Clinical trial results:
A Multicenter Phase 3 randomized, open-label study of bosutinib versus imatinib in adult subjects with newly diagnosed chronic phase chronic myelogenous leukemia (BFORE)

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	

Results information

Result version number	v1
This version publication date	28 July 2018
First version publication date	28 July 2018

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 1-800-718-1021, ClinicalTrials.gov_inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 18007181021, 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	Interim
Date of interim/final analysis	20 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 August 2016
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the proportion of patients 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) patients 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 The study was in compliance 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	Czech Republic: 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	257

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:

Data reported was based on primary analysis date (11 August 2016).

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 chronic myeloid leukemia (CML) received bosutinib at a dose of 400 mg, orally once daily in the core treatment period of 12 months. Subjects who completed the core treatment period, entered into extension period and received same treatment.

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 at a dose of 400 mg, orally once daily in the core treatment period of 12 months. Subjects who completed the core treatment period, entered into extension period and received same treatment.

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	0	0
Not completed	268	268
Deceased	1	6
Consent withdrawn by subject	5	2
Ongoing	260	255
Lost to follow-up	2	2
Randomized, not treated	-	3

Baseline characteristics

Reporting groups	
Reporting group title	Bosutinib
Reporting group description:	
Subjects with Philadelphia chromosome-positive chronic myeloid leukemia (CML) received bosutinib at a dose of 400 mg, orally once daily in the core treatment period of 12 months. Subjects who completed the core treatment period, entered into extension period and received same treatment.	
Reporting group title	Imatinib
Reporting group description:	
Subjects with Philadelphia chromosome-positive CML received imatinib at a dose of 400 mg, orally once daily in the core treatment period of 12 months. Subjects who completed the core treatment period, entered into extension period and received same treatment.	

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			
median	53.0	53.0	
full range (min-max)	18 to 84	19 to 84	-
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 chronic myeloid leukemia (CML) received bosutinib at a dose of 400 mg, orally once daily in the core treatment period of 12 months. Subjects who completed the core treatment period, entered into extension period and received same treatment.	
Reporting group title	Imatinib
Reporting group description:	
Subjects with Philadelphia chromosome-positive CML received imatinib at a dose of 400 mg, orally once daily in the core treatment period of 12 months. Subjects who completed the core treatment period, entered into extension period and received same treatment.	

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 standardized baseline in ratio of Bcr-Abl to Abl transcripts [>=3000 Abl required]) by quantitative reverse transcriptase polymerase chain reaction (RT-qPCR). Modified intent-to-treat (mITT) population included all randomized subjects with Philadephia chromosome positive CML harboring the b2a2 and/or b3a2 transcript and baseline BCR-ABL copies greater than (>) 0 with study drug assignment designated according to initial randomization.	
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 vs Imatinib
Statistical analysis description:	
95% CI for the odds ratio adjusted for sokal risk group and region are based on asymptotic wald confidence limits.	
Comparison groups	Bosutinib v Imatinib

Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.01 [1]
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] - 1-sided p-value was based on a CMH test for general association between treatment and response with stratification by sokal risk group (low, intermediate, high) and region (1-3) as determined at time of randomization.

Secondary: Duration of Major Molecular Response (MMR)

End point title	Duration of Major Molecular Response (MMR)

End point description:

Time from the first date of MMR until the date of the confirmed loss of MMR or censoring. Confirmed Loss of MMR was Bcr-Abl/Abl IS ratio >0.1% in association with a >=5-fold increase in Bcr-Abl/Abl IS ratio from the lowest value achieved up to that time-point confirmed by a second assessment at least 28 days later. Treatment discontinuation due to progressive disease(PD) or death due to PD within 28 days of last dose were considered confirmed loss of MMR. PD was defined as disease progression to accelerated phase(AP) or blast phase(BP) CML. Kaplan-meier analysis was used for determation of duration of MMR.Duration of response will be analyzed for responders only therefore duration of response will be excluded from the long-term family of secondary endpoints.mITT analysis set.N(overall number of subjects analyzed)=number of subjects evaluable for this endpoint.99999 represents median and 95% C.I. could not be reached due to immaturity of events at the data cutoff date.

End point type	Secondary

End point timeframe:

From the date of first MMR until the date of confirmed loss of MMR or censoring (up to 752 days)

End point values	Bosutinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	122		
Units: weeks				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Complete Cytogenetic Response (CCyR) was based on the prevalence of Philadelphia chromosome positive (Ph+) metaphases among cells in metaphase on a bone marrow (BM) aspirate. CCyR was achieved when there was 0 % Ph+ metaphases among cells in a BM sample when at least 20 metaphases from a BM sample were analyzed, or MMR if no BM was available. mITT population included all randomized subjects with Philadephia chromosome positive CML harboring the b2a2 and/or b3a2 transcript and baseline BCR-ABL copies >0 with study drug assignment designated according to initial randomization.

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 vs Imatinib

Statistical analysis description:

95% CI for the odds ratio adjusted for sokal risk group and region are based on asymptotic wald confidence limits.

Comparison groups	Bosutinib v Imatinib
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0037 [2]
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:

[2] - 1-sided p-value was based on a CMH test for general association between treatment and response with stratification by sokal risk group (low, intermediate, high) and region (1-3) as determined at time of randomization.

Secondary: Duration of Complete Cytogenetic Response (CCyR)

End point title	Duration of Complete Cytogenetic Response (CCyR)

End point description:

It was defined as the time from the first date of CCyR until the date of the confirmed loss of CCyR or censoring. 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 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 accelerated phase or blast phase CML. Kaplan meier analysis was used for the determination of duration of CCyR. Duration of response will be analyzed for responders only therefore duration of response will be excluded from the long-term family of secondary endpoints. mITT analysis set. N=number of subjects evaluable for this endpoint. 99999 states that median and 95% C.I. was not estimable due to less number of subjects who had event.

End point type	Secondary

End point timeframe:

From the date of first CCyR until the date of confirmed loss of CCyR or censoring (up to 752 days)

End point values	Bosutinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	197	175		
Units: weeks				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative Incidence of Event Free Survival (EFS) Events at Month 12

End point title	Cumulative Incidence of Event Free Survival (EFS) Events at Month 12

End point description:

EFS was defined as the time from randomization 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 was defined as a hematologic assessment of non-CHR [chronic phase, AP, or BP] confirmed by 2 assessments at least 4 weeks apart). Loss of CCyR was defined as at least 1 Ph+ metaphase from analysis of <100 metaphases confirmed by a follow up cytogenetic analysis after 1 month. Cumulative incidence of EFS event at month 12 was adjusted for competing risk of treatment discontinuation without the event. The comparative analysis between two arms for this member of long term secondary family will be done at the end of the study. mITT population included all randomized subjects with Philadephia chromosome positive CML harboring the b2a2 and/or b3a2 transcript and baseline BCR-ABL copies >0 with study drug assignment designated according to initial randomization.

End point type	Secondary

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%)	3.7 (1.8 to 6.7)	6.4 (3.7 to 10.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS) at Month 12

End point title	Overall survival (OS) at Month 12

End point description:

OS was defined as the time (in months) from randomization to the occurrence of death due to any cause or censoring. Kaplan-meier analysis was used for determination of OS. The comparative analysis between the two arms for this member of the long-term secondary family will be done at the end of the study. mITT population included all randomized subjects with Philadephia chromosome positive CML harboring the b2a2 and/or b3a2 transcript and baseline BCR-ABL copies >0 with study drug assignment designated according to initial randomization.

End point type	Secondary

End point timeframe:

Month 12

End point values	Bosutinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246	241		
Units: Months				
number (confidence interval 95%)	99.6 (97.0 to 99.9)	97.9 (95.0 to 99.1)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Summary of Trough Plasma Concentration by Complete Cytogenetic Response (CCyR)[3]

End point description:

CCyR is 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 analyzed, or MMR if no BM was available. Trough plasma concentration of participants 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 "n" signifies subjects evaluable at specified time points only.

End point type	Other pre-specified

End point timeframe:

Day 28, 56, 84

Notes:

[3] - 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: Descriptive analysis was planned to be reported for Bosutinib arm 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)

End point title	Summary of Trough Plasma Concentration by Major Molecular Response (MMR)[4]

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.

End point type	Other pre-specified

End point timeframe:

Day 28, 56, 84

Notes:

[4] - 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: Descriptive analysis was planned to be reported for Bosutinib arm 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)

End point title	Summary of Trough Plasma Concentration by Presence of Grade 1 or Higher Adverse Events (AEs)[5]

End point description:

An AE was any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. AE was assessed according to maximum severity grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (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" signifies number of subjects evaluable for this endpoint and "n" signifies subjects evaluable at specified time points only.

End point type	Other pre-specified

End point timeframe:

Day 28, 56, 84

Notes:

[5] - 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: Descriptive analysis was planned to be reported for Bosutinib arm 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)

End point title	Summary of Trough Plasma Concentration by Presence of Grade 3 or Higher Adverse Events (AEs)[6]

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 participants who had grade 3 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. "N"=number of subjects evaluable for this endpoint and "n"=subjects evaluable at specified time points only. 99999 states that as only 1 subject was analyzed, standard deviation could not be calculated.

End point type	Other pre-specified

End point timeframe:

Day 28, 56, 84

Notes:

[6] - 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: Descriptive analysis was planned to be reported for Bosutinib arm 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 (SBP) less than (<) 80 millimeter of mercury (mmHg), >210 mmHg; diastolic blood pressure (DBP) <40 mmHg, >130 mmHg; heart rate <40 beats per minute (bpm), >150 bpm; temperature <32 degree celsius, >40 degree celsius. 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 752 days

End point values	Bosutinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	265		
Units: subjects	0	0		

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. 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 752 days

End point values	Bosutinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	265		
Units: subjects				
Grade 1|	15	17		
Grade 2|	84	87		
Grade 3|	114	116		
Grade 4|	54	45		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Electrocardiogram (ECG) Abnormalities of Potential Clinical Concern

End point title	Number of Subjects With Electrocardiogram (ECG) Abnormalities of Potential Clinical Concern

End point description:

Criteria for ECG abnormalities : 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; QT interval using Fridericia's correction (QTcF) >500 msec, increase of >60 msec from baseline, <=450 msec (Men) or <=470 msec (Women), >450 msec (Men) or >470 msec (Women). 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 752 days

End point values	Bosutinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	265		
Units: subjects	6	6		

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 752 days

End point values	Bosutinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	265		
Units: subjects	38	28		

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 4.03)

End point title	Number of Subjects With Treatment-Emergent Adverse Events By National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE) (Version 4.03)

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 4.03. Grade 1 =mild; Grade 2 =moderate; Grade 3 =severe or medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization 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 752 days 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 752 days

End point values	Bosutinib	Imatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	265		
Units: subjects				
Grade 1|	20	44		
Grade 2|	92	100		
Grade 3|	120	90		

Grade 4|	30	19		
Grade 5|	1	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 752 days

Adverse event reporting additional description:

Same event may appear as both an AE and serious adverse event. However, what is presented are distinct events. An event may be categorized as serious in one subject and as non-serious in another, or a subject may have experienced both a serious and non-serious event.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Bosutinib

Reporting group description:

Subjects with Philadelphia chromosome-positive CML received bosutinib at a dose of 400 mg, orally once daily in the core treatment period of 12 months. Subjects who completed the core treatment period, entered into extension period and received same treatment.

Reporting group title	Imatinib

Reporting group description:

Subjects with Philadelphia chromosome-positive CML received imatinib at a dose of 400 mg, orally once daily in the core treatment period of 12 months. Subjects who completed the core treatment period, entered into extension period and received same treatment.

Serious adverse events	Bosutinib	Imatinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	54 / 268 (20.15%)	45 / 265 (16.98%)	
number of deaths (all causes)	0	4	
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 / 1	
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	0 / 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	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	
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	
Vascular disorders			
Hypertensive crisis			
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	
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	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 268 (1.49%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	1 / 4	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	
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	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	1 / 1	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	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	
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	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	3 / 268 (1.12%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	3 / 3	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	
Injury, poisoning and procedural complications			
Fall			

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	
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	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
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 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 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
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	
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	1 / 1	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	
Nervous system disorders			
Cerebrovascular accident			
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 / 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	
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	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	2 / 2	0 / 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	
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	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 268 (1.12%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	3 / 3	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	
Gastrointestinal necrosis			
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			
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	
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%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	1 / 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	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	
Drug-induced liver injury			
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	
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	
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	
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	
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 / 2	
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	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal 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	
Infections and infestations			
Pneumonia			
subjects affected / exposed	4 / 268 (1.49%)	3 / 265 (1.13%)	
occurrences causally related to treatment / all	0 / 4	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastroenteritis			
subjects affected / exposed	5 / 268 (1.87%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	4 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 268 (0.37%)	2 / 265 (0.75%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 268 (0.00%)	2 / 265 (0.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Subcutaneous abscess			
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	
Urinary tract infection			
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	
Abscess limb			

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	
Appendicitis			
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	
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	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	
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	
Necrotising fasciitis			

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	
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	
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	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Bosutinib	Imatinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	263 / 268 (98.13%)	257 / 265 (96.98%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	3 / 268 (1.12%)	0 / 265 (0.00%)	
occurrences (all)	3	0	
Acanthoma			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Adrenal adenoma			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Prostatic adenoma			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Seborrhoeic keratosis			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Skin cancer			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Anogenital warts			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Leukaemic retinopathy			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Skin papilloma			

subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Lipoma			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Melanocytic naevus			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	13 / 268 (4.85%)	16 / 265 (6.04%)	
occurrences (all)	13	16	
Haematoma			
subjects affected / exposed	5 / 268 (1.87%)	3 / 265 (1.13%)	
occurrences (all)	5	3	
Hypotension			
subjects affected / exposed	5 / 268 (1.87%)	5 / 265 (1.89%)	
occurrences (all)	5	5	
Angiopathy			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Capillary fragility			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Deep vein thrombosis			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Flushing			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Hot flush			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Jugular vein distension			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	

Orthostatic hypotension			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Pallor			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Periphlebitis			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Phlebitis			
subjects affected / exposed	1 / 268 (0.37%)	2 / 265 (0.75%)	
occurrences (all)	1	2	
Venous thrombosis limb			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Iliac artery occlusion			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Peripheral coldness			
subjects affected / exposed	0 / 268 (0.00%)	2 / 265 (0.75%)	
occurrences (all)	0	2	
Surgical and medical procedures			
Cholecystectomy			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Debridement			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Hernia hiatus repair			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Hip arthroplasty			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Inguinal hernia repair			

subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Medical induction of coma			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Tooth extraction			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Transfusion			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Cyst drainage			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Endodontic procedure			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Vitrectomy			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Muscle pain/ Joint pain			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	54 / 268 (20.15%)	47 / 265 (17.74%)	
occurrences (all)	54	47	
Pyrexia			
subjects affected / exposed	33 / 268 (12.31%)	21 / 265 (7.92%)	
occurrences (all)	33	21	
Asthenia			
subjects affected / exposed	32 / 268 (11.94%)	18 / 265 (6.79%)	
occurrences (all)	32	18	
Oedema peripheral			

subjects affected / exposed	12 / 268 (4.48%)	36 / 265 (13.58%)	
occurrences (all)	12	36	
Influenza like illness			
subjects affected / exposed	10 / 268 (3.73%)	3 / 265 (1.13%)	
occurrences (all)	10	3	
Non-cardiac chest pain			
subjects affected / exposed	9 / 268 (3.36%)	6 / 265 (2.26%)	
occurrences (all)	9	6	
Chills			
subjects affected / exposed	7 / 268 (2.61%)	6 / 265 (2.26%)	
occurrences (all)	7	6	
Chest pain			
subjects affected / exposed	5 / 268 (1.87%)	6 / 265 (2.26%)	
occurrences (all)	5	6	
Face oedema			
subjects affected / exposed	5 / 268 (1.87%)	15 / 265 (5.66%)	
occurrences (all)	5	15	
Pain			
subjects affected / exposed	4 / 268 (1.49%)	8 / 265 (3.02%)	
occurrences (all)	4	8	
Feeling hot			
subjects affected / exposed	3 / 268 (1.12%)	0 / 265 (0.00%)	
occurrences (all)	3	0	
Malaise			
subjects affected / exposed	3 / 268 (1.12%)	4 / 265 (1.51%)	
occurrences (all)	3	4	
Peripheral swelling			
subjects affected / exposed	3 / 268 (1.12%)	4 / 265 (1.51%)	
occurrences (all)	3	4	
Chest discomfort			
subjects affected / exposed	2 / 268 (0.75%)	3 / 265 (1.13%)	
occurrences (all)	2	3	
Mucosal inflammation			
subjects affected / exposed	2 / 268 (0.75%)	1 / 265 (0.38%)	
occurrences (all)	2	1	
Cyst			

subjects affected / exposed	1 / 268 (0.37%)	2 / 265 (0.75%)	
occurrences (all)	1	2	
Discomfort			
subjects affected / exposed	1 / 268 (0.37%)	2 / 265 (0.75%)	
occurrences (all)	1	2	
Early satiety			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Granuloma			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Mucosal dryness			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Thirst			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Xerosis			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Axillary pain			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Feeling abnormal			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Feeling cold			
subjects affected / exposed	0 / 268 (0.00%)	6 / 265 (2.26%)	
occurrences (all)	0	6	
Impaired healing			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Local swelling			
subjects affected / exposed	0 / 268 (0.00%)	2 / 265 (0.75%)	
occurrences (all)	0	2	
Nodule			

subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Polyp			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Swelling			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Ulcer			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	2 / 268 (0.75%)	2 / 265 (0.75%)	
occurrences (all)	2	2	
Food allergy			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Rubber sensitivity			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Seasonal allergy			
subjects affected / exposed	1 / 268 (0.37%)	2 / 265 (0.75%)	
occurrences (all)	1	2	
Drug hypersensitivity			
subjects affected / exposed	0 / 268 (0.00%)	2 / 265 (0.75%)	
occurrences (all)	0	2	
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	2 / 268 (0.75%)	2 / 265 (0.75%)	
occurrences (all)	2	2	
Benign prostatic hyperplasia			
subjects affected / exposed	2 / 268 (0.75%)	2 / 265 (0.75%)	
occurrences (all)	2	2	
Dysmenorrhoea			

subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)	
occurrences (all)	2	0	
Menstruation irregular			
subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)	
occurrences (all)	2	0	
Adnexa uteri cyst			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Breast haematoma			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Endometriosis			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Menopausal symptoms			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Menorrhagia			
subjects affected / exposed	1 / 268 (0.37%)	3 / 265 (1.13%)	
occurrences (all)	1	3	
Prostatitis			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Prostatomegaly			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Testicular mass			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Erectile dysfunction			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Genital haemorrhage			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Menstruation delayed			

subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Pelvic pain			
subjects affected / exposed	0 / 268 (0.00%)	4 / 265 (1.51%)	
occurrences (all)	0	4	
Prostatic dysplasia			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Sexual dysfunction			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Vaginal haemorrhage			
subjects affected / exposed	0 / 268 (0.00%)	3 / 265 (1.13%)	
occurrences (all)	0	3	
Vulvovaginal pruritus			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	22 / 268 (8.21%)	10 / 265 (3.77%)	
occurrences (all)	22	10	
Cough			
subjects affected / exposed	21 / 268 (7.84%)	18 / 265 (6.79%)	
occurrences (all)	21	18	
Oropharyngeal pain			
subjects affected / exposed	13 / 268 (4.85%)	9 / 265 (3.40%)	
occurrences (all)	13	9	
Epistaxis			
subjects affected / exposed	10 / 268 (3.73%)	7 / 265 (2.64%)	
occurrences (all)	10	7	
Pleural effusion			
subjects affected / exposed	4 / 268 (1.49%)	3 / 265 (1.13%)	
occurrences (all)	4	3	
Productive cough			

subjects affected / exposed	4 / 268 (1.49%)	3 / 265 (1.13%)	
occurrences (all)	4	3	
Rhinorrhoea			
subjects affected / exposed	3 / 268 (1.12%)	2 / 265 (0.75%)	
occurrences (all)	3	2	
Asthma			
subjects affected / exposed	2 / 268 (0.75%)	1 / 265 (0.38%)	
occurrences (all)	2	1	
Catarrh			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Dysphonia			
subjects affected / exposed	1 / 268 (0.37%)	4 / 265 (1.51%)	
occurrences (all)	1	4	
Emphysema			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Haemoptysis			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Lung infiltration			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Nasal congestion			
subjects affected / exposed	1 / 268 (0.37%)	2 / 265 (0.75%)	
occurrences (all)	1	2	
Pleuritic pain			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Respiratory tract congestion			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	

Rhinitis allergic			
subjects affected / exposed	1 / 268 (0.37%)	3 / 265 (1.13%)	
occurrences (all)	1	3	
Sinus congestion			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Throat irritation			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Throat tightness			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Tonsillar hypertrophy			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Wheezing			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Dry throat			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Dyspnoea exertional			
subjects affected / exposed	0 / 268 (0.00%)	2 / 265 (0.75%)	
occurrences (all)	0	2	
Hypoxia			
subjects affected / exposed	0 / 268 (0.00%)	3 / 265 (1.13%)	
occurrences (all)	0	3	
Laryngeal inflammation			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Nasal ulcer			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Rales			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	

Respiratory failure			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Sneezing			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Upper-airway cough syndrome			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	15 / 268 (5.60%)	16 / 265 (6.04%)	
occurrences (all)	15	16	
Anxiety			
subjects affected / exposed	10 / 268 (3.73%)	10 / 265 (3.77%)	
occurrences (all)	10	10	
Depression			
subjects affected / exposed	8 / 268 (2.99%)	10 / 265 (3.77%)	
occurrences (all)	8	10	
Libido decreased			
subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)	
occurrences (all)	2	0	
Confusional state			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Delirium			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Depressive symptom			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Mood altered			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Sleep disorder			

subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Irritability			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Mood swings			
subjects affected / exposed	0 / 268 (0.00%)	2 / 265 (0.75%)	
occurrences (all)	0	2	
Nightmare			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	81 / 268 (30.22%)	15 / 265 (5.66%)	
occurrences (all)	81	15	
Aspartate aminotransferase increased			
subjects affected / exposed	60 / 268 (22.39%)	17 / 265 (6.42%)	
occurrences (all)	60	17	
Lipase increased			
subjects affected / exposed	36 / 268 (13.43%)	22 / 265 (8.30%)	
occurrences (all)	36	22	
Platelet count decreased			
subjects affected / exposed	33 / 268 (12.31%)	20 / 265 (7.55%)	
occurrences (all)	33	20	
Blood alkaline phosphatase increased			
subjects affected / exposed	15 / 268 (5.60%)	9 / 265 (3.40%)	
occurrences (all)	15	9	
Blood creatinine increased			
subjects affected / exposed	15 / 268 (5.60%)	17 / 265 (6.42%)	
occurrences (all)	15	17	
Amylase increased			
subjects affected / exposed	14 / 268 (5.22%)	7 / 265 (2.64%)	
occurrences (all)	14	7	
Blood bilirubin increased			

subjects affected / exposed	13 / 268 (4.85%)	6 / 265 (2.26%)	
occurrences (all)	13	6	
Blood creatine phosphokinase increased			
subjects affected / exposed	9 / 268 (3.36%)	19 / 265 (7.17%)	
occurrences (all)	9	19	
Weight decreased			
subjects affected / exposed	8 / 268 (2.99%)	5 / 265 (1.89%)	
occurrences (all)	8	5	
Weight increased			
subjects affected / exposed	8 / 268 (2.99%)	13 / 265 (4.91%)	
occurrences (all)	8	13	
Blood uric acid increased			
subjects affected / exposed	7 / 268 (2.61%)	2 / 265 (0.75%)	
occurrences (all)	7	2	
Transaminases increased			
subjects affected / exposed	7 / 268 (2.61%)	2 / 265 (0.75%)	
occurrences (all)	7	2	
Blood cholesterol increased			
subjects affected / exposed	6 / 268 (2.24%)	1 / 265 (0.38%)	
occurrences (all)	6	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	6 / 268 (2.24%)	4 / 265 (1.51%)	
occurrences (all)	6	4	
White blood cell count decreased			
subjects affected / exposed	6 / 268 (2.24%)	14 / 265 (5.28%)	
occurrences (all)	6	14	
Electrocardiogram QT prolonged			
subjects affected / exposed	4 / 268 (1.49%)	8 / 265 (3.02%)	
occurrences (all)	4	8	
Hepatic enzyme increased			
subjects affected / exposed	4 / 268 (1.49%)	0 / 265 (0.00%)	
occurrences (all)	4	0	
Neutrophil count decreased			

subjects affected / exposed	4 / 268 (1.49%)	11 / 265 (4.15%)		
occurrences (all)	4	11		
Blood urea increased				
subjects affected / exposed	3 / 268 (1.12%)	2 / 265 (0.75%)		
occurrences (all)	3	2		
Haemoglobin decreased				
subjects affected / exposed	3 / 268 (1.12%)	4 / 265 (1.51%)		
occurrences (all)	3	4		
Lymphocyte count decreased				
subjects affected / exposed	3 / 268 (1.12%)	4 / 265 (1.51%)		
occurrences (all)	3	4		
Blood glucose increased				
subjects affected / exposed	2 / 268 (0.75%)	3 / 265 (1.13%)		
occurrences (all)	2	3		
Blood lactate dehydrogenase increased				
subjects affected / exposed	2 / 268 (0.75%)	1 / 265 (0.38%)		
occurrences (all)	2	1		
Liver function test increased				
subjects affected / exposed	2 / 268 (0.75%)	1 / 265 (0.38%)		
occurrences (all)	2	1		
White blood cell count increased				
subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)		
occurrences (all)	2	0		
Activated partial thromboplastin time prolonged				
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)		
occurrences (all)	1	1		
Aspartate aminotransferase				
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)		
occurrences (all)	1	0		
Blood bicarbonate decreased				
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)		
occurrences (all)	1	0		
Blood chloride increased				

subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Blood iron decreased			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Blood phosphorus decreased			
subjects affected / exposed	1 / 268 (0.37%)	3 / 265 (1.13%)	
occurrences (all)	1	3	
Blood urine present			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
C-reactive protein increased			
subjects affected / exposed	1 / 268 (0.37%)	2 / 265 (0.75%)	
occurrences (all)	1	2	
Cardiac murmur			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Electrocardiogram QT interval			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Electrocardiogram ST-T segment abnormal			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Electrocardiogram T wave amplitude decreased			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Eosinophil count decreased			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Occult blood positive			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Platelet count increased			

subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Protein urine			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Serum ferritin decreased			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Basophil count increased			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Blood creatine phosphokinase MB increased			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Blood folate decreased			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Blood magnesium decreased			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Blood potassium decreased			
subjects affected / exposed	0 / 268 (0.00%)	2 / 265 (0.75%)	
occurrences (all)	0	2	
Blood pressure systolic increased			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Blood triglycerides increased			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Body temperature increased			
subjects affected / exposed	0 / 268 (0.00%)	2 / 265 (0.75%)	
occurrences (all)	0	2	
Eosinophil count increased			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	

Globulins decreased				
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)		
occurrences (all)	0	1		
Heart rate increased				
subjects affected / exposed	0 / 268 (0.00%)	4 / 265 (1.51%)		
occurrences (all)	0	4		
Heart rate irregular				
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)		
occurrences (all)	0	1		
International normalised ratio increased				
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)		
occurrences (all)	0	1		
Lipids abnormal				
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)		
occurrences (all)	0	1		
Lymph node palpable				
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)		
occurrences (all)	0	1		
Lymphocyte count increased				
subjects affected / exposed	0 / 268 (0.00%)	2 / 265 (0.75%)		
occurrences (all)	0	2		
Neutrophil count increased				
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)		
occurrences (all)	0	1		
Nicotinamide decreased				
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)		
occurrences (all)	0	1		
Prostatic specific antigen increased				
subjects affected / exposed	0 / 268 (0.00%)	2 / 265 (0.75%)		
occurrences (all)	0	2		
Protein total decreased				
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)		
occurrences (all)	0	1		
Prothrombin time prolonged				

subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Pulmonary arterial pressure increased			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Urinary sediment present			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Bilirubin conjugated increased			
subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)	
occurrences (all)	2	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	7 / 268 (2.61%)	3 / 265 (1.13%)	
occurrences (all)	7	3	
Fall			
subjects affected / exposed	4 / 268 (1.49%)	0 / 265 (0.00%)	
occurrences (all)	4	0	
Arthropod bite			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Hand fracture			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Heavy exposure to ultraviolet light			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Laceration			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Ligament sprain			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Limb injury			

subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Lip injury			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Nerve injury			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Post procedural haematoma			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Procedural pain			
subjects affected / exposed	1 / 268 (0.37%)	3 / 265 (1.13%)	
occurrences (all)	1	3	
Radius fracture			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Rib fracture			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Spinal fracture			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Sunburn			
subjects affected / exposed	1 / 268 (0.37%)	2 / 265 (0.75%)	
occurrences (all)	1	2	
Tooth fracture			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Wound dehiscence			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Animal bite			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Eye injury			

subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Gun shot wound			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Keratorhexis			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Muscle rupture			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Muscle strain			
subjects affected / exposed	0 / 268 (0.00%)	3 / 265 (1.13%)	
occurrences (all)	0	3	
Poisoning			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Skin abrasion			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Wound			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Ankle fracture			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Foot fracture			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Congenital, familial and genetic disorders			
Trisomy 8			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Cytogenetic abnormality			

subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Cardiac disorders			
Palpitations			
subjects affected / exposed	5 / 268 (1.87%)	8 / 265 (3.02%)	
occurrences (all)	5	8	
Sinus bradycardia			
subjects affected / exposed	4 / 268 (1.49%)	0 / 265 (0.00%)	
occurrences (all)	4	0	
Atrial fibrillation			
subjects affected / exposed	3 / 268 (1.12%)	1 / 265 (0.38%)	
occurrences (all)	3	1	
Angina pectoris			
subjects affected / exposed	3 / 268 (1.12%)	1 / 265 (0.38%)	
occurrences (all)	3	1	
Bradycardia			
subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)	
occurrences (all)	2	0	
Myocardial ischaemia			
subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)	
occurrences (all)	2	0	
Diastolic dysfunction			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Extrasystoles			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Pericardial effusion			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Supraventricular extrasystoles			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	

Tachycardia			
subjects affected / exposed	1 / 268 (0.37%)	2 / 265 (0.75%)	
occurrences (all)	1	2	
Ventricular extrasystoles			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Bundle branch block right			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Left ventricular hypertrophy			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Sinus tachycardia			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Tricuspid valve incompetence			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	49 / 268 (18.28%)	35 / 265 (13.21%)	
occurrences (all)	49	35	
Dizziness			
subjects affected / exposed	19 / 268 (7.09%)	19 / 265 (7.17%)	
occurrences (all)	19	19	
Paraesthesia			
subjects affected / exposed	6 / 268 (2.24%)	2 / 265 (0.75%)	
occurrences (all)	6	2	
Lethargy			
subjects affected / exposed	5 / 268 (1.87%)	6 / 265 (2.26%)	
occurrences (all)	5	6	
Memory impairment			
subjects affected / exposed	5 / 268 (1.87%)	2 / 265 (0.75%)	
occurrences (all)	5	2	
Disturbance in attention			

subjects affected / exposed	4 / 268 (1.49%)	1 / 265 (0.38%)	
occurrences (all)	4	1	
Dysgeusia			
subjects affected / exposed	4 / 268 (1.49%)	9 / 265 (3.40%)	
occurrences (all)	4	9	
Hypoaesthesia			
subjects affected / exposed	4 / 268 (1.49%)	2 / 265 (0.75%)	
occurrences (all)	4	2	
Peripheral sensory neuropathy			
subjects affected / exposed	4 / 268 (1.49%)	1 / 265 (0.38%)	
occurrences (all)	4	1	
Dysaesthesia			
subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)	
occurrences (all)	2	0	
Amnesia			
subjects affected / exposed	1 / 268 (0.37%)	2 / 265 (0.75%)	
occurrences (all)	1	2	
Ataxia			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Burning sensation			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Dizziness postural			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Migraine			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Muscle contractions involuntary			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Nerve compression			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Neuralgia			

subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Neuropathy peripheral			
subjects affected / exposed	1 / 268 (0.37%)	3 / 265 (1.13%)	
occurrences (all)	1	3	
Peripheral motor neuropathy			
subjects affected / exposed	1 / 268 (0.37%)	2 / 265 (0.75%)	
occurrences (all)	1	2	
Presyncope			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Sciatica			
subjects affected / exposed	1 / 268 (0.37%)	4 / 265 (1.51%)	
occurrences (all)	1	4	
Somnolence			
subjects affected / exposed	1 / 268 (0.37%)	6 / 265 (2.26%)	
occurrences (all)	1	6	
Syncope			
subjects affected / exposed	1 / 268 (0.37%)	4 / 265 (1.51%)	
occurrences (all)	1	4	
Tremor			
subjects affected / exposed	1 / 268 (0.37%)	2 / 265 (0.75%)	
occurrences (all)	1	2	
Ageusia			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Balance disorder			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Intercostal neuralgia			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Migraine with aura			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Restless legs syndrome			

subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	63 / 268 (23.51%)	32 / 265 (12.08%)	
occurrences (all)	63	32	
Anaemia			
subjects affected / exposed	47 / 268 (17.54%)	52 / 265 (19.62%)	
occurrences (all)	47	52	
Neutropenia			
subjects affected / exposed	26 / 268 (9.70%)	44 / 265 (16.60%)	
occurrences (all)	26	44	
Leukopenia			
subjects affected / exposed	9 / 268 (3.36%)	15 / 265 (5.66%)	
occurrences (all)	9	15	
Lymphopenia			
subjects affected / exposed	8 / 268 (2.99%)	3 / 265 (1.13%)	
occurrences (all)	8	3	
Leukocytosis			
subjects affected / exposed	7 / 268 (2.61%)	4 / 265 (1.51%)	
occurrences (all)	7	4	
Increased tendency to bruise			
subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)	
occurrences (all)	2	0	
Thrombocytosis			
subjects affected / exposed	2 / 268 (0.75%)	5 / 265 (1.89%)	
occurrences (all)	2	5	
Haemorrhagic anaemia			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Lymphadenopathy			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	

Lymphocytosis			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Mastocytosis			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Microcytosis			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Normochromic normocytic anaemia			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Pancytopenia			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Eosinophilia			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Granulocytopenia			
subjects affected / exposed	0 / 268 (0.00%)	2 / 265 (0.75%)	
occurrences (all)	0	2	
Monocytopenia			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Spontaneous haematoma			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	5 / 268 (1.87%)	2 / 265 (0.75%)	
occurrences (all)	5	2	
Tinnitus			
subjects affected / exposed	5 / 268 (1.87%)	1 / 265 (0.38%)	
occurrences (all)	5	1	
Vertigo			

subjects affected / exposed	3 / 268 (1.12%)	5 / 265 (1.89%)	
occurrences (all)	3	5	
Cerumen impaction			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Deafness			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Inner ear inflammation			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Vertigo positional			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Hypoacusis			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Eye disorders			
Eye swelling			
subjects affected / exposed	4 / 268 (1.49%)	10 / 265 (3.77%)	
occurrences (all)	4	10	
Periorbital oedema			
subjects affected / exposed	4 / 268 (1.49%)	37 / 265 (13.96%)	
occurrences (all)	4	37	
Vision blurred			
subjects affected / exposed	4 / 268 (1.49%)	12 / 265 (4.53%)	
occurrences (all)	4	12	
Eye pain			
subjects affected / exposed	3 / 268 (1.12%)	7 / 265 (2.64%)	
occurrences (all)	3	7	
Conjunctival haemorrhage			
subjects affected / exposed	2 / 268 (0.75%)	8 / 265 (3.02%)	
occurrences (all)	2	8	
Eye haemorrhage			
subjects affected / exposed	2 / 268 (0.75%)	2 / 265 (0.75%)	
occurrences (all)	2	2	

Eye pruritus			
subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)	
occurrences (all)	2	0	
Ocular hyperaemia			
subjects affected / exposed	2 / 268 (0.75%)	3 / 265 (1.13%)	
occurrences (all)	2	3	
Photophobia			
subjects affected / exposed	2 / 268 (0.75%)	1 / 265 (0.38%)	
occurrences (all)	2	1	
Retinal haemorrhage			
subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)	
occurrences (all)	2	0	
Vitreous floaters			
subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)	
occurrences (all)	2	0	
Cataract			
subjects affected / exposed	1 / 268 (0.37%)	2 / 265 (0.75%)	
occurrences (all)	1	2	
Conjunctivitis allergic			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Eye irritation			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Eyelid oedema			
subjects affected / exposed	1 / 268 (0.37%)	25 / 265 (9.43%)	
occurrences (all)	1	25	
Eyelid ptosis			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Lacrimal disorder			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Ocular discomfort			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	

Retinal disorder			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Uveitis			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Visual acuity reduced			
subjects affected / exposed	1 / 268 (0.37%)	2 / 265 (0.75%)	
occurrences (all)	1	2	
Visual impairment			
subjects affected / exposed	1 / 268 (0.37%)	2 / 265 (0.75%)	
occurrences (all)	1	2	
Vitreous detachment			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Conjunctival hyperaemia			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Diabetic retinopathy			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Diplopia			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Dry eye			
subjects affected / exposed	0 / 268 (0.00%)	11 / 265 (4.15%)	
occurrences (all)	0	11	
Eye discharge			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Eye oedema			
subjects affected / exposed	0 / 268 (0.00%)	4 / 265 (1.51%)	
occurrences (all)	0	4	
Eyelid pain			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	

Glaucoma			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Hypermetropia			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Lacrimation increased			
subjects affected / exposed	0 / 268 (0.00%)	16 / 265 (6.04%)	
occurrences (all)	0	16	
Ocular toxicity			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Orbital oedema			
subjects affected / exposed	0 / 268 (0.00%)	6 / 265 (2.26%)	
occurrences (all)	0	6	
Retinal detachment			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Retinopathy haemorrhagic			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Scleral haemorrhage			
subjects affected / exposed	0 / 268 (0.00%)	2 / 265 (0.75%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	189 / 268 (70.52%)	88 / 265 (33.21%)	
occurrences (all)	189	88	
Nausea			
subjects affected / exposed	94 / 268 (35.07%)	102 / 265 (38.49%)	
occurrences (all)	94	102	
Vomiting			
subjects affected / exposed	48 / 268 (17.91%)	43 / 265 (16.23%)	
occurrences (all)	48	43	
Abdominal pain			

subjects affected / exposed	47 / 268 (17.54%)	19 / 265 (7.17%)	
occurrences (all)	47	19	
Constipation			
subjects affected / exposed	26 / 268 (9.70%)	14 / 265 (5.28%)	
occurrences (all)	26	14	
Abdominal pain upper			
subjects affected / exposed	20 / 268 (7.46%)	19 / 265 (7.17%)	
occurrences (all)	20	19	
Dyspepsia			
subjects affected / exposed	18 / 268 (6.72%)	19 / 265 (7.17%)	
occurrences (all)	18	19	
Haemorrhoids			
subjects affected / exposed	10 / 268 (3.73%)	4 / 265 (1.51%)	
occurrences (all)	10	4	
Abdominal distension			
subjects affected / exposed	8 / 268 (2.99%)	3 / 265 (1.13%)	
occurrences (all)	8	3	
Toothache			
subjects affected / exposed	6 / 268 (2.24%)	3 / 265 (1.13%)	
occurrences (all)	6	3	
Flatulence			
subjects affected / exposed	5 / 268 (1.87%)	4 / 265 (1.51%)	
occurrences (all)	5	4	
Gastrooesophageal reflux disease			
subjects affected / exposed	5 / 268 (1.87%)	8 / 265 (3.02%)	
occurrences (all)	5	8	
Abdominal discomfort			
subjects affected / exposed	4 / 268 (1.49%)	6 / 265 (2.26%)	
occurrences (all)	4	6	
Dry mouth			
subjects affected / exposed	4 / 268 (1.49%)	7 / 265 (2.64%)	
occurrences (all)	4	7	
Mouth ulceration			
subjects affected / exposed	4 / 268 (1.49%)	3 / 265 (1.13%)	
occurrences (all)	4	3	
Haematochezia			

subjects affected / exposed	3 / 268 (1.12%)	0 / 265 (0.00%)	
occurrences (all)	3	0	
Epigastric discomfort			
subjects affected / exposed	2 / 268 (0.75%)	2 / 265 (0.75%)	
occurrences (all)	2	2	
Gastritis			
subjects affected / exposed	2 / 268 (0.75%)	2 / 265 (0.75%)	
occurrences (all)	2	2	
Paraesthesia oral			
subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)	
occurrences (all)	2	0	
Proctalgia			
subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)	
occurrences (all)	2	0	
Rectal haemorrhage			
subjects affected / exposed	2 / 268 (0.75%)	3 / 265 (1.13%)	
occurrences (all)	2	3	
Abdominal hernia			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Anal fissure			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Anal incontinence			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Aphthous ulcer			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Colitis			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Colitis ulcerative			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Dental caries			

subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Dental discomfort			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Dysphagia			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Faeces discoloured			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Food poisoning			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Gastric disorder			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Gastric ulcer			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorder			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Gastrointestinal necrosis			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal pain			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Duodenitis			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Gingival erythema			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Glossodynia			

subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Ileus			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Lip pain			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Mouth haemorrhage			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Oral pain			
subjects affected / exposed	1 / 268 (0.37%)	2 / 265 (0.75%)	
occurrences (all)	1	2	
Pancreatitis			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Peristalsis visible			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Proctitis			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Rectal tenesmus			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Retching			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Salivary gland enlargement			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Stomatitis			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Tongue discolouration			

subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Tongue disorder			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Abdominal pain lower			
subjects affected / exposed	0 / 268 (0.00%)	2 / 265 (0.75%)	
occurrences (all)	0	2	
Anal haemorrhage			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Ascites			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Chronic gastritis			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Eructation			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Faeces soft			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Frequent bowel movements			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Gingival bleeding			
subjects affected / exposed	0 / 268 (0.00%)	2 / 265 (0.75%)	
occurrences (all)	0	2	
Gingival pain			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Haematemesis			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Inguinal hernia			

subjects affected / exposed	0 / 268 (0.00%)	2 / 265 (0.75%)	
occurrences (all)	0	2	
Large intestine polyp			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Lip dry			
subjects affected / exposed	0 / 268 (0.00%)	2 / 265 (0.75%)	
occurrences (all)	0	2	
Lip swelling			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Oesophagitis			
subjects affected / exposed	0 / 268 (0.00%)	2 / 265 (0.75%)	
occurrences (all)	0	2	
Salivary hypersecretion			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Tongue dry			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Tooth disorder			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Umbilical hernia			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	4 / 268 (1.49%)	0 / 265 (0.00%)	
occurrences (all)	4	0	
Hyperbilirubinaemia			
subjects affected / exposed	4 / 268 (1.49%)	1 / 265 (0.38%)	
occurrences (all)	4	1	
Drug-induced liver injury			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	

Hepatitis			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Hepatitis toxic			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Hepatocellular injury			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Jaundice			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Cholestasis			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Hepatic steatosis			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Liver disorder			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	53 / 268 (19.78%)	36 / 265 (13.58%)	
occurrences (all)	53	36	
Pruritus			
subjects affected / exposed	25 / 268 (9.33%)	7 / 265 (2.64%)	
occurrences (all)	25	7	
Rash maculo-papular			
subjects affected / exposed	14 / 268 (5.22%)	14 / 265 (5.28%)	
occurrences (all)	14	14	
Alopecia			
subjects affected / exposed	12 / 268 (4.48%)	12 / 265 (4.53%)	
occurrences (all)	12	12	
Dry skin			

subjects affected / exposed	12 / 268 (4.48%)	10 / 265 (3.77%)	
occurrences (all)	12	10	
Erythema			
subjects affected / exposed	9 / 268 (3.36%)	4 / 265 (1.51%)	
occurrences (all)	9	4	
Rash pruritic			
subjects affected / exposed	7 / 268 (2.61%)	0 / 265 (0.00%)	
occurrences (all)	7	0	
Acne			
subjects affected / exposed	6 / 268 (2.24%)	1 / 265 (0.38%)	
occurrences (all)	6	1	
Dermatitis acneiform			
subjects affected / exposed	5 / 268 (1.87%)	1 / 265 (0.38%)	
occurrences (all)	5	1	
Urticaria			
subjects affected / exposed	5 / 268 (1.87%)	3 / 265 (1.13%)	
occurrences (all)	5	3	
Eczema			
subjects affected / exposed	4 / 268 (1.49%)	6 / 265 (2.26%)	
occurrences (all)	4	6	
Hyperhidrosis			
subjects affected / exposed	4 / 268 (1.49%)	6 / 265 (2.26%)	
occurrences (all)	4	6	
Rash papular			
subjects affected / exposed	4 / 268 (1.49%)	0 / 265 (0.00%)	
occurrences (all)	4	0	
Dermatitis			
subjects affected / exposed	3 / 268 (1.12%)	1 / 265 (0.38%)	
occurrences (all)	3	1	
Nail discolouration			
subjects affected / exposed	3 / 268 (1.12%)	1 / 265 (0.38%)	
occurrences (all)	3	1	
Rash erythematous			
subjects affected / exposed	3 / 268 (1.12%)	2 / 265 (0.75%)	
occurrences (all)	3	2	
Skin lesion			

subjects affected / exposed	3 / 268 (1.12%)	1 / 265 (0.38%)	
occurrences (all)	3	1	
Actinic keratosis			
subjects affected / exposed	2 / 268 (0.75%)	1 / 265 (0.38%)	
occurrences (all)	2	1	
Dermatitis allergic			
subjects affected / exposed	2 / 268 (0.75%)	4 / 265 (1.51%)	
occurrences (all)	2	4	
Dyshidrotic eczema			
subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)	
occurrences (all)	2	0	
Miliaria			
subjects affected / exposed	2 / 268 (0.75%)	1 / 265 (0.38%)	
occurrences (all)	2	1	
Pruritus generalised			
subjects affected / exposed	2 / 268 (0.75%)	1 / 265 (0.38%)	
occurrences (all)	2	1	
Skin discolouration			
subjects affected / exposed	2 / 268 (0.75%)	1 / 265 (0.38%)	
occurrences (all)	2	1	
Skin exfoliation			
subjects affected / exposed	2 / 268 (0.75%)	1 / 265 (0.38%)	
occurrences (all)	2	1	
Angioedema			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Blister			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Dermal cyst			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Dermatitis exfoliative			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Drug reaction with eosinophilia and			

systemic symptoms			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Ecchymosis			
subjects affected / exposed	1 / 268 (0.37%)	2 / 265 (0.75%)	
occurrences (all)	1	2	
Generalised erythema			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Hyperkeratosis			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Hypertrichosis			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Ingrowing nail			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Mucocutaneous ulceration			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Nail disorder			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Nail dystrophy			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Perivascular dermatitis			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Photosensitivity reaction			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Purpura			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	

Rash generalised			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Sebaceous glands overactivity			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Skin fragility			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Skin mass			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Skin ulcer			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Swelling face			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Vitiligo			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Dandruff			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Diffuse alopecia			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Eczema asteatotic			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Erythema multiforme			
subjects affected / exposed	0 / 268 (0.00%)	2 / 265 (0.75%)	
occurrences (all)	0	2	
Erythema nodosum			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	

Petechiae			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Psoriasis			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Rash macular			
subjects affected / exposed	0 / 268 (0.00%)	2 / 265 (0.75%)	
occurrences (all)	0	2	
Skin hypopigmentation			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Stasis dermatitis			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Toxic skin eruption			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Papule			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Night sweats			
subjects affected / exposed	5 / 268 (1.87%)	9 / 265 (3.40%)	
occurrences (all)	5	9	
Renal and urinary disorders			
Nocturia			
subjects affected / exposed	3 / 268 (1.12%)	1 / 265 (0.38%)	
occurrences (all)	3	1	
Acute kidney injury			
subjects affected / exposed	2 / 268 (0.75%)	1 / 265 (0.38%)	
occurrences (all)	2	1	
Dysuria			
subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)	
occurrences (all)	2	0	
Haematuria			

subjects affected / exposed	2 / 268 (0.75%)	6 / 265 (2.26%)	
occurrences (all)	2	6	
Pollakiuria			
subjects affected / exposed	2 / 268 (0.75%)	3 / 265 (1.13%)	
occurrences (all)	2	3	
Renal impairment			
subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)	
occurrences (all)	2	0	
Urethritis noninfective			
subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)	
occurrences (all)	2	0	
Bladder diverticulum			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Calculus urinary			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Chromaturia			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Nephritis			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Nephrocalcinosis			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Nephroptosis			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Oliguria			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Polyuria			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Proteinuria			

subjects affected / exposed	1 / 268 (0.37%)	3 / 265 (1.13%)	
occurrences (all)	1	3	
Renal cyst			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Urinary tract pain			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Urine abnormality			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Acute prerenal failure			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Calculus urethral			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Nephropathy			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Nephrotic syndrome			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Renal injury			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Urinary retention			
subjects affected / exposed	0 / 268 (0.00%)	2 / 265 (0.75%)	
occurrences (all)	0	2	
Urinary tract inflammation			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)	
occurrences (all)	2	0	

Hyperparathyroidism			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Thyroid disorder			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Thyroid mass			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	32 / 268 (11.94%)	35 / 265 (13.21%)	
occurrences (all)	32	35	
Back pain			
subjects affected / exposed	22 / 268 (8.21%)	19 / 265 (7.17%)	
occurrences (all)	22	19	
Pain in extremity			
subjects affected / exposed	12 / 268 (4.48%)	34 / 265 (12.83%)	
occurrences (all)	12	34	
Myalgia			
subjects affected / exposed	8 / 268 (2.99%)	41 / 265 (15.47%)	
occurrences (all)	8	41	
Bone pain			
subjects affected / exposed	7 / 268 (2.61%)	18 / 265 (6.79%)	
occurrences (all)	7	18	
Musculoskeletal pain			
subjects affected / exposed	7 / 268 (2.61%)	8 / 265 (3.02%)	
occurrences (all)	7	8	
Muscle spasms			
subjects affected / exposed	6 / 268 (2.24%)	70 / 265 (26.42%)	
occurrences (all)	6	70	
Neck pain			
subjects affected / exposed	6 / 268 (2.24%)	4 / 265 (1.51%)	
occurrences (all)	6	4	
Musculoskeletal chest pain			

subjects affected / exposed	4 / 268 (1.49%)	0 / 265 (0.00%)	
occurrences (all)	4	0	
Flank pain			
subjects affected / exposed	3 / 268 (1.12%)	2 / 265 (0.75%)	
occurrences (all)	3	2	
Muscular weakness			
subjects affected / exposed	2 / 268 (0.75%)	1 / 265 (0.38%)	
occurrences (all)	2	1	
Osteoarthritis			
subjects affected / exposed	2 / 268 (0.75%)	3 / 265 (1.13%)	
occurrences (all)	2	3	
Spinal pain			
subjects affected / exposed	2 / 268 (0.75%)	1 / 265 (0.38%)	
occurrences (all)	2	1	
Synovial cyst			
subjects affected / exposed	2 / 268 (0.75%)	1 / 265 (0.38%)	
occurrences (all)	2	1	
Intervertebral disc disorder			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Joint effusion			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Joint instability			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Limb discomfort			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Muscle fatigue			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal discomfort			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Myopathy			

subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Osteoporosis			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Rheumatoid arthritis			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Spinal column stenosis			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Spinal osteoarthritis			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Arthritis			
subjects affected / exposed	0 / 268 (0.00%)	2 / 265 (0.75%)	
occurrences (all)	0	2	
Dupuytren's contracture			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Foot deformity			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Growing pains			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Joint laxity			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Joint stiffness			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Muscle contracture			

subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Muscle twitching			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Musculoskeletal stiffness			
subjects affected / exposed	0 / 268 (0.00%)	2 / 265 (0.75%)	
occurrences (all)	0	2	
Osteochondrosis			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Pain in jaw			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Rhabdomyolysis			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Temporomandibular joint syndrome			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Tenosynovitis			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Torticollis			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Trismus			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Tendonitis			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	26 / 268 (9.70%)	24 / 265 (9.06%)	
occurrences (all)	26	24	

Upper respiratory tract infection			
subjects affected / exposed	23 / 268 (8.58%)	27 / 265 (10.19%)	
occurrences (all)	23	27	
Urinary tract infection			
subjects affected / exposed	17 / 268 (6.34%)	9 / 265 (3.40%)	
occurrences (all)	17	9	
Bronchitis			
subjects affected / exposed	8 / 268 (2.99%)	4 / 265 (1.51%)	
occurrences (all)	8	4	
Influenza			
subjects affected / exposed	7 / 268 (2.61%)	8 / 265 (3.02%)	
occurrences (all)	7	8	
Sinusitis			
subjects affected / exposed	7 / 268 (2.61%)	5 / 265 (1.89%)	
occurrences (all)	7	5	
Gastroenteritis			
subjects affected / exposed	6 / 268 (2.24%)	5 / 265 (1.89%)	
occurrences (all)	6	5	
Folliculitis			
subjects affected / exposed	5 / 268 (1.87%)	2 / 265 (0.75%)	
occurrences (all)	5	2	
Pharyngitis			
subjects affected / exposed	5 / 268 (1.87%)	6 / 265 (2.26%)	
occurrences (all)	5	6	
Lower respiratory tract infection			
subjects affected / exposed	4 / 268 (1.49%)	1 / 265 (0.38%)	
occurrences (all)	4	1	
Respiratory tract infection			
subjects affected / exposed	4 / 268 (1.49%)	2 / 265 (0.75%)	
occurrences (all)	4	2	
Cellulitis			
subjects affected / exposed	3 / 268 (1.12%)	0 / 265 (0.00%)	
occurrences (all)	3	0	
Conjunctivitis			
subjects affected / exposed	3 / 268 (1.12%)	6 / 265 (2.26%)	
occurrences (all)	3	6	

Otitis media			
subjects affected / exposed	3 / 268 (1.12%)	2 / 265 (0.75%)	
occurrences (all)	3	2	
Pneumonia			
subjects affected / exposed	3 / 268 (1.12%)	1 / 265 (0.38%)	
occurrences (all)	3	1	
Rhinitis			
subjects affected / exposed	3 / 268 (1.12%)	5 / 265 (1.89%)	
occurrences (all)	3	5	
Viral infection			
subjects affected / exposed	3 / 268 (1.12%)	7 / 265 (2.64%)	
occurrences (all)	3	7	
Cystitis			
subjects affected / exposed	2 / 268 (0.75%)	1 / 265 (0.38%)	
occurrences (all)	2	1	
Ear infection			
subjects affected / exposed	2 / 268 (0.75%)	1 / 265 (0.38%)	
occurrences (all)	2	1	
Eye infection			
subjects affected / exposed	2 / 268 (0.75%)	2 / 265 (0.75%)	
occurrences (all)	2	2	
Gastroenteritis viral			
subjects affected / exposed	2 / 268 (0.75%)	2 / 265 (0.75%)	
occurrences (all)	2	2	
Oral herpes			
subjects affected / exposed	2 / 268 (0.75%)	2 / 265 (0.75%)	
occurrences (all)	2	2	
Candida infection			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Chlamydial infection			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Ear lobe infection			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	

Erysipelas			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal infection			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Hepatitis B			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Herpes zoster			
subjects affected / exposed	1 / 268 (0.37%)	3 / 265 (1.13%)	
occurrences (all)	1	3	
Infection			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Lice infestation			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Lip infection			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Lymphadenitis bacterial			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Oral candidiasis			
subjects affected / exposed	1 / 268 (0.37%)	2 / 265 (0.75%)	
occurrences (all)	1	2	
Paronychia			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Pulpitis dental			
subjects affected / exposed	1 / 268 (0.37%)	2 / 265 (0.75%)	
occurrences (all)	1	2	
Respiratory tract infection viral			
subjects affected / exposed	1 / 268 (0.37%)	2 / 265 (0.75%)	
occurrences (all)	1	2	

Skin infection			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Staphylococcal infection			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Tooth abscess			
subjects affected / exposed	1 / 268 (0.37%)	2 / 265 (0.75%)	
occurrences (all)	1	2	
Tooth infection			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Adenovirus infection			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Carbuncle			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Diarrhoea infectious			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Enterocolitis infectious			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Fungal skin infection			
subjects affected / exposed	0 / 268 (0.00%)	3 / 265 (1.13%)	
occurrences (all)	0	3	
Genital abscess			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Gingivitis			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	

Helicobacter infection			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Herpes simplex			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Hordeolum			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Labyrinthitis			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Localised infection			
subjects affected / exposed	0 / 268 (0.00%)	4 / 265 (1.51%)	
occurrences (all)	0	4	
Lung infection			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Meningococcal infection			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Nail infection			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Onychomycosis			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Parainfluenzae virus infection			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Pharyngitis streptococcal			
subjects affected / exposed	0 / 268 (0.00%)	2 / 265 (0.75%)	
occurrences (all)	0	2	
Pneumonia bacterial			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	

Pyelonephritis chronic			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Tonsillitis bacterial			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Vaginal infection			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	26 / 268 (9.70%)	16 / 265 (6.04%)	
occurrences (all)	26	16	
Hyperuricaemia			
subjects affected / exposed	5 / 268 (1.87%)	4 / 265 (1.51%)	
occurrences (all)	5	4	
Hypophosphataemia			
subjects affected / exposed	5 / 268 (1.87%)	14 / 265 (5.28%)	
occurrences (all)	5	14	
Gout			
subjects affected / exposed	4 / 268 (1.49%)	2 / 265 (0.75%)	
occurrences (all)	4	2	
Hyperglycaemia			
subjects affected / exposed	4 / 268 (1.49%)	8 / 265 (3.02%)	
occurrences (all)	4	8	
Hyperkalaemia			
subjects affected / exposed	4 / 268 (1.49%)	4 / 265 (1.51%)	
occurrences (all)	4	4	
Hypertriglyceridaemia			
subjects affected / exposed	4 / 268 (1.49%)	2 / 265 (0.75%)	
occurrences (all)	4	2	
Hypokalaemia			
subjects affected / exposed	4 / 268 (1.49%)	18 / 265 (6.79%)	
occurrences (all)	4	18	
Hypercholesterolaemia			

subjects affected / exposed	3 / 268 (1.12%)	0 / 265 (0.00%)	
occurrences (all)	3	0	
Hypocalcaemia			
subjects affected / exposed	3 / 268 (1.12%)	8 / 265 (3.02%)	
occurrences (all)	3	8	
Hypomagnesaemia			
subjects affected / exposed	3 / 268 (1.12%)	2 / 265 (0.75%)	
occurrences (all)	3	2	
Vitamin D deficiency			
subjects affected / exposed	3 / 268 (1.12%)	0 / 265 (0.00%)	
occurrences (all)	3	0	
Dehydration			
subjects affected / exposed	2 / 268 (0.75%)	2 / 265 (0.75%)	
occurrences (all)	2	2	
Hyperchloraemia			
subjects affected / exposed	2 / 268 (0.75%)	0 / 265 (0.00%)	
occurrences (all)	2	0	
Hyponatraemia			
subjects affected / exposed	2 / 268 (0.75%)	2 / 265 (0.75%)	
occurrences (all)	2	2	
Diabetes mellitus			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Folate deficiency			
subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Hypoalbuminaemia			
subjects affected / exposed	1 / 268 (0.37%)	4 / 265 (1.51%)	
occurrences (all)	1	4	
Hypoglycaemia			
subjects affected / exposed	1 / 268 (0.37%)	5 / 265 (1.89%)	
occurrences (all)	1	5	
Iron deficiency			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Obesity			

subjects affected / exposed	1 / 268 (0.37%)	0 / 265 (0.00%)	
occurrences (all)	1	0	
Vitamin B12 deficiency			
subjects affected / exposed	1 / 268 (0.37%)	1 / 265 (0.38%)	
occurrences (all)	1	1	
Electrolyte imbalance			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Fluid retention			
subjects affected / exposed	0 / 268 (0.00%)	8 / 265 (3.02%)	
occurrences (all)	0	8	
Hypermagnesaemia			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Increased appetite			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	
Metabolic syndrome			
subjects affected / exposed	0 / 268 (0.00%)	1 / 265 (0.38%)	
occurrences (all)	0	1	

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 (eg, schedule of events, pre-randomization Sokal score assessment), timing of assessments, timing for collection of adverse events/reporting, study drug dosing requirements, compliance recording, statitstical analysis (primary and secondary efficacy analysis), pharmacokinetic analysis, and administrative information.
09 September 2016	Updated information for sample size, study populations, efficacy analysis, interim analyses, time to response description, 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