjects affected / exposed	10 / 258 (3.88%)	19 / 258 (7.36%)	
occurrences (all)	18	24	
Influenza			
subjects affected / exposed	12 / 258 (4.65%)	20 / 258 (7.75%)	
occurrences (all)	15	22	
Nasopharyngitis			
subjects affected / exposed	43 / 258 (16.67%)	32 / 258 (12.40%)	
occurrences (all)	93	72	
Pharyngitis			

subjects affected / exposed occurrences (all)	10 / 258 (3.88%) 15	14 / 258 (5.43%) 15	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	28 / 258 (10.85%) 43	30 / 258 (11.63%) 55	
Urinary tract infection subjects affected / exposed occurrences (all)	13 / 258 (5.04%) 19	11 / 258 (4.26%) 17	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	13 / 258 (5.04%) 16	23 / 258 (8.91%) 30	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 July 2007	<ol style="list-style-type: none">1. Modification of the definition of PFS to align with the endpoint used in imatinib first-line trial (IRIS)2. Modification of the definition of time-to treatment failure3. Inclusion of time-in, time-to and duration of cytogenetic response as secondary endpoints4. Inclusion of time-to maximum clinical benefit as a tertiary endpoint5. Removal of the previously permitted prior (up to) 28 days of imatinib from eligibility criteria6. Inclusion of stem cell transplant as a reason for discontinuation of subjects from treatment
13 June 2008	<ol style="list-style-type: none">1. Clarification of the definition of progression and extramedullary disease2. Clarification of the definition of intolerance3. Correction of the formula for Hasford score calculation4. Clarification of dose reduction guidelines
21 July 2009	<ol style="list-style-type: none">1. Change the rank of the secondary endpoints2. Clarify the assessment schedule for the primary endpoint (cytogenetic response)3. Minor clarification in the definition of progression4. Clarification of reasons for discontinuation of subjects from treatment5. Update imatinib information regarding subjects with renal impairment6. Clarifications to the identification of investigational products7. Clarify that treatment decisions based on major molecular response should be from local laboratory results if available and not from research samples of QRT-PCR drawn for this study8. Clarification to collection of mutation analysis samples9. Update the interim analysis section

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported