Clinical trial results:
A Multicenter Phase 3 Randomised, Open-Label Study of Bosutinib Versus Imatinib in Adult Patients With Newly Diagnosed Chronic Phase Chronic Myelogenous Leukemia

Summary

EudraCT number	2013-005101-31
Trial protocol	BE GB IT SE CZ HU SK FI NO ES DK NL PL FR
Global end of trial date	17 April 2020

Results information

Result version number	v2 (current)
This version publication date	03 May 2021
First version publication date	28 July 2018
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	B1871053

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02130557
WHO universal trial number (UTN)	-

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 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, 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	17 April 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 April 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the proportion of subjects demonstrating Major Molecular Response (MMR) at 12 months (48 weeks) in the Bosutinib arm with that of the Imatinib arm in newly diagnosed Philadelphia chromosome positive (Ph+) chronic phase (CP) chronic myelogenous leukemia (CML) subjects harboring b2a2 and/or b3a2 transcripts.

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 Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 July 2014
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	Australia: 7
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Canada: 18
Country: Number of subjects enrolled	Czechia: 11
Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	Finland: 5
Country: Number of subjects enrolled	France: 18
Country: Number of subjects enrolled	Germany: 21
Country: Number of subjects enrolled	Hungary: 22
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Italy: 36
Country: Number of subjects enrolled	Korea, Republic of: 26
Country: Number of subjects enrolled	Mexico: 14
Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Norway: 6
Country: Number of subjects enrolled	Poland: 25
Country: Number of subjects enrolled	Singapore: 17

Country: Number of subjects enrolled	Slovakia: 1
Country: Number of subjects enrolled	South Africa: 10
Country: Number of subjects enrolled	Spain: 35
Country: Number of subjects enrolled	Sweden: 15
Country: Number of subjects enrolled	Taiwan: 7
Country: Number of subjects enrolled	Thailand: 9
Country: Number of subjects enrolled	Ukraine: 81
Country: Number of subjects enrolled	United Kingdom: 42
Country: Number of subjects enrolled	United States: 88
Worldwide total number of subjects	536
EEA total number of subjects	215

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)	435
From 65 to 84 years	101
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

536 subjects were randomised in 1:1 ratio to Bosutinib and Imatinib groups in this study but 3 subjects were not treated in the Imatinib group.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Bosutinib

Arm description:

Subjects with Philadelphia chromosome-positive CML received Bosutinib tablets at a dose of 400 milligram (mg), orally once daily in the core treatment phase of 12 months and continued the same treatment into the extension phase or followed up for safety for up to approximately 4 years, until the end of the study, treatment failure, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first.

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

Dosage and administration details:

Subjects received Bosutinib at a dose of 400 mg, orally once daily.

Arm title	Imatinib

Arm description:

Subjects with Philadelphia chromosome-positive CML received Imatinib tablets at a dose of 400 mg, orally once daily in the core treatment phase of 12 months and continued the same treatment into the extension phase or followed up for safety for up to approximately 4 years, until the end of the study, treatment failure, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first.

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:

Subjects received Imatinib at a dose of 400 mg, orally once daily.

Number of subjects in period 1	Bosutinib	Imatinib
Started	268	268
Treated	268	265
mITT population	246	241
Completed	232	231
Not completed	36	37
Deceased	14	14
Consent withdrawn by subject	12	12
Investigator Request	-	2
Unspecified	2	1
Lost to follow-up	6	7
Missing	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Bosutinib
Reporting group description:	
Subjects with Philadelphia chromosome-positive CML received Bosutinib tablets at a dose of 400 milligram (mg), orally once daily in the core treatment phase of 12 months and continued the same treatment into the extension phase or followed up for safety for up to approximately 4 years, until the end of the study, treatment failure, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first.	
Reporting group title	Imatinib
Reporting group description:	
Subjects with Philadelphia chromosome-positive CML received Imatinib tablets at a dose of 400 mg, orally once daily in the core treatment phase of 12 months and continued the same treatment into the extension phase or followed up for safety for up to approximately 4 years, until the end of the study, treatment failure, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first.	

Reporting group values	Bosutinib	Imatinib	Total
Number of subjects	268	268	536
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)	215	220	435
From 65-84 years	53	48	101
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	50.8	50.9	
standard deviation	± 15.40	± 14.43	-
Sex: Female, Male Units: subjects			
Female	112	113	225
Male	156	155	311

End points

End points reporting groups

Reporting group title	Bosutinib

Reporting group description:

Subjects with Philadelphia chromosome-positive CML received Bosutinib tablets at a dose of 400 milligram (mg), orally once daily in the core treatment phase of 12 months and continued the same treatment into the extension phase or followed up for safety for up to approximately 4 years, until the end of the study, treatment failure, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first.

Reporting group title	Imatinib

Reporting group description:

Subjects with Philadelphia chromosome-positive CML received Imatinib tablets at a dose of 400 mg, orally once daily in the core treatment phase of 12 months and continued the same treatment into the extension phase or followed up for safety for up to approximately 4 years, until the end of the study, treatment failure, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first.

Primary: Percentage of Subjects With Major Molecular Response (MMR) at Month 12

End point title	Percentage of Subjects With Major Molecular Response (MMR) at Month 12

End point description:

MMR was defined as a ratio of breakpoint cluster region to abelson (BCR-ABL/ABL) less than or equal to (<=) 0.1 percent (%) on the international scale (IS) (greater than or equal to [>=] 3 log reduction from standardised baseline in ratio of BCR-ABL to ABL transcripts [>=3000 ABL required]) by quantitative reverse transcriptase polymerase chain reaction (RT-qPCR). The percentage of subjects with MMR at Month 12 are reported. Modified intent-to-treat (mITT) population included all randomised subjects with Ph+ CML harboring the b2a2 and/or b3a2 transcript and baseline BCR-ABL copies greater than (>) 0 with study drug assignment designated according to initial randomisation.

End point type	Primary

End point timeframe:

Month 12

End point values	Bosutinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246	241		
Units: percentage of subjects				
number (confidence interval 95%)	47.2 (40.9 to 53.4)	36.9 (30.8 to 43.0)		

Statistical analyses

Statistical analysis title	Bosutinib versus Imatinib

Statistical analysis description:

95% Confidence Interval (CI) for the odds ratio adjusted for sokal risk group and region are based on Mantel-Haenszel confidence limits.

Comparison groups	Bosutinib v Imatinib

Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.01 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.547
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.072
upper limit	2.233

Notes:

[1] - A total sample size of 500 Ph+ subjects is required for the study to provide >= 90% power to detect at least 15% difference (assuming 25% in the imatinib vs 40% in the bosutinib arm) in the MMR rates at 12 months (48 weeks) with a 1-sided alpha of 2.5%, and 2 interim futility analyses at 33% and 66% of subjects with adequate follow-up with early stopping for futility only (non-binding, O'Brien-Fleming analog beta spending function).

[2] - 1-sided p-value based on CMH test for general association between treatment and response with stratification by sokal risk group (low, intermediate, high) and region (1-3) at time of randomisation. Statistical significance threshold: 1-sided 0.025.

Secondary: Percentage of Subjects With Major Molecular Response (MMR) Up to Month 18

End point title	Percentage of Subjects With Major Molecular Response (MMR) Up to Month 18

End point description:

MMR was defined as a ratio of BCR-ABL/ABL <=0.1% on the international scale (>=3 log reduction from standardised baseline in ratio of BCR-ABL to ABL transcripts [>=3000 ABL required]) by quantitative RT-qPCR. The percentage of subjects with MMR for up to Month 18 are reported. mITT population included all randomised subjects with Ph+ CML harboring the b2a2 and/or b3a2 transcript and baseline BCR-ABL copies >0 with study drug assignment designated according to initial randomisation.

End point type	Secondary

End point timeframe:

Up to Month 18

End point values	Bosutinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246	241		
Units: percentage of subjects				
number (confidence interval 95%)	61.0 (54.9 to 67.1)	52.7 (46.4 to 59.0)		

Statistical analyses

Statistical analysis title	Bosutinib versus Imatinib

Statistical analysis description:

95% CI for the odds ratio adjusted for sokal risk group and region are based on Mantel-Haenszel confidence limits.

Comparison groups	Bosutinib v Imatinib

Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0303 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.418
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.986
upper limit	2.037

Notes:

[3] - If the primary analysis was significant, each member of the short-term family (CCyR by Month 12, MMR by Month 18) was tested via Bonferroni's procedure at the 1-sided level of 0.0125.
[4] - 1-sided p-value based on CMH test for general association between treatment and response with stratification by sokal risk group (low, intermediate, high) and region (1-3) at time of randomisation. Statistical significance threshold: 1-sided 0.0125.

Secondary: Kaplan-Meier Estimate of Probability of Retaining Major Molecular Response (MMR) at Month 48

End point title	Kaplan-Meier Estimate of Probability of Retaining Major Molecular Response (MMR) at Month 48

End point description:

The Kaplan-Meier curve was generated based on first date of MMR until date of confirmed loss of MMR or censoring, objectively documented, for responders only. Confirmed loss of MMR was BCR-ABL/ABL IS ratio >0.1% in association with >=5-fold increase in BCR-ABL/ABL IS ratio from lowest value achieved up to that time-point confirmed by second assessment at least 28 days later. Treatment discontinuation due to suboptimal response/treatment failure, progressive disease (PD) or death due to PD within 28 days of last dose were considered confirmed loss of MMR. PD defined as disease progression to accelerated phase (AP) or blast phase (BP) CML. mITT population included all randomised subjects with Ph+ CML harboring b2a2 and/or b3a2 transcript and baseline BCR-ABL copies >0 with study drug assignment designated according to initial randomisation and who achieved MMR (responders). Here, "Overall number of Subjects Analysed (N)" signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Month 48

End point values	Bosutinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182	158		
Units: percentage of subjects				
number (confidence interval 95%)	92.2 (86.8 to 95.4)	92.0 (85.9 to 95.5)		

Statistical analyses

Statistical analysis title	Bosutinib versus Imatinib

Statistical analysis description:

Hazard ratio (95% CIs) are based on the treatment effect (Bosutinib compared with Imatinib) in a stratified (by Sokal risk group at randomisation and region) Cox proportional hazards model for the

hazard of the respective event.

Comparison groups	Bosutinib v Imatinib
Number of subjects included in analysis	340
Analysis specification	Pre-specified
Analysis type	superiority[5]
Parameter estimate	Hazard ratio (HR)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	2.44

Notes:

[5] - The medians have not been reached in either arm, as such, the premature estimated hazard ratio is provided.

Secondary: Percentage of Subjects With Complete Cytogenetic Response (CCyR) Up to Month 12

End point title	Percentage of Subjects With Complete Cytogenetic Response (CCyR) Up to Month 12

End point description:

Complete Cytogenetic Response (CCyR) was based on the prevalence of Ph+ metaphases among cells in metaphase on a bone marrow (BM) aspirate. CCyR was achieved when there was 0% Ph+ metaphases among cells in a BM sample when at least 20 metaphases from a BM sample were analysed, or MMR if no BM was available. The percentage of subjects with CCyR for up to Month 12 are reported. mITT population included all randomised subjects with Ph+ CML harboring the b2a2 and/or b3a2 transcript and baseline BCR-ABL copies >0 with study drug assignment designated according to initial randomisation.

End point type	Secondary

End point timeframe:

Up to Month 12

End point values	Bosutinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246	241		
Units: percentage of subjects				
number (confidence interval 95%)	77.2 (72.0 to 82.5)	66.4 (60.4 to 72.4)		

Statistical analyses

Statistical analysis title	Bosutinib versus Imatinib

Statistical analysis description:

95% CI for the odds ratio adjusted for sokal risk group and region are based on Mantel-Haenszel confidence limits.

Comparison groups	Bosutinib v Imatinib

Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.0037 [7]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.16
upper limit	2.61

Notes:

[6] - If the primary analysis was significant, each member of the short-term family (CCyR by Month 12, MMR by Month 18) was tested via Bonferroni's procedure at the 1-sided level of 0.0125.
[7] - 1-sided p-value based on CMH test for general association between treatment and response with stratification by sokal risk group (low, intermediate, high) and region (1-3) at time of randomisation. Statistical significance threshold: 1-sided 0.0125.

Secondary: Kaplan-Meier Estimate of Probability of Retaining Complete Cytogenetic Response (CCyR) at Month 48

End point title	Kaplan-Meier Estimate of Probability of Retaining Complete Cytogenetic Response (CCyR) at Month 48

End point description:

The Kaplan-Meier curve was generated based on the first date of CCyR until the date of the confirmed loss of CCyR or censoring, objectively documented, for responders only. Confirmed loss of CCyR was the presence of at least one Ph+ metaphase confirmed by a second assessment at least 28 days later. Treatment discontinuation due to suboptimal response/treatment failure, PD or death due to PD within 28 days of last dose were considered confirmed loss of CCyR. PD was defined as disease progression to AP or BP CML. mITT population included all randomised subjects with Ph+ CML harboring the b2a2 and/or b3a2 transcript and baseline BCR-ABL copies >0 with study drug assignment designated according to initial randomisation and who achieved CCyR (responders). Here, "N" signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Month 48

End point values	Bosutinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	205	185		
Units: percentage of subjects				
number (confidence interval 95%)	97.4 (93.9 to 98.9)	93.7 (88.9 to 96.5)		

Statistical analyses

Statistical analysis title	Bosutinib versus Imatinib

Statistical analysis description:

Hazard ratio (95% CIs) are based on the treatment effect (Bosutinib compared with Imatinib) in a stratified (by Sokal risk group at randomisation and region) Cox proportional hazards model for the hazard of the respective event.

Comparison groups	Bosutinib v Imatinib
Number of subjects included in analysis	390
Analysis specification	Pre-specified
Analysis type	superiority[8]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.14
upper limit	1.13

Notes:

[8] - The medians have not been reached in either arm, as such, the premature estimated hazard ratio is provided.

Secondary: Cumulative Incidence of Event Free Survival (EFS) Events

End point title	Cumulative Incidence of Event Free Survival (EFS) Events

End point description:

EFS: time from randomisation to death due to any cause, transformation to AP or BP at any time, confirmed loss of complete hematologic response (CHR), confirmed loss of CCyR or censoring. Loss of CHR defined as hematologic assessment of non-CHR (chronic phase, AP, or BP) confirmed by 2 assessments at least 4 weeks apart. Loss of CHR defined as appearance of any of the following: WBC count rises to >20.0*10^9/L, platelet count rises to >=600*10^9/L, appearance of palpable spleen or other extramedullary involvement proven by biopsy, appearance of 5% myelocytes in peripheral blood, appearance of blasts or promyelocytes in peripheral blood. Loss of CCyR defined as at least 1 Ph+ metaphase from analysis of <100 metaphases confirmed by follow up cytogenetic analysis after 1 month. Cumulative incidence of EFS defined as percentage of subjects with EFS event at Month 60 and adjusted for competing risk of treatment discontinuation without event. mITT population was analysed.

End point type	Secondary

End point timeframe:

Up to Month 60

End point values	Bosutinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246	241		
Units: percentage of subjects				
number (confidence interval 95%)	6.9 (4.2 to 10.5)	10.4 (6.9 to 14.6)		

Statistical analyses

Statistical analysis title	Bosutinib versus Imatinib

Statistical analysis description:

The hazard ratio (95% CIs) are based on the proportional subdistribution hazards model stratified by Sokal risk group and region.

Comparison groups	Bosutinib v Imatinib

Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.0749 [10]
Method	Gray's test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	1.17

Notes:

[9] - If each member of the short-term family (CCyR by Month 12, MMR by Month 18) was significant, EFS and OS were tested sequentially via the Holm's testing procedure at the 1-sided family wise level of 0.025. If one member of the short-term family was significant, EFS and OS were tested sequentially at 1-sided 0.0125.

[10] - 1-sided p-value based on Gray's test for comparing cumulative incidence function between treatment arms stratified by sokal risk group (low, intermediate, high) and region (1-3). Statistical significance threshold: 1-sided 0.0125.

Secondary: Overall Survival (OS) Rate

End point title	Overall Survival (OS) Rate

End point description:

OS was defined as the time (in months) from randomisation to the occurrence of death due to any cause or censoring. Kaplan-meier analysis was used for determination of OS. Percentage of subjects who were alive were estimated in this endpoint. mITT population included all randomised subjects with Ph+ CML harboring the b2a2 and/or b3a2 transcript and baseline BCR-ABL copies >0 with study drug assignment designated according to initial randomisation.

End point type	Secondary

End point timeframe:

Up to Month 60

End point values	Bosutinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246	241		
Units: percentage of subjects				
number (confidence interval 95%)	94.9 (91.1 to 97.0)	94.0 (90.1 to 96.4)		

Statistical analyses

Statistical analysis title	Bosutinib versus Imatinib

Statistical analysis description:

The hazard ratio (95% CIs) are based on the treatment effect (Bosutinib compared with Imatinib) in a stratified (by Sokal risk group at randomisation and region) Cox proportional hazards model for the hazard of the respective event.

Comparison groups	Bosutinib v Imatinib

Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.2827 [12]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	1.73

Notes:

[11] - If each member of the short-term family (CCyR by Month 12, MMR by Month 18) was significant, EFS and OS were tested sequentially via the Holm's testing procedure at the 1-sided family wise level of 0.025. If one member of the short-term family was significant, EFS and OS were tested sequentially at 1-sided 0.0125.

[12] - 1-sided p-value based on log-rank test for comparing survival curves between treatment arms stratified by sokal risk group and region. OS was not tested as EFS was not significant.

Other pre-specified: Summary of Trough Plasma Concentration by Complete Cytogenetic Response (CCyR) of Bosutinib

End point title	Summary of Trough Plasma Concentration by Complete Cytogenetic Response (CCyR) of Bosutinib[13]

End point description:

CCyR was based on the prevalence of Ph+ metaphases among cells in metaphase on a BM aspirate. CCyR was achieved when there was 0% Ph+ metaphases among cells in a BM sample when at least 20 metaphases from a BM sample were analysed, or MMR if no BM was available. Trough plasma concentration of subjects who had CCyR are presented in this endpoint. Pharmacokinetic (PK) population included all enrolled subjects who received at least 1 dose of bosutinib and had sufficient plasma results available. Here, "N" signifies number of subjects evaluable for this endpoint and "number analysed (n)" signifies subjects evaluable at specified time points only. Data for this endpoint was not planned to be collected and analysed for Imatinib arm as pre-specified in the protocol.

End point type	Other pre-specified

End point timeframe:

Pre-dose on Days 28, 56 and 84

Notes:

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

Justification: This endpoint was planned to be analysed for reporting arm “Bosutinib” only.

End point values	Bosutinib			
Subject group type	Reporting group			
Number of subjects analysed	191			
Units: nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Day 28 (n= 181)	71.282 (± 46.0545)			
Day 56 (n= 184)	73.069 (± 45.1349)			
Day 84 (n= 184)	83.973 (± 64.3206)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Summary of Trough Plasma Concentration by Major Molecular Response (MMR) of Bosutinib

End point title	Summary of Trough Plasma Concentration by Major Molecular Response (MMR) of Bosutinib[14]

End point description:

MMR was defined as a ratio of BCR-ABL/ABL <=0.1% on the international scale (>=3 log reduction from standardized baseline in ratio of BCR-ABL to ABL transcripts) by quantitative RT-qPCR. Trough plasma concentration of subjects who had MMR are presented in this endpoint. PK population included all enrolled subjects who received at least 1 dose of bosutinib and had sufficient plasma results available. Here, "N" signifies number of subjects evaluable for this endpoint and "n" signifies subjects evaluable at specified time points only. Data for this endpoint was not planned to be collected and analysed for Imatinib arm as pre-specified in the protocol.

End point type	Other pre-specified

End point timeframe:

Pre-dose on Days 28, 56 and 84

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be analysed for reporting arm “Bosutinib” only.

End point values	Bosutinib			
Subject group type	Reporting group			
Number of subjects analysed	141			
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 28 (n= 140)	75.050 (± 51.9551)			
Day 56 (n= 140)	78.437 (± 43.6019)			
Day 84 (n= 141)	91.081 (± 72.1500)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Summary of Trough Plasma Concentration by Presence of Grade 1 or Higher Adverse Events (AEs) of Bosutinib

End point title	Summary of Trough Plasma Concentration by Presence of Grade 1 or Higher Adverse Events (AEs) of Bosutinib[15]

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. AE was assessed according to maximum severity grading based on NCI-CTCAE version 4.0. Grade 1=mild; Grade 2=moderate; within normal limits, Grade 3=severe or medically significant but not immediately life-threatening; Grade 4=life-threatening or disabling; urgent intervention indicated; Grade 5=death. Trough plasma concentration of subjects who had grade 1 or higher AE are presented in this endpoint. Data of plasma concentration is reported separately for each preferred term of AE. PK population included all enrolled subjects who received at least 1 dose of bosutinib and had sufficient plasma results available. Here, "N"=number of subjects evaluable for this endpoint and "n"=subjects evaluable at specified time points only. Data for this endpoint was not planned to be collected and analysed for Imatinib arm.

End point type	Other pre-specified

End point timeframe:

Pre-dose on Days 28, 56 and 84

Notes:

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

Justification: This endpoint was planned to be analysed for reporting arm "Bosutinib" only.

End point values	Bosutinib			
Subject group type	Reporting group			
Number of subjects analysed	177			
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 28: Diarrhea (n= 177)	69.402 (± 55.5005)			
Day 28: Thrombocytopenia (n= 60)	63.529 (± 40.9949)			
Day 28: Rash (n= 84)	74.779 (± 60.6257)			
Day 28: Nausea (n= 86)	66.011 (± 42.6437)			
Day 28: Vomiting (n= 44)	71.684 (± 60.7208)			
Day 56: Diarrhea (n= 172)	68.834 (± 42.6621)			
Day 56: Thrombocytopenia (n= 61)	65.327 (± 43.2859)			
Day 56: Rash (n= 84)	70.016 (± 38.7506)			
Day 56: Nausea (n= 85)	61.626 (± 44.4007)			
Day 56: Vomiting (n= 40)	65.980 (± 45.9064)			
Day 84: Diarrhea (n= 165)	81.269 (± 64.6462)			
Day 84: Thrombocytopenia (n= 63)	71.585 (± 33.6674)			
Day 84: Rash (n= 85)	89.080 (± 69.5237)			
Day 84: Nausea (n= 80)	77.702 (± 61.6179)			
Day 84: Vomiting (n= 41)	86.949 (± 55.3041)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Summary of Trough Plasma Concentration by Presence of Grade 3 or Higher Adverse Events (AEs) of Bosutinib

End point title	Summary of Trough Plasma Concentration by Presence of Grade 3 or Higher Adverse Events (AEs) of Bosutinib[16]

End point description:

AE: any untoward medical occurrence in subject who received study drug without regard to possibility of

causal relationship. AE assessed according to maximum severity grading based on NCI-CTCAE version 4.0. Grade 1=mild; Grade 2=moderate; within normal limits, Grade 3=severe or medically significant but not immediately life-threatening; Grade 4=life-threatening or disabling; urgent intervention indicated; Grade 5=death. Trough plasma concentration of subjects who had grade 3 or higher AE are presented. Data of plasma concentration is reported separately for each preferred term of AE. PK population included all enrolled subjects who received at least 1 dose of bosutinib, had sufficient plasma results available. "N"=number of subjects evaluable for this endpoint and "n"=subjects evaluable at specified time points only. 99999=as only 1 subject was analysed, standard deviation could not be calculated. Data for this endpoint was not planned to be collected and analysed for Imatinib arm.

End point type	Other pre-specified

End point timeframe:

Pre-dose on Days 28, 56 and 84

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was planned to be analysed for reporting arm "Bosutinib" only.

End point values	Bosutinib			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 28: Diarrhea (n= 19)	87.769 (± 102.6181)			
Day 28: Thrombocytopenia (n= 23)	49.220 (± 36.3461)			
Day 28: Rash (n= 4)	71.150 (± 43.3246)			
Day 28: Vomiting (n= 3)	14.663 (± 21.5799)			
Day 56: Diarrhea (n= 16)	68.513 (± 45.2672)			
Day 56: Thrombocytopenia (n= 24)	56.853 (± 34.3892)			
Day 56: Rash (n= 4)	58.925 (± 18.8656)			
Day 56: Vomiting (n= 1)	38.200 (± 99999)			
Day 84: Diarrhea (n= 17)	76.782 (± 46.3006)			
Day 84: Thrombocytopenia (n= 23)	67.623 (± 35.3084)			
Day 84: Rash (n= 3)	83.967 (± 19.2542)			
Day 84: Vomiting (n= 1)	12.400 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Vital Signs Abnormalities

End point title	Number of Subjects With Vital Signs Abnormalities

End point description:

Criteria for vital signs abnormalities: systolic blood pressure <80 millimeter of mercury (mmHg), >210 mmHg; diastolic blood pressure <40 mmHg, >130 mmHg; heart rate <40 beats per minute (bpm), >150 bpm; temperature <32 degree celsius, >40 degree celsius; weight >=10% increase from baseline, >=10% decrease from baseline. The number of subjects with any vital sign abnormalities during On-treatment period are reported. On-Treatment was defined as values collected after the date of the first dose of test article until the last date of test article +28 days. Safety population included all subjects who received at least 1 dose of study medication with treatment assignments designated to actual study treatment received. Here, "N" signifies number of subjects evaluable for this endpoint.

End point type	Other pre-specified

End point timeframe:

Baseline up to end of treatment (up to Month 60)

End point values	Bosutinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	262	263		
Units: subjects	107	109		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Laboratory Test Abnormalities Based on National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE) Version 4.03

End point title	Number of Subjects With Laboratory Test Abnormalities Based on National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE) Version 4.03

End point description:

Laboratory parameters included hematological (haemoglobin, lymphocytes [absolute], neutrophils [absolute], platelets and leukocytes) and biochemistry (albumin, alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, amylase, bilirubin, creatinine kinase, calcium, creatinine, glucose, potassium, lipase, magnesium, phosphate, sodium, urate) parameters. Abnormalities in laboratory tests were graded by NCI-CTCAE version 4.03 as Grade 1=mild; Grade 2=moderate; Grade 3=severe and Grade 4=life-threatening or disabling. The number of subjects with laboratory test abnormalities were reported. Safety population included all subjects who received at least 1 dose of study medication with treatment assignments designated to actual study treatment received.

End point type	Other pre-specified

End point timeframe:

Baseline up to end of treatment (up to Month 60)

End point values	Bosutinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	265		
Units: subjects				
Grade 1	6	7		
Grade 2	67	59		
Grade 3	133	154		

Grade 4	61	45		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Clinically Significant Electrocardiogram (ECG) Abnormalities

End point title	Number of Subjects With Clinically Significant Electrocardiogram (ECG) Abnormalities

End point description:

Criteria for ECG abnormalities included heart rate: increase of >15 bpm from baseline value and >=120 bpm, decrease of >15 bpm from baseline value and <=45 bpm; PR interval: change of >=20 msec from baseline value and >=220 milliseconds (msec); QRS interval >=120 msec; QTcB interval >500 msec, increase of >60 msec from baseline; >450 msec (Men) or >470 msec (Women); QT interval using Fridericia's correction (QTcF) >500 msec, increase of >60 msec from baseline, >450 msec (Men) or >470 msec (Women). The number of subjects with ECG abnormalities during On-treatment period are reported. On-Treatment was defined as values collected after the date of the first dose of test article until the last date of test article +28 days. Safety population included all subjects who received at least 1 dose of study medication with treatment assignments designated to actual study treatment received. Here, "N" signifies number of subjects evaluable for this endpoint.

End point type	Other pre-specified

End point timeframe:

Baseline up to end of treatment (up to Month 60)

End point values	Bosutinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	266	262		
Units: subjects	16	13		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Adverse Events (AEs) Leading to Study Drug Discontinuation

End point title	Number of Subjects With Adverse Events (AEs) Leading to Study Drug Discontinuation

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. Safety population included all subjects who received at least 1 dose of study medication with treatment assignments designated to actual study treatment received.

End point type	Other pre-specified

End point timeframe:

Baseline up to end of treatment (up to Month 60)

End point values	Bosutinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	265		
Units: subjects	68	38		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Treatment-Emergent Adverse Events by National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE) (Version 4.0)

End point title	Number of Subjects With Treatment-Emergent Adverse Events by National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE) (Version 4.0)

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. AE was assessed according to severity grading based on NCI-CTCAE version 4.0. Grade 1=mild; Grade 2=moderate; Grade 3=severe or medically significant but not immediately life-threatening, hospitalisation or prolongation of hospitalisation indicated; Grade 4=life-threatening or disabling, urgent intervention indicated; Grade 5=death. Treatment-emergent events were events between first dose of study drug and up to 60 months that were absent before treatment that worsened relative to pretreatment state. If the same subject in a given treatment had more than 1 adverse event, only the maximum CTCAE was reported. Safety population included all subjects who received at least 1 dose of study medication with treatment assignments designated to actual study treatment received.

End point type	Other pre-specified

End point timeframe:

Baseline up to end of treatment (up to Month 60)

End point values	Bosutinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	265		
Units: subjects				
Grade 1	7	24		
Grade 2	61	86		
Grade 3	144	120		
Grade 4	50	28		
Grade 5	3	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of drug up to 28 days after last dose (up to Month 60)

Adverse event reporting additional description:

Total deaths in study (randomisation up to month 60): for all randomised subjects (n=268 bosutinib; n=268 imatinib), not only for treated subjects, included deaths occurred after 28 days post last drug dose. SAEs, Non-SAEs: safety population (all subjects, regardless of Ph chromosome or transcript status, received at least 1 dose of study drug).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Bosutinib

Reporting group description:

Subjects with Philadelphia chromosome-positive CML received bosutinib tablets at a dose of 400 mg, orally once daily in the core treatment phase of 12 months and continued the same treatment into the extension phase or followed up for safety for up to approximately 4 years, until the end of the study, treatment failure, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first.

Reporting group title	Imatinib

Reporting group description:

Subjects with Philadelphia chromosome-positive CML received imatinib tablets at a dose of 400 mg, orally once daily in the core treatment phase of 12 months and continued the same treatment into the extension phase or followed up for safety for up to approximately 4 years, until the end of the study, treatment failure, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first.

Serious adverse events	Bosutinib	Imatinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	98 / 268 (36.57%)	68 / 265 (25.66%)	
number of deaths (all causes)	14	14	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Chronic myeloid leukaemia			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			

subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic adenoma			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer			
subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder papilloma			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carcinoid tumour of the caecum			

subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer metastatic			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial cancer metastatic			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fallopian tube cancer stage III			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fibromatosis			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			

subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Unintended pregnancy			
subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	5 / 268 (1.87%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hyperthermia			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implant site haematoma			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swelling face			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Pregnancy of partner			
subjects affected / exposed	2 / 268 (0.75%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatic dysplasia			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine haemorrhage			

subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (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 / 268 (0.00%)	1 / 265 (0.38%)	
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 / 268 (0.37%)	0 / 265 (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			
Dyspnoea			
subjects affected / exposed	2 / 268 (0.75%)	2 / 265 (0.75%)	
occurrences causally related to treatment / all	1 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	4 / 268 (1.49%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	3 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			

subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary toxicity			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory disorder			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 268 (2.24%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood sodium decreased			

subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (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			
Fall			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			

subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
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 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 268 (0.75%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	4 / 268 (1.49%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Coronary artery disease			
subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pericarditis			
subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial thrombosis			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			

subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuropericarditis			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Headache			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			

subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 268 (0.37%)	3 / 265 (1.13%)	
occurrences causally related to treatment / all	1 / 1	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 268 (0.75%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	5 / 5	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 268 (0.00%)	2 / 265 (0.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Agranulocytosis			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolysis			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			

Vertigo positional			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal vein occlusion			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye haemorrhage			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ocular hypertension			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinopathy			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 268 (1.87%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	5 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Colitis			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising oesophagitis			

subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall haematoma			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fissure			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia oral			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haematoma			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedematous pancreatitis			

subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (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 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 268 (0.00%)	2 / 265 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			

subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 268 (0.00%)	2 / 265 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis allergic			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lichen planus			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
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	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus bladder			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
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	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	4 / 268 (1.49%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Endocrine disorders			
Thyroid disorder			

subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteochondrosis			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 268 (0.37%)	2 / 265 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	8 / 268 (2.99%)	5 / 265 (1.89%)	
occurrences causally related to treatment / all	2 / 8	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	

Gastroenteritis			
subjects affected / exposed	6 / 268 (2.24%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	4 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	3 / 268 (1.12%)	2 / 265 (0.75%)	
occurrences causally related to treatment / all	3 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 268 (0.00%)	3 / 265 (1.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Urinary tract infection			
subjects affected / exposed	1 / 268 (0.37%)	2 / 265 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	0 / 268 (0.00%)	2 / 265 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 268 (0.00%)	2 / 265 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida pneumonia			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective pericardial effusion			

subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 268 (0.37%)	2 / 265 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic infection			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			

subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis infective			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fournier's gangrene			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis E			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected dermal cyst			

subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningococcal sepsis			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngitis fungal			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic abscess			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	1 / 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	Bosutinib	Imatinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	264 / 268 (98.51%)	260 / 265 (98.11%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	26 / 268 (9.70%)	29 / 265 (10.94%)	
occurrences (all)	47	48	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	57 / 268 (21.27%)	54 / 265 (20.38%)	
occurrences (all)	68	89	
Pyrexia			
subjects affected / exposed	44 / 268 (16.42%)	29 / 265 (10.94%)	
occurrences (all)	70	45	
Asthenia			
subjects affected / exposed	34 / 268 (12.69%)	24 / 265 (9.06%)	
occurrences (all)	49	36	
Oedema peripheral			
subjects affected / exposed	20 / 268 (7.46%)	43 / 265 (16.23%)	
occurrences (all)	38	73	
Influenza like illness			
subjects affected / exposed	16 / 268 (5.97%)	6 / 265 (2.26%)	
occurrences (all)	26	7	
Face oedema			
subjects affected / exposed	7 / 268 (2.61%)	17 / 265 (6.42%)	
occurrences (all)	8	29	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	29 / 268 (10.82%)	14 / 265 (5.28%)	
occurrences (all)	39	21	
Cough			
subjects affected / exposed	30 / 268 (11.19%)	26 / 265 (9.81%)	
occurrences (all)	40	36	
Oropharyngeal pain			

subjects affected / exposed	17 / 268 (6.34%)	10 / 265 (3.77%)	
occurrences (all)	27	14	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	18 / 268 (6.72%)	19 / 265 (7.17%)	
occurrences (all)	24	23	
Anxiety			
subjects affected / exposed	15 / 268 (5.60%)	15 / 265 (5.66%)	
occurrences (all)	19	16	
Depression			
subjects affected / exposed	9 / 268 (3.36%)	14 / 265 (5.28%)	
occurrences (all)	11	16	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	90 / 268 (33.58%)	16 / 265 (6.04%)	
occurrences (all)	264	28	
Aspartate aminotransferase increased			
subjects affected / exposed	69 / 268 (25.75%)	18 / 265 (6.79%)	
occurrences (all)	169	25	
Lipase increased			
subjects affected / exposed	56 / 268 (20.90%)	30 / 265 (11.32%)	
occurrences (all)	156	49	
Blood alkaline phosphatase increased			
subjects affected / exposed	17 / 268 (6.34%)	7 / 265 (2.64%)	
occurrences (all)	21	9	
Blood creatinine increased			
subjects affected / exposed	18 / 268 (6.72%)	22 / 265 (8.30%)	
occurrences (all)	40	56	
Amylase increased			
subjects affected / exposed	25 / 268 (9.33%)	10 / 265 (3.77%)	
occurrences (all)	72	13	
Blood bilirubin increased			
subjects affected / exposed	17 / 268 (6.34%)	7 / 265 (2.64%)	
occurrences (all)	31	9	
Blood creatine phosphokinase increased			

subjects affected / exposed	14 / 268 (5.22%)	33 / 265 (12.45%)	
occurrences (all)	35	57	
Weight increased			
subjects affected / exposed	8 / 268 (2.99%)	20 / 265 (7.55%)	
occurrences (all)	10	24	
Nervous system disorders			
Headache			
subjects affected / exposed	58 / 268 (21.64%)	41 / 265 (15.47%)	
occurrences (all)	119	90	
Dizziness			
subjects affected / exposed	25 / 268 (9.33%)	23 / 265 (8.68%)	
occurrences (all)	34	42	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	96 / 268 (35.82%)	53 / 265 (20.00%)	
occurrences (all)	262	130	
Anaemia			
subjects affected / exposed	59 / 268 (22.01%)	59 / 265 (22.26%)	
occurrences (all)	117	161	
Neutropenia			
subjects affected / exposed	33 / 268 (12.31%)	61 / 265 (23.02%)	
occurrences (all)	85	190	
Leukopenia			
subjects affected / exposed	18 / 268 (6.72%)	34 / 265 (12.83%)	
occurrences (all)	36	107	
Lymphopenia			
subjects affected / exposed	15 / 268 (5.60%)	8 / 265 (3.02%)	
occurrences (all)	52	29	
Eye disorders			
Periorbital oedema			
subjects affected / exposed	4 / 268 (1.49%)	44 / 265 (16.60%)	
occurrences (all)	6	58	
Vision blurred			
subjects affected / exposed	5 / 268 (1.87%)	14 / 265 (5.28%)	
occurrences (all)	6	20	
Conjunctival haemorrhage			

subjects affected / exposed	2 / 268 (0.75%)	18 / 265 (6.79%)	
occurrences (all)	3	30	
Eyelid oedema			
subjects affected / exposed	3 / 268 (1.12%)	24 / 265 (9.06%)	
occurrences (all)	5	42	
Dry eye			
subjects affected / exposed	4 / 268 (1.49%)	16 / 265 (6.04%)	
occurrences (all)	4	16	
Lacrimation increased			
subjects affected / exposed	1 / 268 (0.37%)	18 / 265 (6.79%)	
occurrences (all)	1	22	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	201 / 268 (75.00%)	106 / 265 (40.00%)	
occurrences (all)	674	319	
Nausea			
subjects affected / exposed	100 / 268 (37.31%)	112 / 265 (42.26%)	
occurrences (all)	194	218	
Vomiting			
subjects affected / exposed	55 / 268 (20.52%)	54 / 265 (20.38%)	
occurrences (all)	123	92	
Abdominal pain			
subjects affected / exposed	61 / 268 (22.76%)	25 / 265 (9.43%)	
occurrences (all)	88	36	
Constipation			
subjects affected / exposed	36 / 268 (13.43%)	17 / 265 (6.42%)	
occurrences (all)	44	19	
Abdominal pain upper			
subjects affected / exposed	28 / 268 (10.45%)	26 / 265 (9.81%)	
occurrences (all)	64	63	
Dyspepsia			
subjects affected / exposed	26 / 268 (9.70%)	24 / 265 (9.06%)	
occurrences (all)	32	33	
Abdominal distension			
subjects affected / exposed	14 / 268 (5.22%)	8 / 265 (3.02%)	
occurrences (all)	15	9	

Toothache			
subjects affected / exposed	14 / 268 (5.22%)	7 / 265 (2.64%)	
occurrences (all)	16	8	
Gastrooesophageal reflux disease			
subjects affected / exposed	8 / 268 (2.99%)	14 / 265 (5.28%)	
occurrences (all)	8	14	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	61 / 268 (22.76%)	39 / 265 (14.72%)	
occurrences (all)	93	59	
Pruritus			
subjects affected / exposed	30 / 268 (11.19%)	10 / 265 (3.77%)	
occurrences (all)	42	10	
Rash maculo-papular			
subjects affected / exposed	13 / 268 (4.85%)	16 / 265 (6.04%)	
occurrences (all)	21	26	
Alopecia			
subjects affected / exposed	15 / 268 (5.60%)	14 / 265 (5.28%)	
occurrences (all)	17	15	
Dry skin			
subjects affected / exposed	20 / 268 (7.46%)	14 / 265 (5.28%)	
occurrences (all)	23	17	
Night sweats			
subjects affected / exposed	5 / 268 (1.87%)	14 / 265 (5.28%)	
occurrences (all)	6	15	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	48 / 268 (17.91%)	49 / 265 (18.49%)	
occurrences (all)	75	76	
Back pain			
subjects affected / exposed	32 / 268 (11.94%)	25 / 265 (9.43%)	
occurrences (all)	45	29	
Pain in extremity			
subjects affected / exposed	26 / 268 (9.70%)	39 / 265 (14.72%)	
occurrences (all)	33	48	
Myalgia			

subjects affected / exposed	13 / 268 (4.85%)	48 / 265 (18.11%)	
occurrences (all)	21	60	
Bone pain			
subjects affected / exposed	8 / 268 (2.99%)	19 / 265 (7.17%)	
occurrences (all)	19	23	
Muscle spasms			
subjects affected / exposed	10 / 268 (3.73%)	81 / 265 (30.57%)	
occurrences (all)	20	138	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	36 / 268 (13.43%)	30 / 265 (11.32%)	
occurrences (all)	55	50	
Upper respiratory tract infection			
subjects affected / exposed	36 / 268 (13.43%)	33 / 265 (12.45%)	
occurrences (all)	56	59	
Urinary tract infection			
subjects affected / exposed	26 / 268 (9.70%)	18 / 265 (6.79%)	
occurrences (all)	34	25	
Bronchitis			
subjects affected / exposed	19 / 268 (7.09%)	6 / 265 (2.26%)	
occurrences (all)	24	7	
Influenza			
subjects affected / exposed	24 / 268 (8.96%)	14 / 265 (5.28%)	
occurrences (all)	31	32	
Sinusitis			
subjects affected / exposed	15 / 268 (5.60%)	8 / 265 (3.02%)	
occurrences (all)	20	8	
Gastroenteritis			
subjects affected / exposed	12 / 268 (4.48%)	17 / 265 (6.42%)	
occurrences (all)	14	22	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	29 / 268 (10.82%)	17 / 265 (6.42%)	
occurrences (all)	37	17	
Hypophosphataemia			

subjects affected / exposed	7 / 268 (2.61%)	19 / 265 (7.17%)	
occurrences (all)	18	39	
Hypokalaemia			
subjects affected / exposed	6 / 268 (2.24%)	23 / 265 (8.68%)	
occurrences (all)	11	34	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 March 2014	Updated information for assessments of vital signs, inclusion/exclusion criteria, laboratory assessments, timing of efficacy endpoints, exploratory efficacy endpoints, study durations, timing of assessments, terms and definitions, study populations, adverse event assessments, and administrative information.
14 January 2015	Updated information for contact details, study duration, subject populations, inclusion/exclusion criteria definitions, bosutinib formulation details, assessment timings (e.g., schedule of events, pre-randomisation Sokal score assessment), timing of assessments, timing for collection of adverse events/reporting, study drug dosing requirements, compliance recording, statistical analysis (primary and secondary efficacy analysis), pharmacokinetic analysis, and administrative information.
07 December 2016	Updated information for change of sponsor details, sample size, study populations, methodology for statistical analyses, efficacy analysis, interim analyses, time to response description, extension phase visit window, sample drug diary cards, and administrative information.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported