Clinical trial results:
A Phase III multi-center, open-label, randomized study of imatinib versus nilotinib in adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase (CML-CP)

Summary

EudraCT number	2007-000208-34
Trial protocol	SE CZ BE IT ES SK AT FR NL FI DK DE PT HU GB
Global end of trial date	21 August 2019

Results information

Result version number	v1 (current)
This version publication date	02 September 2020
First version publication date	02 September 2020

Trial information

Trial identification

Sponsor protocol code	CAMN107A2303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00471497
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma, AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111, novartis.email@novartis.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 August 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To compare the efficacy (major molecular response (MMR) rate at 12 months) of nilotinib at 400 mg bid with that of imatinib 400 mg qd in newly diagnosed, previously untreated Ph+ CML-CP patients.
- To compare the efficacy (MMR rate at 12 months) of nilotinib at 300 mg bid with that of imatinib 400 mg qd in newly diagnosed, previously untreated Ph+ CML-CP patients.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the
clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 July 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 6
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Brazil: 67
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Colombia: 3
Country: Number of subjects enrolled	Czech Republic: 5
Country: Number of subjects enrolled	Denmark: 5
Country: Number of subjects enrolled	Egypt: 8
Country: Number of subjects enrolled	Finland: 11
Country: Number of subjects enrolled	France: 86
Country: Number of subjects enrolled	Germany: 51

Country: Number of subjects enrolled	United Kingdom: 32
Country: Number of subjects enrolled	Hong Kong: 4
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Italy: 63
Country: Number of subjects enrolled	Japan: 77
Country: Number of subjects enrolled	Korea, Republic of: 58
Country: Number of subjects enrolled	Malaysia: 1
Country: Number of subjects enrolled	Mexico: 6
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Norway: 10
Country: Number of subjects enrolled	Poland: 42
Country: Number of subjects enrolled	Russian Federation: 13
Country: Number of subjects enrolled	Singapore: 18
Country: Number of subjects enrolled	Slovakia: 8
Country: Number of subjects enrolled	South Africa: 14
Country: Number of subjects enrolled	Spain: 40
Country: Number of subjects enrolled	Sweden: 27
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	Taiwan: 11
Country: Number of subjects enrolled	Thailand: 39
Country: Number of subjects enrolled	Turkey: 13
Country: Number of subjects enrolled	United States: 94
Country: Number of subjects enrolled	Venezuela, Bolivarian Republic of: 7
Worldwide total number of subjects	846
EEA total number of subjects	397

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)	748
From 65 to 84 years	97
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study over-enrolled, and 846 patients (283 in the imatinib 400 mg arm, 282 in the nilotinib 300 mg arm and 281 in the nilotinib 400 mg arm) were randomized. DP = disease progression, SOR/TF = Suboptimal response or treatment failure

Pre-assignment

Screening details:

Randomization was planned for a total of 771 patients.

Period 1

Period 1 title	Core Treatment Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Imatinib 400 mg QD

Arm description:

Patients randomized to this arm were to receive 400 mg imatinib once a day (QD). If the patient required a dose escalation from 400 mg/day, the patient was to receive 400 mg imatinib twice daily orally. Imatinib was taken with food and a large glass of water. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits during the study. In cases of vomiting doses were not to be repeated

Arm type	Active comparator
Investigational medicinal product name	Imatinib
Investigational medicinal product code	STI571
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Imatinib was supplied as 100 mg and/or 400 mg tablets. Patients imatinib 400 mg qd orally. If the patient required a dose escalation from 400 mg/day, the patient was to receive 400 mg bid orally. Imatinib was to be taken with food and a large glass of water.

Arm title	Nilotinb 300 mg BID

Arm description:

Patients who were randomized to this arm were to receive nilotinib 300 mg twice a day (BID) by mouth each morning and evening approximately 12 hours apart. If the morning or evening dose was delayed for more than 4 hours, the patient was to skip this dose and resume dosing with the next dose as per the original schedule in order to prevent overdosing. No imatinib washout period was necessary prior to administration of nilotinib. Nilotinib was not to be taken with food. No food was to be consumed for at least 2 hours before the dose was taken and no additional oral intake other than water was to be consumed for at least one hour after the dose was taken. Patients were instructed to swallow capsules whole with a full 8 ounce glass of water, and not to chew them. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits. Vomited doses were not to be repeated.

Arm type	Experimental
Investigational medicinal product name	Nilotinib
Investigational medicinal product code	AMN107
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Nilotinib was supplied as 50 mg, 150 mg, or 200 mg hard gelatin capsules and was dosed on a flat scale and not dosed by body weight. Patients were randomized to receive nilotinib 300 mg bid by mouth each morning and evening approximately 12 hours apart.

Arm title	Nilotinib 400 mg BID

Arm description:

Patients who were randomized to this arm were to receive nilotinib 400 mg twice a day (BID) by mouth each morning and evening approximately 12 hours apart. If the morning or evening dose was delayed for more than 4 hours, the patient was to skip this dose and resume dosing with the next dose as per the original schedule in order to prevent overdosing. No imatinib washout period was necessary prior to administration of nilotinib. Nilotinib was not to be taken with food. No food was to be consumed for at least 2 hours before the dose was taken and no additional oral intake other than water was to be consumed for at least one hour after the dose was taken. Patients were instructed to swallow capsules whole with a full 8 ounce glass of water, and not to chew them. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits. Vomited doses were not to be repeated.

Arm type	Experimental
Investigational medicinal product name	Nilotinib
Investigational medicinal product code	AMN107
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Nilotinib was supplied as 50 mg, 150 mg, or 200 mg hard gelatin capsules and was dosed on a flat scale and not dosed by body weight. Patients were randomized to receive nilotinib 400 mg bid by mouth each morning and evening approximately 12 hours apart.

Number of subjects in period 1	Imatinib 400 mg QD	Nilotinb 300 mg BID	Nilotinib 400 mg BID
Started	283	282	281
Safety Analysis Set	280	279	277
Discon. Core/Did not enter Ext.	235	256	278
Discontinued Core/Entered Ext.	48 [1]	26 [2]	3 [3]
Completed	99	107	99
Not completed	184	175	182
Adverse event, serious fatal	3	9	3
Sub optimal response or treat. failure	19	11	13
Abnormal Test Procedures	1	-	1
Abnormal Laboratory Values	3	9	9
Administrative problems	14	14	12
Disc. Core/Entered Ext.- SOR/TF	46	26	3
Disease Progression	10	2	4
Consent withdrawn by subject	31	29	34
Disc. Core/Entered Ext. - DP progression	2	-	-
Adverse event, non-fatal	43	53	89

Condition no longer requires study drug	-	1	-
Lost to follow-up	6	6	3
Protocol deviation	6	15	11

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Extension period was optional a and so not all who completed Core moved into Extension period.
[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Extension period was optional a and so not all who completed Core moved into Extension period.
[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Extension period was optional a and so not all who completed Core moved into Extension period.

Period 2

Period 2 title	Extension Phase
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Imatinib 400 mg QD (Treatment taken during core phase)

Arm description:

Patients randomized to this arm were to receive 400 mg imatinib once a day (QD). If the patient required a dose escalation from 400 mg/day, the patient was to receive 400 mg imatinib twice daily orally. Imatinib was taken with food and a large glass of water. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits during the study. In cases of vomiting doses were not to be repeated

Arm type	Active comparator
Investigational medicinal product name	Imatinib
Investigational medicinal product code	STI571
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Imatinib was supplied as 100 mg and/or 400 mg tablets. Patients imatinib 400 mg qd orally. If the patient required a dose escalation from 400 mg/day, the patient was to receive 400 mg bid orally. Imatinib was to be taken with food and a large glass of water.

Arm title	Nilotinb 300 mg BID (Treatment taken during core phase)

Arm description:

Patients who were randomized to this arm were to receive nilotinib 300 mg twice a day (BID) by mouth each morning and evening approximately 12 hours apart. If the morning or evening dose was delayed for more than 4 hours, the patient was to skip this dose and resume dosing with the next dose as per the original schedule in order to prevent overdosing. No imatinib washout period was necessary prior to administration of nilotinib. Nilotinib was not to be taken with food. No food was to be consumed for at least 2 hours before the dose was taken and no additional oral intake other than water was to be consumed for at least one hour after the dose was taken. Patients were instructed to swallow capsules whole with a full 8 ounce glass of water, and not to chew them. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits. Vomited

doses were not to be repeated.

Arm type	Experimental
Investigational medicinal product name	Nilotinib
Investigational medicinal product code	AMN107
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Nilotinib was supplied as 50 mg, 150 mg, or 200 mg hard gelatin capsules and was dosed on a flat scale and not dosed by body weight. Patients were randomized to receive nilotinib 300 mg bid by mouth each morning and evening approximately 12 hours apart.

Arm title	Nilotinib 400 mg BID (Treatment taken during core phase)

Arm description:

Patients who were randomized to this arm were to receive nilotinib 400 mg twice a day (BID) by mouth each morning and evening approximately 12 hours apart. If the morning or evening dose was delayed for more than 4 hours, the patient was to skip this dose and resume dosing with the next dose as per the original schedule in order to prevent overdosing. No imatinib washout period was necessary prior to administration of nilotinib. Nilotinib was not to be taken with food. No food was to be consumed for at least 2 hours before the dose was taken and no additional oral intake other than water was to be consumed for at least one hour after the dose was taken. Patients were instructed to swallow capsules whole with a full 8 ounce glass of water, and not to chew them. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits. Vomited doses were not to be repeated.

Arm type	Experimental
Investigational medicinal product name	Nilotinib
Investigational medicinal product code	AMN107
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Nilotinib was supplied as 50 mg, 150 mg, or 200 mg hard gelatin capsules and was dosed on a flat scale and not dosed by body weight. Patients were randomized to receive nilotinib 400 mg bid by mouth each morning and evening approximately 12 hours apart.

Number of subjects in period 2[4]	Imatinib 400 mg QD (Treatment taken during core phase)	Nilotinb 300 mg BID (Treatment taken during core phase)	Nilotinib 400 mg BID (Treatment taken during core phase)
Started	48	26	3
Completed	21	12	2
Not completed	27	14	1
Adverse event, serious fatal	1	-	-
Consent withdrawn by subject	3	1	-
Adverse event, non-fatal	9	5	1
Unsatisfactory therapeutic effect	8	6	-
Lost to follow-up	2	-	-
Disease Progression	2	-	-
Protocol deviation	2	2	-

Notes:

[4] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Extension period was optional a and so not all who completed Core moved into Extension period.

Baseline characteristics

Reporting groups	
Reporting group title	Imatinib 400 mg QD

Reporting group description:

Patients randomized to this arm were to receive 400 mg imatinib once a day (QD). If the patient required a dose escalation from 400 mg/day, the patient was to receive 400 mg imatinib twice daily orally. Imatinib was taken with food and a large glass of water. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits during the study. In cases of vomiting doses were not to be repeated

Reporting group title	Nilotinb 300 mg BID

Reporting group description:

Patients who were randomized to this arm were to receive nilotinib 300 mg twice a day (BID) by mouth each morning and evening approximately 12 hours apart. If the morning or evening dose was delayed for more than 4 hours, the patient was to skip this dose and resume dosing with the next dose as per the original schedule in order to prevent overdosing. No imatinib washout period was necessary prior to administration of nilotinib. Nilotinib was not to be taken with food. No food was to be consumed for at least 2 hours before the dose was taken and no additional oral intake other than water was to be consumed for at least one hour after the dose was taken. Patients were instructed to swallow capsules whole with a full 8 ounce glass of water, and not to chew them. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits. Vomited doses were not to be repeated.

Reporting group title	Nilotinib 400 mg BID

Reporting group description:

Patients who were randomized to this arm were to receive nilotinib 400 mg twice a day (BID) by mouth each morning and evening approximately 12 hours apart. If the morning or evening dose was delayed for more than 4 hours, the patient was to skip this dose and resume dosing with the next dose as per the original schedule in order to prevent overdosing. No imatinib washout period was necessary prior to administration of nilotinib. Nilotinib was not to be taken with food. No food was to be consumed for at least 2 hours before the dose was taken and no additional oral intake other than water was to be consumed for at least one hour after the dose was taken. Patients were instructed to swallow capsules whole with a full 8 ounce glass of water, and not to chew them. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits. Vomited doses were not to be repeated.

Reporting group values	Imatinib 400 mg QD	Nilotinb 300 mg BID	Nilotinib 400 mg BID
Number of subjects	283	282	281
Age Categorical Units: Participants			
<35 years	63	67	65
>= 35 - <45 years	67	50	59
>=45 - <55 years	63	72	65
>=55 - < 65 years	55	57	65
>=65 years	35	36	27
Age continuous Units: years			
arithmetic mean	47.1	47.2	46.7
standard deviation	± 14.34	± 14.53	± 13.90
Sex: Female, Male Units:			
Female	125	124	106
Male	158	158	175
Race/Ethnicity, Customized Units: Subjects			
Caucasian	187	170	185

Black	7	12	11
Asian	71	76	66
Native American	1	0	2
Other	17	24	17

Reporting group values	Total		
Number of subjects	846		
Age Categorical Units: Participants			
<35 years	195		
>= 35 - <45 years	176		
>=45 - <55 years	200		
>=55 - < 65 years	177		
>=65 years	98		
Age continuous Units: years arithmetic mean standard deviation	- -		
Sex: Female, Male Units:			
Female	355		
Male	491		
Race/Ethnicity, Customized Units: Subjects			
Caucasian	542		
Black	30		
Asian	213		
Native American	3		
Other	58		

End points reporting groups

Reporting group title	Imatinib 400 mg QD

Reporting group description:

Patients randomized to this arm were to receive 400 mg imatinib once a day (QD). If the patient required a dose escalation from 400 mg/day, the patient was to receive 400 mg imatinib twice daily orally. Imatinib was taken with food and a large glass of water. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits during the study. In cases of vomiting doses were not to be repeated

Reporting group title	Nilotinb 300 mg BID

Reporting group description:

Patients who were randomized to this arm were to receive nilotinib 300 mg twice a day (BID) by mouth each morning and evening approximately 12 hours apart. If the morning or evening dose was delayed for more than 4 hours, the patient was to skip this dose and resume dosing with the next dose as per the original schedule in order to prevent overdosing. No imatinib washout period was necessary prior to administration of nilotinib. Nilotinib was not to be taken with food. No food was to be consumed for at least 2 hours before the dose was taken and no additional oral intake other than water was to be consumed for at least one hour after the dose was taken. Patients were instructed to swallow capsules whole with a full 8 ounce glass of water, and not to chew them. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits. Vomited doses were not to be repeated.

Reporting group title	Nilotinib 400 mg BID

Reporting group description:

Patients who were randomized to this arm were to receive nilotinib 400 mg twice a day (BID) by mouth each morning and evening approximately 12 hours apart. If the morning or evening dose was delayed for more than 4 hours, the patient was to skip this dose and resume dosing with the next dose as per the original schedule in order to prevent overdosing. No imatinib washout period was necessary prior to administration of nilotinib. Nilotinib was not to be taken with food. No food was to be consumed for at least 2 hours before the dose was taken and no additional oral intake other than water was to be consumed for at least one hour after the dose was taken. Patients were instructed to swallow capsules whole with a full 8 ounce glass of water, and not to chew them. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits. Vomited doses were not to be repeated.

Reporting group title	Imatinib 400 mg QD (Treatment taken during core phase)

Reporting group description:

Patients randomized to this arm were to receive 400 mg imatinib once a day (QD). If the patient required a dose escalation from 400 mg/day, the patient was to receive 400 mg imatinib twice daily orally. Imatinib was taken with food and a large glass of water. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits during the study. In cases of vomiting doses were not to be repeated

Reporting group title	Nilotinb 300 mg BID (Treatment taken during core phase)

Reporting group description:

Patients who were randomized to this arm were to receive nilotinib 300 mg twice a day (BID) by mouth each morning and evening approximately 12 hours apart. If the morning or evening dose was delayed for more than 4 hours, the patient was to skip this dose and resume dosing with the next dose as per the original schedule in order to prevent overdosing. No imatinib washout period was necessary prior to administration of nilotinib. Nilotinib was not to be taken with food. No food was to be consumed for at least 2 hours before the dose was taken and no additional oral intake other than water was to be consumed for at least one hour after the dose was taken. Patients were instructed to swallow capsules whole with a full 8 ounce glass of water, and not to chew them. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits. Vomited doses were not to be repeated.

Reporting group title	Nilotinib 400 mg BID (Treatment taken during core phase)

Reporting group description:

Patients who were randomized to this arm were to receive nilotinib 400 mg twice a day (BID) by mouth each morning and evening approximately 12 hours apart. If the morning or evening dose was delayed for more than 4 hours, the patient was to skip this dose and resume dosing with the next dose as per the original schedule in order to prevent overdosing. No imatinib washout period was necessary prior to administration of nilotinib. Nilotinib was not to be taken with food. No food was to be consumed for at least 2 hours before the dose was taken and no additional oral intake other than water was to be consumed for at least one hour after the dose was taken. Patients were instructed to swallow capsules

whole with a full 8 ounce glass of water, and not to chew them. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits. Vomited doses were not to be repeated.

Primary: Major molecular response rate (MMR) at 12 months between all 3 arms - with imputation

End point title	Major molecular response rate (MMR) at 12 months between all 3 arms - with imputation

End point description:

MMR is defined as the percentage of participants in MMR (reduction of ≥ 3 logs in BCR-ABL transcripts compared to the standardized baseline established in IRIS, or ≤ 0.1% BCR-ABL/ABL % by international scale and measured by real-time quantitative polymerase chain reaction (RQ-PCR)) at 12 months.

End point type	Primary

End point timeframe:

Baseline, 12 months

End point values	Imatinib 400 mg QD	Nilotinb 300 mg BID	Nilotinib 400 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	283	282	281	
Units: Percentage of participants				
number (confidence interval 95%)	22.3 (17.6 to 27.6)	44.3 (38.4 to 50.3)	42.7 (36.8 to 48.7)	

Statistical analyses

Statistical analysis title	Imatinib 400 mg qd vs nilotinib 300mg bid
Comparison groups	Imatinib 400 mg QD v Nilotinb 300 mg BID
Number of subjects included in analysis	565
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in response rate
Point estimate	22.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.5
upper limit	29.6

Statistical analysis title	Imatinib 400 mg qd vs nilotinib 400mg bid
Comparison groups	Imatinib 400 mg QD v Nilotinib 400 mg BID

Number of subjects included in analysis	564
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in response rate
Point estimate	20.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.9
upper limit	28

Primary: MMR rates at 12 months between all 3 arms by Sokal risk group with imputation (Low Sokal risk group)

End point title	MMR rates at 12 months between all 3 arms by Sokal risk group with imputation (Low Sokal risk group)

End point description:

MMR is defined as the proportion of patients in MMR (reduction of ≥ 3 logs in BCR-ABL transcripts compared to the standardized baseline established in IRIS, or ≤ 0.1% BCR-ABL/ABL % by international scale and measured by real-time quantitative polymerase chain reaction (RQ-PCR)) at 12 months.

End point type	Primary

End point timeframe:

12 months

End point values	Imatinib 400 mg QD	Nilotinb 300 mg BID	Nilotinib 400 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	103	103	
Units: Percentage of participants				
number (confidence interval 95%)				
Sokal risk group = Low (n=104,103,103)	26.0 (17.9 to 35.5)	40.8 (31.2 to 50.9)	53.4 (43.3 to 63.3)	

Statistical analyses

Statistical analysis title	SS Low: Imatinib 400mg qd vs nilotinib 300mg bid

Statistical analysis description:

(Low)

Comparison groups	Imatinib 400 mg QD v Nilotinb 300 mg BID

Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in response rate
Point estimate	14.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.1
upper limit	27.5

Statistical analysis title	SS Low: Imatinib 400 mg qd vs nilotinib 400mg bid
Statistical analysis description: (Low)	
Comparison groups	Imatinib 400 mg QD v Nilotinib 400 mg BID
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in response rate
Point estimate	27.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.6
upper limit	40.2

Primary: MMR rates at 12 months between all 3 arms by Sokal risk group with imputation (Intermediate Sokal risk group)

End point title	MMR rates at 12 months between all 3 arms by Sokal risk group with imputation (Intermediate Sokal risk group)

End point description:

MMR is defined as the proportion of patients in MMR reduction of ≥ 3 logs in BCR-ABL transcripts compared to the standardized baseline established in IRIS, or ≤ 0.1% BCR-ABL/ABL % by international scale and measured by real-time quantitative polymerase chain reaction (RQ-PCR)) at 12 months.

End point type	Primary

End point timeframe:

12 months

End point values	Imatinib 400 mg QD	Nilotinb 300 mg BID	Nilotinib 400 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101	101	100	
Units: Percentage of participants				
number (confidence interval 95%)	22.8 (15.0 to 32.2)	50.5 (40.4 to 60.6)	40.0 (30.3 to 50.3)	

Statistical analyses

Statistical analysis title	MMR Inter:Imatinib 400mg qd vs nilotinib
Statistical analysis description: (Intermediate)	
Comparison groups	Imatinib 400 mg QD v Nilotinb 300 mg BID
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in response rate
Point estimate	27.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	15
upper limit	40.4

Statistical analysis title	MMR Inter:Imatinib 400mg qd vs nilotinib
Statistical analysis description: (Intermediate)	
Comparison groups	Imatinib 400 mg QD v Nilotinb 400 mg BID
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in response rate
Point estimate	17.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.6
upper limit	29.8

Primary: MMR rates at 12 months between all 3 arms by Sokal risk group with imputation (High Sokal risk group)

End point title	MMR rates at 12 months between all 3 arms by Sokal risk group with imputation (High Sokal risk group)

End point description:

MMR is defined as the proportion of patients in MMR (reduction of ≥ 3 logs in BCR-ABL transcripts compared to the standardized baseline established in IRIS, or ≤ 0.1% BCR-ABL/ABL % by international scale and measured by real-time quantitative polymerase chain reaction (RQ-PCR)) at 12 months.

End point type	Primary
End point timeframe: 12 months	

End point values	Imatinib 400 mg QD	Nilotinb 300 mg BID	Nilotinib 400 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	78	78	78	
Units: Percentage of participants				
number (confidence interval 95%)	16.7 (9.2 to 26.8)	41.0 (30.0 to 52.7)	32.1 (21.9 to 43.6)	

Statistical analyses

Statistical analysis title	MMR High:Imatinib 400mg qd vs nilotinib
Statistical analysis description: (High)	
Comparison groups	Imatinib 400 mg QD v Nilotinb 300 mg BID
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in response rate
Point estimate	24.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.7
upper limit	38.1

Statistical analysis title	MMR High:Imatinib 400mg qd vs nilotinib
Statistical analysis description: (High)	
Comparison groups	Imatinib 400 mg QD v Nilotinib 400 mg BID
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in response rate
Point estimate	15.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.1
upper limit	28.6

Secondary: Rates of durable MMR at 24 months between all 3 arms	
End point title	Rates of durable MMR at 24 months between all 3 arms
End point description:	
Durable MMR at 24 months is defined as having MMR both at 12 months and at 24 months, and with no documented loss of MMR between these 12 month and 24 month time points.	
End point type	Secondary
End point timeframe:	
24 months	

End point values	Imatinib 400 mg QD	Nilotinb 300 mg BID	Nilotinib 400 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	283	282	281	
Units: Percentage of participants				
number (confidence interval 95%)	20.5 (15.9 to 25.7)	41.8 (36.0 to 47.8)	39.1 (33.4 to 45.1)	

Statistical analyses

Statistical analysis title	Dur. MMR: Imatinib 400mg qd vs nilotinib 300mg bid
Comparison groups	Imatinib 400 mg QD v Nilotinb 300 mg BID
Number of subjects included in analysis	565
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in response rate
Point estimate	21.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.9
upper limit	28.8

Statistical analysis title	Dur. MMR: Imatinib 400mg qd vs nilotinib 400mg bid
Comparison groups	Imatinib 400 mg QD v Nilotinib 400 mg BID
Number of subjects included in analysis	564
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in response rate
Point estimate	18.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	11.3
upper limit	26

Secondary: Rate of complete cytogenetic response (CCyR) in nilotinib treatment arms with imatinib at 12 months and beyond 12 months

End point title	Rate of complete cytogenetic response (CCyR) in nilotinib treatment arms with imatinib at 12 months and beyond 12 months

End point description:

CCyR is defined as 0% Ph+ metaphases based on at least 20 metaphases from bone marrow cytogenetics. Patients with no CCyR as the best response by any specific time point, all missing cytogenetic evaluations by that time point or Ph- at baseline are combined as "Nocomplete cytogenetic response".

End point type	Secondary

End point timeframe:

12, 24, 36, 48, 60, 72 months (M)

End point values	Imatinib 400 mg QD	Nilotinb 300 mg BID	Nilotinib 400 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	283	282	281	
Units: Percentage of participants				
number (not applicable)				
CCyR at M12	55.5	70.2	68.7	
CCyR at M24	61.5	66.0	66.2	
CCyR at M36	14.1	9.2	12.8	
CCyR at M48	11.3	8.9	13.5	
CCyR at M60	2.5	2.8	2.8	
CCyR at M72	1.8	1.8	2.8	

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Major molecular response (MMR) at 12 months between two nilotinib arms

End point title	Rate of Major molecular response (MMR) at 12 months between two nilotinib arms[1]

End point description:

MMR is defined as the percentage of participants in MMR (reduction of ≥ 3 logs in BCR-ABL transcripts compared to the standardized baseline established in IRIS, or ≤ 0.1% BCR-ABL/ABL % by international scale and measured by real-time quantitative polymerase chain reaction (RQ-PCR)) at 12 months.

End point type	Secondary

End point timeframe:

12 months

Notes:

[1] - 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: There was no plan to report statistical analysis for this endpoint

End point values	Nilotinb 300 mg BID	Nilotinib 400 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	282	281		
Units: Percentage of participants				
number (confidence interval 95%)	44.3 (38.4 to 50.3)	42.7 (36.8 to 48.7)		

Statistical analyses

Statistical analysis title	MMR: nilotinib 300mg bid vs nilotinib 400mg bid
Comparison groups	Nilotinb 300 mg BID v Nilotinib 400 mg BID
Number of subjects included in analysis	563
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6987
Method	Cochran-Mantel-Haenszel
Parameter estimate	Absolute difference
Point estimate	-1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.8
upper limit	6.6

Secondary: Rate of MMR at 6 months and beyond 12 months in all 3 treatment arms

End point title	Rate of MMR at 6 months and beyond 12 months in all 3 treatment arms

End point description:

MMR is defined as the percentage of participants in MMR (reduction of ≥ 3 logs in BCR-ABL transcripts compared to the standardized baseline established in IRIS, or ≤ 0.1% BCR-ABL/ABL % by international scale and measured by real-time quantitative polymerase chain reaction (RQ-PCR)) at 6 months and 12 months and beyond 12 months.

End point type	Secondary

End point timeframe:

6, 12, 24, 36, 48, 60, 72, 84, 96, 108 and 120 months

End point values	Imatinib 400 mg QD	Nilotinb 300 mg BID	Nilotinib 400 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	283	282	281	
Units: Percentage of participants				
number (confidence interval 95%)				
MMR at M6	12.0 (8.5 to 16.4)	33.0 (27.5 to 38.8)	29.5 (24.3 to 35.2)	
MMR at M12	22.3 (17.6 to 27.6)	44.7 (38.8 to 50.7)	43.1 (37.2 to 49.1)	
MMR at M24	37.5 (31.8 to 43.4)	61.7 (55.8 to 67.4)	59.1 (53.1 to 64.9)	
MMR at M36	38.5 (32.8 to 44.5)	59.2 (53.2 to 65.0)	57.3 (51.3 to 63.2)	
MMR at M48	43.8 (38.0 to 49.8)	59.9 (54.0 to 65.7)	55.2 (49.1 to 61.1)	
MMR at M60	49.1 (43.2 to 55.1)	62.8 (56.8 to 68.4)	61.2 (55.2 to 66.9)	
MMR at M72	41.7 (35.9 to 47.7)	52.5 (46.5 to 58.4)	57.7 (51.6 to 63.5)	
MMR at M84	40.3 (34.5 to 46.3)	50.0 (44.0 to 56.0)	50.9 (44.9 to 56.9)	
MMR at M96	37.5 (31.8 to 43.4)	46.1 (40.2 to 52.1)	46.3 (40.3 to 52.3)	
MMR at M108	37.5 (31.8 to 43.4)	43.3 (37.4 to 49.3)	40.2 (34.4 to 46.2)	
MMR at M120	36.4 (30.8 to 42.3)	37.9 (32.3 to 43.9)	39.1 (33.4 to 45.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of a ≥ 4 log reduction in BCR-ABL transcripts in nilotinib treatment arms with imatinib

End point title	Rate of a ≥ 4 log reduction in BCR-ABL transcripts in nilotinib treatment arms with imatinib

End point description:

Molecular response of <=0.01% is defined as BCR-ABL ratio (%) on IS <= 0.01% (corresponds to >=4 log reduction of BCR-ABL transcripts from standardized baseline value)

End point type	Secondary

End point timeframe:

at 6, 12, 24, 36, 48, 60, 72, 84, 96, 108 and 120 months

End point values	Imatinib 400 mg QD	Nilotinb 300 mg BID	Nilotinib 400 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	283	282	281	
Units: Percentage of participants				
number (confidence interval 95%)				
Molecular response of <=0.01% at 6 months	1.1 (0.2 to 3.1)	8.9 (5.8 to 12.8)	5.7 (3.3 to 9.1)	

Molecular response of <=0.01% at 12 months	3.9 (2.0 to 6.8)	12.1 (8.5 to 16.4)	8.9 (5.8 to 12.9)	
Molecular response of <=0.01% at 24 months	10.2 (7.0 to 14.4)	24.5 (19.6 to 29.9)	22.1 (17.4 to 27.4)	
Molecular response of <=0.01% at 36 months	14.1 (10.3 to 18.7)	29.4 (24.2 to 35.1)	23.8 (19.0 to 29.3)	
Molecular response of <=0.01% at 48 months	19.8 (15.3 to 24.9)	33.0 (27.5 to 38.8)	29.9 (24.6 to 35.6)	
Molecular response of <=0.01% at 60 months	31.1 (25.7 to 36.8)	47.9 (41.9 to 53.9)	43.4 (37.5 to 49.4)	
Molecular response of <=0.01% at 72 months	27.2 (22.1 to 32.8)	44.3 (38.4 to 50.3)	45.2 (39.3 to 51.2)	
Molecular response of <=0.01% at 84 months	29.0 (23.8 to 34.6)	42.9 (37.1 to 48.9)	40.6 (34.8 to 46.6)	
Molecular response of <=0.01% at 96 months	28.3 (23.1 to 33.9)	39.7 (34.0 to 45.7)	38.1 (32.4 to 44.0)	
Molecular response of <=0.01% at 108 months	32.2 (26.7 to 37.9)	40.4 (34.6 to 46.4)	34.9 (29.3 to 40.8)	
Molecular response of <=0.01% at 120 months	28.3 (23.1 to 33.9)	35.5 (29.9 to 41.4)	33.8 (28.3 to 39.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of a ≥ 4.5 log reduction in BCR-ABL transcripts in nilotinib treatment arms with imatinib

End point title	Rate of a ≥ 4.5 log reduction in BCR-ABL transcripts in nilotinib treatment arms with imatinib

End point description:

This is the molecular response of <=0.0032% is defined as BCR-ABL ratio (%) on IS <= 0.0032% (corresponds to >=4.5 log reduction of BCR-ABL transcripts from standardized baseline value)

End point type	Secondary

End point timeframe:

at 6, 12, 24, 36, 48, 60, 72, 84, 96, 108 and 120 months

End point values	Imatinib 400 mg QD	Nilotinb 300 mg BID	Nilotinib 400 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	283	282	281	
Units: Percentage of participants				
number (confidence interval 95%)				
Molecular response of <=0.0032% at 6 months	0.0 (0.0 to 1.3)	3.5 (1.7 to 6.4)	1.4 (0.4 to 3.6)	
Molecular response of <=0.0032% at 12 months	0.4 (0.0 to 2.0)	4.6 (2.5 to 7.8)	5.0 (2.8 to 8.2)	
Molecular response of <=0.0032% at 24 months	2.8 (1.2 to 5.5)	12.4 (8.8 to 16.8)	7.8 (5.0 to 11.6)	
Molecular response of <=0.0032% at 36 months	8.1 (5.2 to 11.9)	13.8 (10.0 to 18.4)	12.1 (8.5 to 16.5)	
Molecular response of <=0.01032 at 48 months	10.2 (7.0 to 14.4)	16.3 (12.2 to 21.2)	17.1 (12.9 to 22.0)	

Molecular response of <=0.0032% at 60 months	19.8 (15.3 to 24.9)	32.3 (26.8 to 38.1)	29.5 (24.3 to 35.2)	
Molecular response of <=0.0032% at 72 months	18.0 (13.7 to 23.0)	31.2 (25.8 to 37.0)	28.8 (23.6 to 34.5)	
Molecular response of <=0.0032% at 84 months	19.1 (14.7 to 24.2)	31.6 (26.2 to 37.3)	28.8 (23.6 to 34.5)	
Molecular response of <=0.01% at 96 months	23.3 (18.5 to 28.7)	31.9 (26.5 to 37.7)	32.4 (26.9 to 38.2)	
Molecular response of <=0.0032% at 108 months	24.0 (19.2 to 29.4)	31.9 (26.5 to 37.7)	28.1 (22.9 to 33.8)	
Molecular response of <=0.0032% at 120 months	21.2 (16.6 to 26.4)	27.0 (21.9 to 32.5)	25.6 (20.6 to 31.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first MMR

End point title	Time to first MMR

End point description:

Time to MMR is defined as time from date of randomization to the date of the first documented MMR in nilotinib treatment arms, compared to imatinib in adult patients with Ph+ CML in CP.

End point type	Secondary

End point timeframe:

up to 84 months

End point values	Imatinib 400 mg QD	Nilotinb 300 mg BID	Nilotinib 400 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	283	282	281	
Units: Months				
median (confidence interval 95%)	14.13 (11.60 to 17.31)	8.31 (6.21 to 8.48)	8.53 (8.31 to 11.07)	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of MMR

End point title	Duration of MMR

End point description:

Duration of MMR for patients with MMR is defined as the time between date of MMR and the earliest of the following: loss of MMR, CML-related death or progression to AP/BC during study treatment The time will be censored at last molecular assessment (PCR) date for patients for whom none of the above events is reported.

End point type	Secondary

End point timeframe:

approx. 12 years

End point values	Imatinib 400 mg QD	Nilotinb 300 mg BID	Nilotinib 400 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	283	282	281	
Units: Months				
median (confidence interval 95%)	999 (999 to 999)	999 (999 to 999)	999 (999 to 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to both a ≥ 4 and ≥ 4.5 log reduction in BCR-ABL transcripts

End point title	Time to both a ≥ 4 and ≥ 4.5 log reduction in BCR-ABL transcripts

End point description:

Time to BCR-ABL ratio of ≤ 0.01% and ≤ 0.0032% is defined as: date of first BCR-ABL ratio of ≤ 0.01% and ≤ 0.0032% - date of randomization +1.

End point type	Secondary

End point timeframe:

up to 84 months

End point values	Imatinib 400 mg QD	Nilotinb 300 mg BID	Nilotinib 400 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	283	282	281	
Units: Months				
median (confidence interval 95%)				
time to first molecular response of <=0.01%	30.46 (24.11 to 36.01)	19.38 (16.62 to 22.34)	22.70 (19.48 to 27.63)	
time to first molecular response of <=0.0032%	37.29 (33.45 to 41.63)	32.46 (23.23 to 38.67)	35.94 (30.39 to 41.00)	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of both a ≥ 4 and ≥ 4.5 log reduction in BCR-ABL transcripts

End point title	Duration of both a ≥ 4 and ≥ 4.5 log reduction in BCR-ABL transcripts

End point description:

It is defined as the time from the date of first documented BCR-ABL ratio of ≤ 0.01% and ≤ 0.0032% to the earliest of the following: Loss of BCR-ABL ratio of ≤ 0.01% and ≤ 0.0032%, respectively, CML-

related death or progression to AP/BC during study treatment. The time will be censored at last molecular assessment (PCR) date for patients for whom none of the above events is reported.

End point type	Secondary

End point timeframe:

approx. 12 years

End point values	Imatinib 400 mg QD	Nilotinb 300 mg BID	Nilotinib 400 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	283	282	281	
Units: Months				
median (confidence interval 95%)				
duration of first molecular response of <=0.01%	999 (999 to 999)	999 (999 to 999)	999 (999 to 999)	
duration of first molecular response of <=0.0032%	999 (999 to 999)	999 (999 to 999)	999 (999 to 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of hematologic response

End point title	Rate of hematologic response

End point description:

Rate of hematologic response is defined as the percentage of participants in complete hematologic response (defined as the following present for at least 4 weeks: WBC count <10 x 109/L, Platelet count <450 x 109/L, Basophils <5%, No blasts and promyelocytes in peripheral blood, Myelocytes + metamyelocytes < 5% in peripheral blood, No evidence of extramedullary disease, including spleen and liver).

End point type	Secondary

End point timeframe:

12 months, 24 months, Overall (beyond 120 months & up to LPLV)

End point values	Imatinib 400 mg QD	Nilotinb 300 mg BID	Nilotinib 400 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	283	282	281	
Units: Percentage of participants				
number (confidence interval 95%)				
Complete hematologic response (CHR) by M12	93.3 (89.7 to 95.9)	90.1 (86.0 to 93.3)	89.0 (84.7 to 92.4)	
CHR by M24	93.6 (90.1 to 96.2)	90.8 (86.8 to 93.9)	90.4 (86.3 to 93.6)	
CHR Overall	94.0 (90.6 to 96.5)	92.2 (88.4 to 95.0)	90.7 (86.7 to 93.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Complete cytogenic response (CCyR)

End point title	Time to Complete cytogenic response (CCyR)

End point description:

Time to CCyR is defined as the time from the date of randomization to the date of first documented CCyR

End point type	Secondary

End point timeframe:

24 months

End point values	Imatinib 400 mg QD	Nilotinb 300 mg BID	Nilotinib 400 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	283	282	281	
Units: Months				
median (confidence interval 95%)	8.5 (5.8 to 10.9)	5.7 (5.6 to 5.7)	5.7 (5.7 to 5.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of CCyR

End point title	Duration of CCyR

End point description:

Duration of CCyR is defined as the time from date of first documented CCyR to the earliest date of loss of CCyR.

End point type	Secondary

End point timeframe:

up to 72 months

End point values	Imatinib 400 mg QD	Nilotinb 300 mg BID	Nilotinib 400 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	283	282	281	
Units: Months				
median (confidence interval 95%)	999 (999 to 999)	999 (999 to 999)	999 (999 to 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

Progression-free survival is defined as the time from the date of randomization to the date of event defined as the first documented disease progression to AP/BC or the date of death from any cause occurring in the core or extension study, or during the follow-up period after discontinuation of core or extension study

End point type	Secondary

End point timeframe:

approx. 12 years

End point values	Imatinib 400 mg QD	Nilotinb 300 mg BID	Nilotinib 400 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	283	282	281	
Units: Months				
median (confidence interval 95%)	999 (999 to 999)	999 (999 to 999)	999 (999 to 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Event-free survival (EFS)

End point title	Event-free survival (EFS)

End point description:

Event-free survival is defined as the time from the date of randomization to the date of first occurrence of any of the following: death due to any cause (if death is the primary reason for discontinuation), progression to AP or BC, loss of PCyR, loss of CCyR, loss of CHR

End point type	Secondary

End point timeframe:

approx. 12 years

End point values	Imatinib 400 mg QD	Nilotinb 300 mg BID	Nilotinib 400 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	283	282	281	
Units: Months				
median (confidence interval 95%)	999 (999 to 999)	999 (999 to 999)	999 (999 to 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

OS is defined as the time from the date of randomization to the date death. Up to 10 calendar years of follow up from the date when the last patient randomized received the first dose of study drug in all active treatment arms of adult patients with Ph+ CML CP.

End point type	Secondary

End point timeframe:

approx. 12 years

End point values	Imatinib 400 mg QD	Nilotinb 300 mg BID	Nilotinib 400 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	283	282	281	
Units: Months				
median (confidence interval 95%)	999 (999 to 999)	999 (999 to 999)	999 (999 to 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Actual dose-intensity

End point title	Actual dose-intensity

End point description:

Actual dose intensity is defined as total dose over time on treatment

End point type	Secondary

End point timeframe:

approx. 12 years

End point values	Imatinib 400 mg QD	Nilotinb 300 mg BID	Nilotinib 400 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	280	279	277	
Units: mg/day				
median (full range (min-max))	400.0 (206 to 800)	591.1 (186 to 699)	758.9 (232 to 800)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression to AP/BC

End point title	Time to progression to AP/BC

End point description:

Time to progression to AP/BC is defined as the time from the date of randomization to the date of event defined as the first documented disease progression to AP/BC or the date of CML related death.

End point type	Secondary

End point timeframe:

approx. 12 years

End point values	Imatinib 400 mg QD	Nilotinb 300 mg BID	Nilotinib 400 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	283	282	281	
Units: Months				
median (confidence interval 95%)	999 (999 to 999)	999 (999 to 999)	999 (999 to 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics as per Cmax at 12 months

End point title	Pharmacokinetics as per Cmax at 12 months[2]

End point description:

Cmax is defined as the maximum serum concentration after dose

End point type	Secondary

End point timeframe:

any day after day 8 at pre-dose (0 hour), 1 hour, 2 hours, 3 hours, 5 hours, 8 hours, and 12 hours after dose administration

Notes:

[2] - 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: There was no plan to report statistical analysis for this endpoint

End point values	Nilotinb 300 mg BID	Nilotinib 400 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: ng/mL				
median (inter-quartile range (Q1-Q3))	1555 (1340 to 2300)	1440 (1002 to 2125)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics as per Cmin at 12 months

End point title	Pharmacokinetics as per Cmin at 12 months[3]

End point description:

Cmin is defined as the minimum serum concentration after dose

End point type	Secondary

End point timeframe:

any day after day 8 at pre-dose (0 hour), 1 hour, 2 hours, 3 hours, 5 hours, 8 hours, and 12 hours after dose administration

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: There was no plan to report statistical analysis for this endpoint

End point values	Nilotinb 300 mg BID	Nilotinib 400 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: ng/mL				
median (inter-quartile range (Q1-Q3))	1430 (1250 to 1740)	915 (752 to 2080)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics as per Tmax at 12 months

End point title	Pharmacokinetics as per Tmax at 12 months[4]

End point description:

Tmax is defined as the sampling time when maximum measured serum concentration occurs

End point type	Secondary

End point timeframe:

any day after day 8 at pre-dose (0 hour), 1 hour, 2 hours, 3 hour

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: There was no plan to report statistical analysis for this endpoint

End point values	Nilotinb 300 mg BID	Nilotinib 400 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: hour (h)				
median (inter-quartile range (Q1-Q3))	1.47 (0.50 to 2.04)	1.50 (0.00 to 2.02)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics as per AUC0-last at 12 months

End point title	Pharmacokinetics as per AUC0-last at 12 months[5]

End point description:

AUC0 - last is defined as area under concentration-time curve from time zero to the last measurable sample, calculated by log-linear trapezoidal method

End point type	Secondary

End point timeframe:

any day after day 8 at pre-dose (0 hour), 1 hour, 2 hours, 3 hour

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: There was no plan to report statistical analysis for this endpoint

End point values	Nilotinb 300 mg BID	Nilotinib 400 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: h.ng/mL				
median (inter-quartile range (Q1-Q3))	14446 (12806 to 17411)	11689 (7925 to 18678)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of hematologic response on nilotinib 400 mg BID therapy after insufficient response during core treatment and switch to extension phase (Extension)

End point title	Rate of hematologic response on nilotinib 400 mg BID therapy after insufficient response during core treatment and switch to extension phase (Extension)

End point description:

Rate of hematologic response is defined as the percentage of participants in complete hematologic

response (defined as the following present for at least 4 weeks: WBC count <10 x 109/L, Platelet count <450 x 109/L, Basophils <5%, No blasts and promyelocytes in peripheral blood, Myelocytes + metamyelocytes < 5% in peripheral blood, No evidence of extramedullary disease, including spleen and liver).

End point type	Secondary

End point timeframe:

Overall (beyond 120 months and up to LPLV)

End point values	Imatinib 400 mg QD (Treatment taken during core phase)	Nilotinb 300 mg BID (Treatment taken during core phase)	Nilotinib 400 mg BID (Treatment taken during core phase)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	26	3	
Units: Percentage of participants				
number (confidence interval 95%)	83.3 (69.8 to 92.5)	84.6 (65.1 to 95.6)	66.7 (9.4 to 99.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of complete cytogenetic response (CCyR) on nilotinib 400 mg BID therapy after insufficient response during core treatment and switch to extension phase (Extension)

End point title	Rate of complete cytogenetic response (CCyR) on nilotinib 400 mg BID therapy after insufficient response during core treatment and switch to extension phase (Extension)

End point description:

Rate of CCyR is defined as the percentage of participants in complete cytogenetic response (CCyR). CcyR is defined as 0% of Ph+ metaphases in the bone marrow.

End point type	Secondary

End point timeframe:

Overall (beyond 120 months and up to LPLV)

End point values	Imatinib 400 mg QD (Treatment taken during core phase)	Nilotinb 300 mg BID (Treatment taken during core phase)	Nilotinib 400 mg BID (Treatment taken during core phase)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	26	3	
Units: Percentage of participants				
number (confidence interval 95%)	72.9 (58.2 to 84.7)	73.1 (52.2 to 88.4)	66.7 (9.4 to 99.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of major molecular response (MMR) on nilotinib 400 mg BID therapy after insufficient response during core treatment and switch to extension phase (Extension)

End point title	Rate of major molecular response (MMR) on nilotinib 400 mg BID therapy after insufficient response during core treatment and switch to extension phase (Extension)

End point description:

Rate of MMR is defined as the percentage pf participants in MMR (reduction of ≥ 3 logs in BCR-ABL transcripts compared to the standardized baseline established in IRIS, or ≤ 0.1% BCR-ABL/ABL % by international scale and measured by real-time quantitative polymerase chain reaction (RQ-PCR))

End point type	Secondary

End point timeframe:

Overall (beyond 120 months and up to LPLV)

End point values	Imatinib 400 mg QD (Treatment taken during core phase)	Nilotinb 300 mg BID (Treatment taken during core phase)	Nilotinib 400 mg BID (Treatment taken during core phase)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	26	3	
Units: Percentage of participants				
number (confidence interval 95%)	64.6 (49.5 to 77.8)	73.1 (52.2 to 88.4)	66.7 (9.4 to 99.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of a ≥ 4 log reduction in BCR-ABL transcripts on nilotinib 400 mg BID therapy after insufficient response during core treatment and switch to extension phase (Extension)

End point title	Rate of a ≥ 4 log reduction in BCR-ABL transcripts on nilotinib 400 mg BID therapy after insufficient response during core treatment and switch to extension phase (Extension)

End point description:

Molecular response of <=0.01% is defined as BCR-ABL ratio (%) on IS <= 0.01% (corresponds to >=4 log reduction of BCR-ABL transcripts from standardized baseline value)

End point type	Secondary

End point timeframe:

Overall (beyond 120 months and up to LPLV)

End point values	Imatinib 400 mg QD (Treatment taken during core phase)	Nilotinb 300 mg BID (Treatment taken during core phase)	Nilotinib 400 mg BID (Treatment taken during core phase)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	26	3	
Units: Percentage of participants				
number (confidence interval 95%)	43.8 (29.5 to 58.8)	57.7 (36.9 to 76.6)	33.3 (0.8 to 90.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of ≥ 4.5 log reduction in BCR-ABL transcripts on nilotinib 400 mg BID therapy after insufficient response during core treatment and switch to extension phase (Extension)

End point title	Rate of ≥ 4.5 log reduction in BCR-ABL transcripts on nilotinib 400 mg BID therapy after insufficient response during core treatment and switch to extension phase (Extension)

End point description:

Molecular response of <=0.0032% is defined as BCR-ABL ratio (%) on IS <= 0.0032% (corresponds to >=4.5 log reduction of BCR-ABL transcripts from standardized baseline value)

End point type	Secondary

End point timeframe:

Overall (beyond 120 months and up to LPLV)

End point values	Imatinib 400 mg QD (Treatment taken during core phase)	Nilotinb 300 mg BID (Treatment taken during core phase)	Nilotinib 400 mg BID (Treatment taken during core phase)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	26	3	
Units: Percentage of participants				
number (confidence interval 95%)	35.4 (22.2 to 50.5)	38.5 (20.2 to 59.4)	33.3 (0.8 to 90.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Presence of newly observed BCR-ABL mutations in patients post-baseline and correlate with response to treatment with imatinib and nilotinib (Extension)

End point title	Presence of newly observed BCR-ABL mutations in patients post-baseline and correlate with response to treatment with imatinib and nilotinib (Extension)

End point description:

This is the percentage of patients with any emergent mutation on extension treatment. The mutation comprised of T315T, less sensitive to nilotinib, unknown and sensitive to nilotinib.

End point type	Secondary

End point timeframe:

Overall (beyond 120 months and up to LPLV)

End point values	Imatinib 400 mg QD (Treatment taken during core phase)	Nilotinb 300 mg BID (Treatment taken during core phase)	Nilotinib 400 mg BID (Treatment taken during core phase)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	26	3	
Units: Percentage of participants				
number (not applicable)	20.8	11.5	33.3	

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

Adverse Event (AE) timeframe: Adverse events were collected from first dose of study treatment until end of study treatment plus 28 days post treatment, up to maximum duration of 136.6 months in the Core phase and 121.9 months in the Extension phase.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Imatinib 400 mg QD

Reporting group description:

Patients randomized to this arm were to receive 400 mg imatinib once a day (QD). If the patient required a dose escalation from 400 mg/day, the patient was to receive 400 mg imatinib twice daily orally. Imatinib was taken with food and a large glass of water. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits during the study. In cases of vomiting doses were not to be repeated.

Reporting group title	Nilotinib 300 mg BID

Reporting group description:

Patients who were randomized to this arm were to receive nilotinib 300 mg twice a day (BID) by mouth each morning and evening approximately 12 hours apart. If the morning or evening dose was delayed for more than 4 hours, the patient was to skip this dose and resume dosing with the next dose as per the original schedule in order to prevent overdosing. No imatinib washout period was necessary prior to administration of nilotinib. Nilotinib was not to be taken with food. No food was to be consumed for at least 2 hours before the dose was taken and no additional oral intake other than water was to be consumed for at least one hour after the dose was taken. Patients were instructed to swallow capsules whole with a full 8 ounce glass of water, and not to chew them. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits. Vomited doses were not to be repeated.

Reporting group title	Nilotinib 400 mg BID

Reporting group description:

Patients who were randomized to this arm were to receive nilotinib 400 mg twice a day (BID) by mouth each morning and evening approximately 12 hours apart. If the morning or evening dose was delayed for more than 4 hours, the patient was to skip this dose and resume dosing with the next dose as per the original schedule in order to prevent overdosing. No imatinib washout period was necessary prior to administration of nilotinib. Nilotinib was not to be taken with food. No food was to be consumed for at least 2 hours before the dose was taken and no additional oral intake other than water was to be consumed for at least one hour after the dose was taken. Patients were instructed to swallow capsules whole with a full 8 ounce glass of water, and not to chew them. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits. Vomited doses were not to be repeated.

Reporting group title	All Patients

Reporting group description:

All patients randomized in the study to all 3 arms and received at lease one dose of study drug.

Serious adverse events	Imatinib 400 mg QD	Nilotinib 300 mg BID	Nilotinib 400 mg BID
Total subjects affected by serious adverse events			
subjects affected / exposed	81 / 280 (28.93%)	106 / 279 (37.99%)	124 / 277 (44.77%)
number of deaths (all causes)	3	10	5
number of deaths resulting from adverse events	0	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of colon			
subjects affected / exposed	1 / 280 (0.36%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
B-cell lymphoma			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign uterine neoplasm			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blast crisis in myelogenous leukaemia			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			

subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chloroma			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon adenoma			
subjects affected / exposed	2 / 280 (0.71%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 10	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal stromal tumour			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glioblastoma			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular carcinoma			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Histiocytosis			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leiomyoma			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukaemic retinopathy			

subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipoma			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liposarcoma			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma in situ			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningioma			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to abdominal wall			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to liver			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lung			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lymph nodes			

subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic malignant melanoma			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic neoplasm			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cancer			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian epithelial cancer			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic neuroendocrine tumour			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papilloma			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraproteinaemia			

subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pituitary tumour benign			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Plasma cell myeloma			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Plasmacytoma			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	3 / 280 (1.07%)	1 / 279 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	2 / 6	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatic adenoma			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal cancer			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rosai-Dorfman syndrome			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin cancer			

subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superficial spreading melanoma stage III			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid cancer			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transitional cell carcinoma			
subjects affected / exposed	0 / 280 (0.00%)	2 / 279 (0.72%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Angiopathy			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic aneurysm			

subjects affected / exposed	1 / 280 (0.36%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic stenosis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arterial occlusive disease			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arterial stenosis			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extremity necrosis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 2	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			

subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemic shock			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intermittent claudication			
subjects affected / exposed	0 / 280 (0.00%)	2 / 279 (0.72%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 280 (0.00%)	3 / 279 (1.08%)	5 / 277 (1.81%)
occurrences causally related to treatment / all	0 / 0	8 / 8	6 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery occlusion			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	8 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery stenosis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	4 / 277 (1.44%)
occurrences causally related to treatment / all	0 / 0	0 / 2	8 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral vascular disorder			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis			

subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicose vein			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vena cava thrombosis			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Retained products of conception			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 280 (0.00%)	2 / 279 (0.72%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest discomfort			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 280 (0.36%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 2	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 1	1 / 2

Drug interaction			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	1 / 280 (0.36%)	1 / 279 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	2 / 2	0 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised oedema			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hernia			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inflammation			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	3 / 277 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	1 / 280 (0.36%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Performance status decreased			

subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral swelling			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	2 / 280 (0.71%)	6 / 279 (2.15%)	5 / 277 (1.81%)
occurrences causally related to treatment / all	4 / 4	0 / 12	2 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular stent stenosis			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Adenomyosis			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adnexa uteri pain			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast swelling			

subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial hyperplasia			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gynaecomastia			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menorrhagia			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menstruation irregular			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metrorrhagia			
subjects affected / exposed	0 / 280 (0.00%)	2 / 279 (0.72%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst ruptured			
subjects affected / exposed	2 / 280 (0.71%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	2 / 8	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scrotal swelling			

subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine polyp			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal haemorrhage			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspiration			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atelectasis			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchial obstruction			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 280 (0.00%)	5 / 279 (1.79%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 10	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			

subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemothorax			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mediastinal cyst			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal septum deviation			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive airways disorder			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Painful respiration			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngeal oedema			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			

subjects affected / exposed	2 / 280 (0.71%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	2 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax spontaneous			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Alcohol abuse			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alcohol withdrawal syndrome			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			

subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bipolar disorder			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Completed suicide			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Confusional state			
subjects affected / exposed	0 / 280 (0.00%)	2 / 279 (0.72%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	2 / 280 (0.71%)	3 / 279 (1.08%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 4	0 / 6	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental disorder			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somatic symptom disorder			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			

subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Thrombosis in device			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Amylase increased			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blast cell count increased			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Blood creatine phosphokinase MB increased			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardioactive drug level increased			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipase increased			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	3 / 277 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	4 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin I increased			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin T increased			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urine output decreased			

subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Abdominal injury			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alcohol poisoning			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain contusion			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac valve replacement complication			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest injury			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	2 / 280 (0.71%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 8	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial bones fracture			

subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gun shot wound			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	2 / 280 (0.71%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 4	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heat illness			

subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incorrect dose administered			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional overdose			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaw fracture			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint injury			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kidney contusion			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament injury			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament sprain			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb injury			

subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple fractures			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle rupture			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax traumatic			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	3 / 280 (1.07%)	0 / 279 (0.00%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skeletal injury			

subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin laceration			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord injury cervical			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sternal fracture			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	1 / 280 (0.36%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haemorrhage			
subjects affected / exposed	1 / 280 (0.36%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			

subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic vertebral fracture			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic haemothorax			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular graft occlusion			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Trisomy 8			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Acute coronary syndrome			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 280 (0.00%)	2 / 279 (0.72%)	5 / 277 (1.81%)
occurrences causally related to treatment / all	0 / 0	4 / 4	4 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	1 / 280 (0.36%)	3 / 279 (1.08%)	10 / 277 (3.61%)
occurrences causally related to treatment / all	0 / 2	2 / 10	8 / 30
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	2 / 280 (0.71%)	1 / 279 (0.36%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 4	2 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	4 / 277 (1.44%)
occurrences causally related to treatment / all	0 / 0	2 / 2	4 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial thrombosis			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brugada syndrome			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			

subjects affected / exposed	1 / 280 (0.36%)	2 / 279 (0.72%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 280 (0.36%)	1 / 279 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	4 / 4	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 280 (0.36%)	3 / 279 (1.08%)	10 / 277 (3.61%)
occurrences causally related to treatment / all	0 / 2	0 / 6	14 / 22
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	3 / 277 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 2	6 / 14
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 280 (0.00%)	2 / 279 (0.72%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	4 / 4	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	2 / 280 (0.71%)	2 / 279 (0.72%)	6 / 277 (2.17%)
occurrences causally related to treatment / all	0 / 4	0 / 4	6 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Myocardial ischaemia			

subjects affected / exposed	2 / 280 (0.71%)	1 / 279 (0.36%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 4	0 / 2	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	1 / 280 (0.36%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis constrictive			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right ventricular failure			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular arrhythmia			

subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular extrasystoles			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Basilar artery stenosis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain oedema			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid arteriosclerosis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery stenosis			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	4 / 277 (1.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	8 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Central nervous system lesion			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebellar stroke			

subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral artery stenosis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	1 / 280 (0.36%)	2 / 279 (0.72%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	0 / 280 (0.00%)	2 / 279 (0.72%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 280 (0.00%)	2 / 279 (0.72%)	3 / 277 (1.08%)
occurrences causally related to treatment / all	0 / 0	2 / 4	2 / 6
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cerebrovascular disorder			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical radiculopathy			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Demyelination			

subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressed level of consciousness			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 280 (0.36%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Essential tremor			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Focal dyscognitive seizures			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head discomfort			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 280 (0.36%)	3 / 279 (1.08%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 2	2 / 6	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			

subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoaesthesia			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 280 (0.00%)	2 / 279 (0.72%)	3 / 277 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 4	2 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Miller Fisher syndrome			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple sclerosis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuralgia			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy peripheral			

subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parkinson's disease			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parkinsonism			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyneuropathy			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Speech disorder			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	2 / 280 (0.71%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			

subjects affected / exposed	0 / 280 (0.00%)	2 / 279 (0.72%)	4 / 277 (1.44%)
occurrences causally related to treatment / all	0 / 0	0 / 4	6 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebral artery stenosis			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 280 (1.07%)	2 / 279 (0.72%)	5 / 277 (1.81%)
occurrences causally related to treatment / all	0 / 6	0 / 4	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia macrocytic			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 0	2 / 2	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoplastic anaemia			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iron deficiency anaemia			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukocytosis			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			

subjects affected / exposed	2 / 280 (0.71%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	4 / 4	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 280 (0.36%)	3 / 279 (1.08%)	4 / 277 (1.44%)
occurrences causally related to treatment / all	2 / 2	6 / 6	10 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	2 / 280 (0.71%)	4 / 279 (1.43%)	4 / 277 (1.44%)
occurrences causally related to treatment / all	4 / 4	8 / 8	8 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Otosclerosis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo			
subjects affected / exposed	0 / 280 (0.00%)	2 / 279 (0.72%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 0	2 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Amaurosis fugax			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blindness unilateral			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract			

subjects affected / exposed	0 / 280 (0.00%)	2 / 279 (0.72%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular fibrosis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Photophobia			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinopathy			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual impairment			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 280 (0.71%)	5 / 279 (1.79%)	6 / 277 (2.17%)
occurrences causally related to treatment / all	0 / 4	0 / 12	4 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain lower			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	3 / 280 (1.07%)	1 / 279 (0.36%)	4 / 277 (1.44%)
occurrences causally related to treatment / all	0 / 6	0 / 2	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal inflammation			

subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic gastritis			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 280 (0.00%)	2 / 279 (0.72%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 280 (0.36%)	1 / 279 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	2 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			

subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecal vomiting			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Food poisoning			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric mucosa erythema			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorder			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 280 (0.36%)	1 / 279 (0.36%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 4	0 / 6	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoidal haemorrhage			

subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	1 / 280 (0.36%)	1 / 279 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus paralytic			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incarcerated inguinal hernia			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal haemorrhage			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	3 / 277 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal stenosis			

subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mechanical ileus			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 280 (0.36%)	2 / 279 (0.72%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 2	0 / 4	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal ulcer			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic fistula			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 280 (0.00%)	2 / 279 (0.72%)	3 / 277 (1.08%)
occurrences causally related to treatment / all	0 / 0	4 / 6	4 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	3 / 277 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	6 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peptic ulcer			

subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periodontal disease			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneal haematoma			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneal haemorrhage			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 280 (0.00%)	3 / 279 (1.08%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 6	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retroperitoneal haematoma			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal haemorrhage			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 18
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			

subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toothache			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 280 (0.71%)	3 / 279 (1.08%)	4 / 277 (1.44%)
occurrences causally related to treatment / all	2 / 4	0 / 6	8 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 280 (0.00%)	2 / 279 (0.72%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 4	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic function abnormal			

subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	3 / 277 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	4 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic steatosis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatotoxicity			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic foot			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psoriasis			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			

subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 280 (1.07%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 8	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anuria			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Azotaemia			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder obstruction			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvi-ureteric obstruction			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			

subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	2 / 280 (0.71%)	1 / 279 (0.36%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal infarct			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypothyroidism			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	2 / 280 (0.71%)	2 / 279 (0.72%)	6 / 277 (2.17%)
occurrences causally related to treatment / all	2 / 4	0 / 6	0 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot deformity			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gouty arthritis			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma muscle			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc disorder			
subjects affected / exposed	1 / 280 (0.36%)	1 / 279 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	4 / 280 (1.43%)	6 / 279 (2.15%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 10	0 / 14	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle spasms			

subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	1 / 280 (0.36%)	1 / 279 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myofascial pain syndrome			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	1 / 280 (0.36%)	1 / 279 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 280 (0.36%)	2 / 279 (0.72%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 2	2 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid arthritis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			

subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal ligament ossification			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondyloarthropathy			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylolisthesis			
subjects affected / exposed	0 / 280 (0.00%)	2 / 279 (0.72%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Anal infection			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 280 (0.36%)	2 / 279 (0.72%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	2 / 280 (0.71%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Campylobacter gastroenteritis			

subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	4 / 280 (1.43%)	1 / 279 (0.36%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	2 / 10	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epididymitis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	3 / 280 (1.07%)	0 / 279 (0.00%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 10	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis salmonella			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal viral infection			

subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
H1N1 influenza			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma infection			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected skin ulcer			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Measles			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral infection			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis chronic			

subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media chronic			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perihepatic abscess			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periodontitis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	2 / 280 (0.71%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pilonidal cyst			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	7 / 280 (2.50%)	6 / 279 (2.15%)	6 / 277 (2.17%)
occurrences causally related to treatment / all	0 / 16	0 / 12	0 / 16
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 0
Pneumonia legionella			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			

subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonal sepsis			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulpitis dental			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal abscess			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhinitis			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salpingitis			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Septic shock			

subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	1 / 280 (0.36%)	1 / 279 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 4	0 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal sepsis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheobronchitis			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 280 (0.71%)	1 / 279 (0.36%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 280 (0.00%)	2 / 279 (0.72%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral rash			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			

subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 280 (0.71%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	1 / 280 (0.36%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 280 (0.00%)	1 / 279 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid overload			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gout			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			

subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 280 (0.00%)	0 / 279 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophosphataemia			
subjects affected / exposed	1 / 280 (0.36%)	0 / 279 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	All Patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	311 / 836 (37.20%)		
number of deaths (all causes)	18		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	1 / 836 (0.12%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Adenocarcinoma of colon			
subjects affected / exposed	2 / 836 (0.24%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
B-cell lymphoma			
subjects affected / exposed	1 / 836 (0.12%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	2 / 836 (0.24%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		

Benign uterine neoplasm				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Blast crisis in myelogenous leukaemia				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Breast cancer				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Chloroma				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Colon adenoma				
subjects affected / exposed	3 / 836 (0.36%)			
occurrences causally related to treatment / all	0 / 14			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal stromal tumour				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Glioblastoma				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hepatocellular carcinoma				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Histiocytosis				

subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Leiomyoma				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Leukaemic retinopathy				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Lipoma				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Liposarcoma				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Malignant melanoma in situ				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Meningioma				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Metastases to abdominal wall				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Metastases to liver				

subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Metastases to lung				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Metastases to lymph nodes				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Metastatic malignant melanoma				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Metastatic neoplasm				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Ovarian cancer				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Ovarian epithelial cancer				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pancreatic carcinoma				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pancreatic neuroendocrine tumour				

subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Papilloma				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Paraproteinaemia				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Pituitary tumour benign				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Plasma cell myeloma				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Plasmacytoma				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Prostate cancer				
subjects affected / exposed	5 / 836 (0.60%)			
occurrences causally related to treatment / all	2 / 10			
deaths causally related to treatment / all	0 / 0			
Prostatic adenoma				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Rectal cancer				

subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Rosai-Dorfman syndrome				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Skin cancer				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of skin				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Superficial spreading melanoma stage III				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Thyroid cancer				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Transitional cell carcinoma				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Uterine leiomyoma				

subjects affected / exposed	1 / 836 (0.12%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Angiopathy			
subjects affected / exposed	1 / 836 (0.12%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Aortic aneurysm			
subjects affected / exposed	2 / 836 (0.24%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Aortic stenosis			
subjects affected / exposed	2 / 836 (0.24%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Arterial occlusive disease			
subjects affected / exposed	1 / 836 (0.12%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Arterial stenosis			
subjects affected / exposed	1 / 836 (0.12%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Arteriosclerosis			
subjects affected / exposed	1 / 836 (0.12%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Extremity necrosis			
subjects affected / exposed	1 / 836 (0.12%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypertension			

subjects affected / exposed	3 / 836 (0.36%)			
occurrences causally related to treatment / all	2 / 6			
deaths causally related to treatment / all	0 / 0			
Hypertensive crisis				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hypovolaemic shock				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Intermittent claudication				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Peripheral arterial occlusive disease				
subjects affected / exposed	8 / 836 (0.96%)			
occurrences causally related to treatment / all	14 / 18			
deaths causally related to treatment / all	0 / 0			
Peripheral artery occlusion				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	8 / 8			
deaths causally related to treatment / all	0 / 0			
Peripheral artery stenosis				
subjects affected / exposed	5 / 836 (0.60%)			
occurrences causally related to treatment / all	8 / 12			
deaths causally related to treatment / all	0 / 0			
Peripheral ischaemia				

subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Peripheral vascular disorder				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Thrombophlebitis				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Varicose vein				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Vena cava thrombosis				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pregnancy, puerperium and perinatal conditions				
Retained products of conception				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Asthenia				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Chest discomfort				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			

Chest pain			
subjects affected / exposed	2 / 836 (0.24%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	3 / 836 (0.36%)		
occurrences causally related to treatment / all	2 / 6		
deaths causally related to treatment / all	1 / 3		
Drug interaction			
subjects affected / exposed	1 / 836 (0.12%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	3 / 836 (0.36%)		
occurrences causally related to treatment / all	4 / 6		
deaths causally related to treatment / all	0 / 0		
Generalised oedema			
subjects affected / exposed	1 / 836 (0.12%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hernia			
subjects affected / exposed	1 / 836 (0.12%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Inflammation			
subjects affected / exposed	1 / 836 (0.12%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 836 (0.12%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Non-cardiac chest pain			

subjects affected / exposed	3 / 836 (0.36%)			
occurrences causally related to treatment / all	2 / 12			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Performance status decreased				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Peripheral swelling				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	13 / 836 (1.56%)			
occurrences causally related to treatment / all	6 / 28			
deaths causally related to treatment / all	0 / 0			
Systemic inflammatory response syndrome				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Vascular stent stenosis				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Adenomyosis				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Adnexa uteri pain				

subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Benign prostatic hyperplasia				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Breast swelling				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Endometrial hyperplasia				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gynaecomastia				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Menorrhagia				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Menstruation irregular				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Metrorrhagia				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Ovarian cyst				

subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Ovarian cyst ruptured				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	2 / 8			
deaths causally related to treatment / all	0 / 0			
Scrotal swelling				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Uterine polyp				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Vaginal haemorrhage				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory distress syndrome				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Aspiration				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Atelectasis				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bronchial obstruction				

subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	7 / 836 (0.84%)			
occurrences causally related to treatment / all	4 / 14			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Haemothorax				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Interstitial lung disease				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Mediastinal cyst				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Nasal septum deviation				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Obstructive airways disorder				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Painful respiration				

subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pharyngeal oedema				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	3 / 836 (0.36%)			
occurrences causally related to treatment / all	2 / 6			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumothorax spontaneous				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pulmonary haemorrhage				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Alcohol abuse				

subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Alcohol withdrawal syndrome				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Anxiety				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bipolar disorder				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Completed suicide				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Confusional state				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Depression				
subjects affected / exposed	7 / 836 (0.84%)			
occurrences causally related to treatment / all	0 / 14			
deaths causally related to treatment / all	0 / 0			
Mental disorder				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Mental status changes				

subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Somatic symptom disorder				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Suicidal ideation				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Suicide attempt				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Product issues				
Thrombosis in device				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Investigations				
Alanine aminotransferase increased				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Amylase increased				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			

Blast cell count increased				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Blood alkaline phosphatase increased				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Blood creatine phosphokinase MB increased				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Blood creatinine increased				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Cardioactive drug level increased				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Electrocardiogram QT prolonged				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Gamma-glutamyltransferase increased				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Lipase increased				
subjects affected / exposed	3 / 836 (0.36%)			
occurrences causally related to treatment / all	4 / 6			
deaths causally related to treatment / all	0 / 0			
Troponin I increased				

subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Troponin T increased				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Urine output decreased				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Abdominal injury				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Alcohol poisoning				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Brain contusion				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac valve replacement complication				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Chest injury				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Concussion				

subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Contusion				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 0			
Facial bones fracture				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Femoral neck fracture				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	3 / 836 (0.36%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Foot fracture				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gun shot wound				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hand fracture				

subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Head injury				
subjects affected / exposed	3 / 836 (0.36%)			
occurrences causally related to treatment / all	2 / 6			
deaths causally related to treatment / all	0 / 0			
Heat illness				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Incorrect dose administered				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Intentional overdose				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Jaw fracture				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Joint injury				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Kidney contusion				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Ligament injury				

subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Ligament sprain				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Limb injury				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Lower limb fracture				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Multiple fractures				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Muscle rupture				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Pneumothorax traumatic				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Procedural pain				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Rib fracture				

subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Road traffic accident				
subjects affected / exposed	5 / 836 (0.60%)			
occurrences causally related to treatment / all	0 / 10			
deaths causally related to treatment / all	0 / 0			
Skeletal injury				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Skin laceration				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Spinal compression fracture				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Spinal cord injury cervical				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Spinal fracture				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Sternal fracture				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Subdural haematoma				

subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Subdural haemorrhage				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Tendon rupture				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Thoracic vertebral fracture				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Toxicity to various agents				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Traumatic haemothorax				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Upper limb fracture				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Vascular graft occlusion				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Wrist fracture				

subjects affected / exposed	1 / 836 (0.12%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Trisomy 8			
subjects affected / exposed	1 / 836 (0.12%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 836 (0.12%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	7 / 836 (0.84%)		
occurrences causally related to treatment / all	8 / 14		
deaths causally related to treatment / all	0 / 0		
Angina pectoris			
subjects affected / exposed	14 / 836 (1.67%)		
occurrences causally related to treatment / all	10 / 42		
deaths causally related to treatment / all	0 / 0		
Angina unstable			
subjects affected / exposed	5 / 836 (0.60%)		
occurrences causally related to treatment / all	2 / 10		
deaths causally related to treatment / all	0 / 0		
Arrhythmia			
subjects affected / exposed	1 / 836 (0.12%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	5 / 836 (0.60%)		
occurrences causally related to treatment / all	6 / 14		
deaths causally related to treatment / all	0 / 0		

Atrial thrombosis			
subjects affected / exposed	1 / 836 (0.12%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Brugada syndrome			
subjects affected / exposed	1 / 836 (0.12%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	3 / 836 (0.36%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 3		
Cardiac failure congestive			
subjects affected / exposed	3 / 836 (0.36%)		
occurrences causally related to treatment / all	4 / 8		
deaths causally related to treatment / all	0 / 0		
Cardio-respiratory arrest			
subjects affected / exposed	1 / 836 (0.12%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiogenic shock			
subjects affected / exposed	1 / 836 (0.12%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Coronary artery disease			
subjects affected / exposed	14 / 836 (1.67%)		
occurrences causally related to treatment / all	14 / 30		
deaths causally related to treatment / all	0 / 0		
Coronary artery stenosis			
subjects affected / exposed	4 / 836 (0.48%)		
occurrences causally related to treatment / all	6 / 16		
deaths causally related to treatment / all	0 / 0		
Ischaemic cardiomyopathy			

subjects affected / exposed	3 / 836 (0.36%)			
occurrences causally related to treatment / all	6 / 6			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	10 / 836 (1.20%)			
occurrences causally related to treatment / all	6 / 20			
deaths causally related to treatment / all	0 / 1			
Myocardial ischaemia				
subjects affected / exposed	5 / 836 (0.60%)			
occurrences causally related to treatment / all	2 / 10			
deaths causally related to treatment / all	0 / 0			
Palpitations				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Pericardial effusion				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Pericarditis				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Pericarditis constrictive				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Right ventricular failure				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				

subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Tachycardia				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Ventricular arrhythmia				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Ventricular extrasystoles				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Ventricular tachycardia				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Basilar artery stenosis				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Brain oedema				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Carotid arteriosclerosis				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Carotid artery stenosis				

subjects affected / exposed	4 / 836 (0.48%)			
occurrences causally related to treatment / all	8 / 8			
deaths causally related to treatment / all	0 / 0			
Central nervous system lesion				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cerebellar stroke				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Cerebral artery stenosis				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cerebral haemorrhage				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Cerebral infarction				
subjects affected / exposed	3 / 836 (0.36%)			
occurrences causally related to treatment / all	2 / 6			
deaths causally related to treatment / all	0 / 0			
Cerebral ischaemia				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	5 / 836 (0.60%)			
occurrences causally related to treatment / all	4 / 10			
deaths causally related to treatment / all	0 / 1			
Cerebrovascular disorder				

subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Cervical radiculopathy				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Demyelination				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Depressed level of consciousness				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Essential tremor				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Focal dyscognitive seizures				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Head discomfort				

subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	5 / 836 (0.60%)			
occurrences causally related to treatment / all	2 / 10			
deaths causally related to treatment / all	0 / 0			
Hemiparesis				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hypoaesthesia				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Ischaemic stroke				
subjects affected / exposed	5 / 836 (0.60%)			
occurrences causally related to treatment / all	2 / 14			
deaths causally related to treatment / all	0 / 0			
Loss of consciousness				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Migraine				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Miller Fisher syndrome				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Multiple sclerosis				

subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Neuralgia				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Neuropathy peripheral				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Parkinson's disease				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Parkinsonism				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Polyneuropathy				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Sciatica				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Speech disorder				

subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	3 / 836 (0.36%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	6 / 836 (0.72%)			
occurrences causally related to treatment / all	6 / 12			
deaths causally related to treatment / all	0 / 0			
Vertebral artery stenosis				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	10 / 836 (1.20%)			
occurrences causally related to treatment / all	0 / 20			
deaths causally related to treatment / all	0 / 0			
Anaemia macrocytic				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	3 / 836 (0.36%)			
occurrences causally related to treatment / all	6 / 6			
deaths causally related to treatment / all	0 / 0			
Hypoplastic anaemia				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Iron deficiency anaemia				

subjects affected / exposed	1 / 836 (0.12%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Leukocytosis			
subjects affected / exposed	1 / 836 (0.12%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Leukopenia			
subjects affected / exposed	3 / 836 (0.36%)		
occurrences causally related to treatment / all	6 / 6		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	8 / 836 (0.96%)		
occurrences causally related to treatment / all	18 / 18		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	2 / 836 (0.24%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	10 / 836 (1.20%)		
occurrences causally related to treatment / all	20 / 20		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Otosclerosis			
subjects affected / exposed	1 / 836 (0.12%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vertigo			
subjects affected / exposed	4 / 836 (0.48%)		
occurrences causally related to treatment / all	2 / 8		
deaths causally related to treatment / all	0 / 0		
Eye disorders			

Amaurosis fugax				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Blindness unilateral				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Cataract				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Macular fibrosis				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Photophobia				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Retinopathy				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Visual impairment				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	13 / 836 (1.56%)			
occurrences causally related to treatment / all	4 / 28			
deaths causally related to treatment / all	0 / 0			
Abdominal pain lower				

subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	8 / 836 (0.96%)			
occurrences causally related to treatment / all	0 / 16			
deaths causally related to treatment / all	0 / 0			
Anal inflammation				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Chronic gastritis				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Colitis ischaemic				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	3 / 836 (0.36%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	3 / 836 (0.36%)			
occurrences causally related to treatment / all	2 / 6			
deaths causally related to treatment / all	0 / 0			
Duodenal ulcer				

subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Dyspepsia				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Enteritis				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Faecal vomiting				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Food poisoning				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastric mucosa erythema				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorder				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				

subjects affected / exposed	4 / 836 (0.48%)			
occurrences causally related to treatment / all	0 / 16			
deaths causally related to treatment / all	0 / 0			
Gastrooesophageal reflux disease				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Haemorrhoidal haemorrhage				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Haemorrhoids				
subjects affected / exposed	3 / 836 (0.36%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 0			
Ileus paralytic				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Incarcerated inguinal hernia				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Inguinal hernia				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Intestinal haemorrhage				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				

subjects affected / exposed	4 / 836 (0.48%)			
occurrences causally related to treatment / all	0 / 10			
deaths causally related to treatment / all	0 / 1			
Intestinal perforation				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Intestinal stenosis				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Mechanical ileus				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	5 / 836 (0.60%)			
occurrences causally related to treatment / all	4 / 10			
deaths causally related to treatment / all	0 / 0			
Oesophageal ulcer				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Oesophagitis				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pancreatic fistula				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				

subjects affected / exposed	5 / 836 (0.60%)			
occurrences causally related to treatment / all	8 / 12			
deaths causally related to treatment / all	0 / 0			
Pancreatitis acute				
subjects affected / exposed	3 / 836 (0.36%)			
occurrences causally related to treatment / all	6 / 6			
deaths causally related to treatment / all	0 / 0			
Peptic ulcer				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Periodontal disease				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Peritoneal haematoma				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Peritoneal haemorrhage				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	4 / 836 (0.48%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 0			
Retroperitoneal haematoma				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Small intestinal haemorrhage				

subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 20			
deaths causally related to treatment / all	0 / 0			
Subileus				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Toothache				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	9 / 836 (1.08%)			
occurrences causally related to treatment / all	10 / 20			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Biliary colic				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed	3 / 836 (0.36%)			
occurrences causally related to treatment / all	2 / 6			
deaths causally related to treatment / all	0 / 0			
Cholelithiasis				

subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Drug-induced liver injury				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Hepatic function abnormal				
subjects affected / exposed	3 / 836 (0.36%)			
occurrences causally related to treatment / all	4 / 6			
deaths causally related to treatment / all	0 / 0			
Hepatic steatosis				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hepatitis				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hepatotoxicity				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Hyperbilirubinaemia				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Angioedema				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Diabetic foot				

subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Psoriasis				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Urticaria				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	4 / 836 (0.48%)			
occurrences causally related to treatment / all	0 / 10			
deaths causally related to treatment / all	0 / 0			
Anuria				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Azotaemia				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Bladder obstruction				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Chronic kidney disease				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Nephrolithiasis				

subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pelvi-ureteric obstruction				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Renal colic				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	5 / 836 (0.60%)			
occurrences causally related to treatment / all	0 / 10			
deaths causally related to treatment / all	0 / 0			
Renal impairment				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Renal infarct				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Ureterolithiasis				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Urinary retention				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Endocrine disorders				
Hyperthyroidism				

subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Hypothyroidism				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Arthralgia				
subjects affected / exposed	3 / 836 (0.36%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Back pain				
subjects affected / exposed	10 / 836 (1.20%)			
occurrences causally related to treatment / all	2 / 22			
deaths causally related to treatment / all	0 / 0			
Foot deformity				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Gouty arthritis				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Haematoma muscle				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Intervertebral disc disorder				
subjects affected / exposed	3 / 836 (0.36%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 0			
Intervertebral disc protrusion				

subjects affected / exposed	10 / 836 (1.20%)		
occurrences causally related to treatment / all	0 / 24		
deaths causally related to treatment / all	0 / 0		
Lumbar spinal stenosis			
subjects affected / exposed	1 / 836 (0.12%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Muscle spasms			
subjects affected / exposed	1 / 836 (0.12%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	1 / 836 (0.12%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal pain			
subjects affected / exposed	3 / 836 (0.36%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Myalgia			
subjects affected / exposed	1 / 836 (0.12%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Myofascial pain syndrome			
subjects affected / exposed	1 / 836 (0.12%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	3 / 836 (0.36%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			

subjects affected / exposed	4 / 836 (0.48%)			
occurrences causally related to treatment / all	2 / 8			
deaths causally related to treatment / all	0 / 0			
Rheumatoid arthritis				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Rotator cuff syndrome				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Spinal ligament ossification				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Spinal pain				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Spondyloarthropathy				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Spondylolisthesis				
subjects affected / exposed	3 / 836 (0.36%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Anal infection				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Appendicitis				

subjects affected / exposed	3 / 836 (0.36%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Campylobacter gastroenteritis				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	7 / 836 (0.84%)			
occurrences causally related to treatment / all	2 / 16			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Epididymitis				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Escherichia urinary tract infection				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	5 / 836 (0.60%)			
occurrences causally related to treatment / all	0 / 14			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis salmonella				

subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal infection				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal viral infection				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
H1N1 influenza				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Haematoma infection				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Infected skin ulcer				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Measles				

subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Oral infection				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Osteomyelitis chronic				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Otitis media chronic				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Perihepatic abscess				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Periodontitis				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	3 / 836 (0.36%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Pilonidal cyst				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Pneumonia				

subjects affected / exposed	19 / 836 (2.27%)			
occurrences causally related to treatment / all	0 / 44			
deaths causally related to treatment / all	0 / 3			
Pneumonia legionella				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Postoperative wound infection				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pseudomonal sepsis				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pulpitis dental				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis acute				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Rectal abscess				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Rhinitis				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Salpingitis				

subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	3 / 836 (0.36%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 1			
Septic shock				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Sinusitis				
subjects affected / exposed	3 / 836 (0.36%)			
occurrences causally related to treatment / all	2 / 8			
deaths causally related to treatment / all	0 / 0			
Streptococcal sepsis				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Tracheobronchitis				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	5 / 836 (0.60%)			
occurrences causally related to treatment / all	0 / 10			
deaths causally related to treatment / all	0 / 0			
Viral infection				

subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Viral rash				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Wound infection				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Diabetes mellitus				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Diabetes mellitus inadequate control				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Electrolyte imbalance				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Fluid overload				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gout				

subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hyperkalaemia				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hypoglycaemia				
subjects affected / exposed	2 / 836 (0.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Hypophosphataemia				
subjects affected / exposed	1 / 836 (0.12%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	Imatinib 400 mg QD	Nilotinib 300 mg BID	Nilotinib 400 mg BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	274 / 280 (97.86%)	276 / 279 (98.92%)	271 / 277 (97.83%)
Vascular disorders			
Hypertension			
subjects affected / exposed	17 / 280 (6.07%)	44 / 279 (15.77%)	55 / 277 (19.86%)
occurrences (all)	34	92	122
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	40 / 280 (14.29%)	38 / 279 (13.62%)	29 / 277 (10.47%)
occurrences (all)	138	98	84
Chills			

subjects affected / exposed	9 / 280 (3.21%)	11 / 279 (3.94%)	14 / 277 (5.05%)
occurrences (all)	22	24	28
Face oedema			
subjects affected / exposed	40 / 280 (14.29%)	2 / 279 (0.72%)	7 / 277 (2.53%)
occurrences (all)	114	4	14
Fatigue			
subjects affected / exposed	57 / 280 (20.36%)	68 / 279 (24.37%)	56 / 277 (20.22%)
occurrences (all)	136	182	176
Influenza like illness			
subjects affected / exposed	14 / 280 (5.00%)	15 / 279 (5.38%)	14 / 277 (5.05%)
occurrences (all)	42	62	50
Non-cardiac chest pain			
subjects affected / exposed	16 / 280 (5.71%)	16 / 279 (5.73%)	24 / 277 (8.66%)
occurrences (all)	38	40	58
Oedema peripheral			
subjects affected / exposed	63 / 280 (22.50%)	32 / 279 (11.47%)	43 / 277 (15.52%)
occurrences (all)	188	82	130
Pyrexia			
subjects affected / exposed	38 / 280 (13.57%)	42 / 279 (15.05%)	49 / 277 (17.69%)
occurrences (all)	110	138	154
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	41 / 280 (14.64%)	55 / 279 (19.71%)	61 / 277 (22.02%)
occurrences (all)	136	176	180
Dyspnoea			
subjects affected / exposed	21 / 280 (7.50%)	33 / 279 (11.83%)	30 / 277 (10.83%)
occurrences (all)	52	82	80
Oropharyngeal pain			
subjects affected / exposed	21 / 280 (7.50%)	34 / 279 (12.19%)	29 / 277 (10.47%)
occurrences (all)	72	90	66
Psychiatric disorders			
Anxiety			
subjects affected / exposed	26 / 280 (9.29%)	23 / 279 (8.24%)	22 / 277 (7.94%)
occurrences (all)	60	60	52
Depression			

subjects affected / exposed	20 / 280 (7.14%)	18 / 279 (6.45%)	18 / 277 (6.50%)
occurrences (all)	50	38	42
Insomnia			
subjects affected / exposed	26 / 280 (9.29%)	38 / 279 (13.62%)	37 / 277 (13.36%)
occurrences (all)	60	100	92
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	25 / 280 (8.93%)	80 / 279 (28.67%)	87 / 277 (31.41%)
occurrences (all)	58	292	364
Amylase increased			
subjects affected / exposed	10 / 280 (3.57%)	22 / 279 (7.89%)	23 / 277 (8.30%)
occurrences (all)	34	70	86
Aspartate aminotransferase increased			
subjects affected / exposed	20 / 280 (7.14%)	48 / 279 (17.20%)	44 / 277 (15.88%)
occurrences (all)	50	158	148
Blood alkaline phosphatase increased			
subjects affected / exposed	12 / 280 (4.29%)	8 / 279 (2.87%)	16 / 277 (5.78%)
occurrences (all)	30	22	40
Blood bilirubin increased			
subjects affected / exposed	4 / 280 (1.43%)	36 / 279 (12.90%)	41 / 277 (14.80%)
occurrences (all)	10	176	202
Blood cholesterol increased			
subjects affected / exposed	1 / 280 (0.36%)	15 / 279 (5.38%)	15 / 277 (5.42%)
occurrences (all)	2	34	40
Blood creatinine increased			
subjects affected / exposed	21 / 280 (7.50%)	4 / 279 (1.43%)	10 / 277 (3.61%)
occurrences (all)	58	14	32
Blood phosphorus decreased			
subjects affected / exposed	6 / 280 (2.14%)	9 / 279 (3.23%)	14 / 277 (5.05%)
occurrences (all)	32	28	54
Haemoglobin decreased			
subjects affected / exposed	14 / 280 (5.00%)	7 / 279 (2.51%)	15 / 277 (5.42%)
occurrences (all)	46	18	42
Lipase increased			

subjects affected / exposed	14 / 280 (5.00%)	37 / 279 (13.26%)	38 / 277 (13.72%)
occurrences (all)	36	114	188
Weight decreased			
subjects affected / exposed	8 / 280 (2.86%)	15 / 279 (5.38%)	13 / 277 (4.69%)
occurrences (all)	16	38	28
Weight increased			
subjects affected / exposed	27 / 280 (9.64%)	24 / 279 (8.60%)	22 / 277 (7.94%)
occurrences (all)	66	72	62
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	4 / 280 (1.43%)	12 / 279 (4.30%)	14 / 277 (5.05%)
occurrences (all)	8	38	28
Cardiac disorders			
Palpitations			
subjects affected / exposed	11 / 280 (3.93%)	18 / 279 (6.45%)	19 / 277 (6.86%)
occurrences (all)	38	40	48
Nervous system disorders			
Dizziness			
subjects affected / exposed	31 / 280 (11.07%)	34 / 279 (12.19%)	34 / 277 (12.27%)
occurrences (all)	94	94	82
Headache			
subjects affected / exposed	67 / 280 (23.93%)	93 / 279 (33.33%)	105 / 277 (37.91%)
occurrences (all)	224	392	436
Hypoaesthesia			
subjects affected / exposed	7 / 280 (2.50%)	15 / 279 (5.38%)	10 / 277 (3.61%)
occurrences (all)	18	32	20
Paraesthesia			
subjects affected / exposed	12 / 280 (4.29%)	14 / 279 (5.02%)	11 / 277 (3.97%)
occurrences (all)	32	34	28
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	67 / 280 (23.93%)	38 / 279 (13.62%)	45 / 277 (16.25%)
occurrences (all)	188	150	132
Leukopenia			
subjects affected / exposed	47 / 280 (16.79%)	23 / 279 (8.24%)	22 / 277 (7.94%)
occurrences (all)	198	62	66

Neutropenia			
subjects affected / exposed	58 / 280 (20.71%)	44 / 279 (15.77%)	30 / 277 (10.83%)
occurrences (all)	258	134	92
Thrombocytopenia			
subjects affected / exposed	53 / 280 (18.93%)	54 / 279 (19.35%)	57 / 277 (20.58%)
occurrences (all)	174	162	180
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	11 / 280 (3.93%)	13 / 279 (4.66%)	14 / 277 (5.05%)
occurrences (all)	34	40	44
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	25 / 280 (8.93%)	3 / 279 (1.08%)	5 / 277 (1.81%)
occurrences (all)	80	8	10
Dry eye			
subjects affected / exposed	20 / 280 (7.14%)	20 / 279 (7.17%)	21 / 277 (7.58%)
occurrences (all)	44	44	42
Eyelid oedema			
subjects affected / exposed	43 / 280 (15.36%)	3 / 279 (1.08%)	5 / 277 (1.81%)
occurrences (all)	114	6	12
Periorbital oedema			
subjects affected / exposed	44 / 280 (15.71%)	1 / 279 (0.36%)	4 / 277 (1.44%)
occurrences (all)	106	2	8
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	13 / 280 (4.64%)	12 / 279 (4.30%)	15 / 277 (5.42%)
occurrences (all)	34	24	36
Abdominal pain			
subjects affected / exposed	37 / 280 (13.21%)	43 / 279 (15.41%)	48 / 277 (17.33%)
occurrences (all)	92	128	116
Abdominal pain upper			
subjects affected / exposed	41 / 280 (14.64%)	51 / 279 (18.28%)	61 / 277 (22.02%)
occurrences (all)	130	170	178
Constipation			
subjects affected / exposed	26 / 280 (9.29%)	63 / 279 (22.58%)	52 / 277 (18.77%)
occurrences (all)	56	168	160
Diarrhoea			

subjects affected / exposed	133 / 280 (47.50%)	58 / 279 (20.79%)	67 / 277 (24.19%)
occurrences (all)	552	202	216
Dyspepsia			
subjects affected / exposed	37 / 280 (13.21%)	32 / 279 (11.47%)	36 / 277 (13.00%)
occurrences (all)	98	90	92
Flatulence			
subjects affected / exposed	12 / 280 (4.29%)	12 / 279 (4.30%)	15 / 277 (5.42%)
occurrences (all)	24	30	34
Gastritis			
subjects affected / exposed	11 / 280 (3.93%)	9 / 279 (3.23%)	18 / 277 (6.50%)
occurrences (all)	26	20	42
Gastrooesophageal reflux disease			
subjects affected / exposed	20 / 280 (7.14%)	15 / 279 (5.38%)	17 / 277 (6.14%)
occurrences (all)	50	36	46
Haemorrhoids			
subjects affected / exposed	18 / 280 (6.43%)	9 / 279 (3.23%)	19 / 277 (6.86%)
occurrences (all)	48	20	40
Nausea			
subjects affected / exposed	118 / 280 (42.14%)	61 / 279 (21.86%)	88 / 277 (31.77%)
occurrences (all)	436	290	264
Toothache			
subjects affected / exposed	18 / 280 (6.43%)	13 / 279 (4.66%)	11 / 277 (3.97%)
occurrences (all)	36	36	26
Vomiting			
subjects affected / exposed	79 / 280 (28.21%)	45 / 279 (16.13%)	60 / 277 (21.66%)
occurrences (all)	344	210	204
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	5 / 280 (1.79%)	53 / 279 (19.00%)	53 / 277 (19.13%)
occurrences (all)	20	218	218
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	21 / 280 (7.50%)	41 / 279 (14.70%)	58 / 277 (20.94%)
occurrences (all)	42	88	140
Dry skin			

subjects affected / exposed	17 / 280 (6.07%)	34 / 279 (12.19%)	40 / 277 (14.44%)
occurrences (all)	36	92	102
Eczema			
subjects affected / exposed	10 / 280 (3.57%)	16 / 279 (5.73%)	11 / 277 (3.97%)
occurrences (all)	28	42	34
Erythema			
subjects affected / exposed	10 / 280 (3.57%)	15 / 279 (5.38%)	18 / 277 (6.50%)
occurrences (all)	20	32	44
Hyperhidrosis			
subjects affected / exposed	4 / 280 (1.43%)	13 / 279 (4.66%)	16 / 277 (5.78%)
occurrences (all)	10	36	36
Night sweats			
subjects affected / exposed	8 / 280 (2.86%)	10 / 279 (3.58%)	18 / 277 (6.50%)
occurrences (all)	20	28	44
Pruritus			
subjects affected / exposed	20 / 280 (7.14%)	61 / 279 (21.86%)	56 / 277 (20.22%)
occurrences (all)	46	178	162
Rash			
subjects affected / exposed	57 / 280 (20.36%)	110 / 279 (39.43%)	124 / 277 (44.77%)
occurrences (all)	186	378	480
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	60 / 280 (21.43%)	72 / 279 (25.81%)	65 / 277 (23.47%)
occurrences (all)	158	220	180
Back pain			
subjects affected / exposed	54 / 280 (19.29%)	64 / 279 (22.94%)	65 / 277 (23.47%)
occurrences (all)	178	194	178
Bone pain			
subjects affected / exposed	16 / 280 (5.71%)	21 / 279 (7.53%)	29 / 277 (10.47%)
occurrences (all)	36	60	60
Muscle spasms			
subjects affected / exposed	97 / 280 (34.64%)	38 / 279 (13.62%)	37 / 277 (13.36%)
occurrences (all)	370	104	118
Musculoskeletal pain			

subjects affected / exposed	24 / 280 (8.57%)	27 / 279 (9.68%)	38 / 277 (13.72%)
occurrences (all)	66	78	96
Myalgia			
subjects affected / exposed	56 / 280 (20.00%)	57 / 279 (20.43%)	55 / 277 (19.86%)
occurrences (all)	152	146	166
Neck pain			
subjects affected / exposed	8 / 280 (2.86%)	19 / 279 (6.81%)	11 / 277 (3.97%)
occurrences (all)	18	44	24
Pain in extremity			
subjects affected / exposed	47 / 280 (16.79%)	47 / 279 (16.85%)	52 / 277 (18.77%)
occurrences (all)	122	154	162
Infections and infestations			
Bronchitis			
subjects affected / exposed	27 / 280 (9.64%)	27 / 279 (9.68%)	19 / 277 (6.86%)
occurrences (all)	82	94	56
Conjunctivitis			
subjects affected / exposed	20 / 280 (7.14%)	21 / 279 (7.53%)	18 / 277 (6.50%)
occurrences (all)	50	48	42
Folliculitis			
subjects affected / exposed	3 / 280 (1.07%)	15 / 279 (5.38%)	17 / 277 (6.14%)
occurrences (all)	6	34	60
Gastroenteritis			
subjects affected / exposed	30 / 280 (10.71%)	24 / 279 (8.60%)	21 / 277 (7.58%)
occurrences (all)	76	56	56
Herpes zoster			
subjects affected / exposed	13 / 280 (4.64%)	14 / 279 (5.02%)	8 / 277 (2.89%)
occurrences (all)	28	28	16
Influenza			
subjects affected / exposed	36 / 280 (12.86%)	45 / 279 (16.13%)	51 / 277 (18.41%)
occurrences (all)	132	140	154
Nasopharyngitis			
subjects affected / exposed	65 / 280 (23.21%)	81 / 279 (29.03%)	67 / 277 (24.19%)
occurrences (all)	298	536	396
Pharyngitis			
subjects affected / exposed	15 / 280 (5.36%)	16 / 279 (5.73%)	17 / 277 (6.14%)
occurrences (all)	46	44	42

Sinusitis			
subjects affected / exposed	20 / 280 (7.14%)	23 / 279 (8.24%)	29 / 277 (10.47%)
occurrences (all)	72	72	104
Upper respiratory tract infection			
subjects affected / exposed	44 / 280 (15.71%)	56 / 279 (20.07%)	67 / 277 (24.19%)
occurrences (all)	152	226	248
Urinary tract infection			
subjects affected / exposed	12 / 280 (4.29%)	16 / 279 (5.73%)	27 / 277 (9.75%)
occurrences (all)	54	46	102
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	13 / 280 (4.64%)	28 / 279 (10.04%)	22 / 277 (7.94%)
occurrences (all)	32	76	54
Hypercholesterolaemia			
subjects affected / exposed	3 / 280 (1.07%)	33 / 279 (11.83%)	39 / 277 (14.08%)
occurrences (all)	8	78	98
Hyperglycaemia			
subjects affected / exposed	8 / 280 (2.86%)	28 / 279 (10.04%)	28 / 277 (10.11%)
occurrences (all)	24	92	122
Hyperlipidaemia			
subjects affected / exposed	1 / 280 (0.36%)	19 / 279 (6.81%)	15 / 277 (5.42%)
occurrences (all)	2	46	40
Hyperuricaemia			
subjects affected / exposed	5 / 280 (1.79%)	12 / 279 (4.30%)	15 / 277 (5.42%)
occurrences (all)	12	32	38
Hypokalaemia			
subjects affected / exposed	15 / 280 (5.36%)	19 / 279 (6.81%)	11 / 277 (3.97%)
occurrences (all)	40	50	40
Hypophosphataemia			
subjects affected / exposed	50 / 280 (17.86%)	45 / 279 (16.13%)	55 / 277 (19.86%)
occurrences (all)	220	166	202

Non-serious adverse events	All Patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	821 / 836 (98.21%)		
Vascular disorders			

Hypertension			
subjects affected / exposed	116 / 836 (13.88%)		
occurrences (all)	248		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	107 / 836 (12.80%)		
occurrences (all)	320		
Chills			
subjects affected / exposed	34 / 836 (4.07%)		
occurrences (all)	74		
Face oedema			
subjects affected / exposed	49 / 836 (5.86%)		
occurrences (all)	132		
Fatigue			
subjects affected / exposed	181 / 836 (21.65%)		
occurrences (all)	494		
Influenza like illness			
subjects affected / exposed	43 / 836 (5.14%)		
occurrences (all)	154		
Non-cardiac chest pain			
subjects affected / exposed	56 / 836 (6.70%)		
occurrences (all)	136		
Oedema peripheral			
subjects affected / exposed	138 / 836 (16.51%)		
occurrences (all)	400		
Pyrexia			
subjects affected / exposed	129 / 836 (15.43%)		
occurrences (all)	402		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	157 / 836 (18.78%)		
occurrences (all)	492		
Dyspnoea			
subjects affected / exposed	84 / 836 (10.05%)		
occurrences (all)	214		
Oropharyngeal pain			

subjects affected / exposed	84 / 836 (10.05%)		
occurrences (all)	228		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	71 / 836 (8.49%)		
occurrences (all)	172		
Depression			
subjects affected / exposed	56 / 836 (6.70%)		
occurrences (all)	130		
Insomnia			
subjects affected / exposed	101 / 836 (12.08%)		
occurrences (all)	252		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	192 / 836 (22.97%)		
occurrences (all)	714		
Amylase increased			
subjects affected / exposed	55 / 836 (6.58%)		
occurrences (all)	190		
Aspartate aminotransferase increased			
subjects affected / exposed	112 / 836 (13.40%)		
occurrences (all)	356		
Blood alkaline phosphatase increased			
subjects affected / exposed	36 / 836 (4.31%)		
occurrences (all)	92		
Blood bilirubin increased			
subjects affected / exposed	81 / 836 (9.69%)		
occurrences (all)	388		
Blood cholesterol increased			
subjects affected / exposed	31 / 836 (3.71%)		
occurrences (all)	76		
Blood creatinine increased			
subjects affected / exposed	35 / 836 (4.19%)		
occurrences (all)	104		
Blood phosphorus decreased			

subjects affected / exposed occurrences (all) Haemoglobin decreased subjects affected / exposed occurrences (all) Lipase increased subjects affected / exposed occurrences (all) Weight decreased subjects affected / exposed occurrences (all) Weight increased subjects affected / exposed occurrences (all)	29 / 836 (3.47%) 114 36 / 836 (4.31%) 106 89 / 836 (10.65%) 338 36 / 836 (4.31%) 82 73 / 836 (8.73%) 200		
Injury, poisoning and procedural complications Procedural pain subjects affected / exposed occurrences (all)	30 / 836 (3.59%) 74		
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	48 / 836 (5.74%) 126		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Hypoaesthesia subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all)	99 / 836 (11.84%) 270 265 / 836 (31.70%) 1052 32 / 836 (3.83%) 70 37 / 836 (4.43%) 94		
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	150 / 836 (17.94%)		
occurrences (all)	470		
Leukopenia			
subjects affected / exposed	92 / 836 (11.00%)		
occurrences (all)	326		
Neutropenia			
subjects affected / exposed	132 / 836 (15.79%)		
occurrences (all)	484		
Thrombocytopenia			
subjects affected / exposed	164 / 836 (19.62%)		
occurrences (all)	516		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	38 / 836 (4.55%)		
occurrences (all)	118		
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	33 / 836 (3.95%)		
occurrences (all)	98		
Dry eye			
subjects affected / exposed	61 / 836 (7.30%)		
occurrences (all)	130		
Eyelid oedema			
subjects affected / exposed	51 / 836 (6.10%)		
occurrences (all)	132		
Periorbital oedema			
subjects affected / exposed	49 / 836 (5.86%)		
occurrences (all)	116		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	40 / 836 (4.78%)		
occurrences (all)	94		
Abdominal pain			
subjects affected / exposed	128 / 836 (15.31%)		
occurrences (all)	336		
Abdominal pain upper			

subjects affected / exposed	153 / 836 (18.30%)		
occurrences (all)	478		
Constipation			
subjects affected / exposed	141 / 836 (16.87%)		
occurrences (all)	384		
Diarrhoea			
subjects affected / exposed	258 / 836 (30.86%)		
occurrences (all)	970		
Dyspepsia			
subjects affected / exposed	105 / 836 (12.56%)		
occurrences (all)	280		
Flatulence			
subjects affected / exposed	39 / 836 (4.67%)		
occurrences (all)	88		
Gastritis			
subjects affected / exposed	38 / 836 (4.55%)		
occurrences (all)	88		
Gastrooesophageal reflux disease			
subjects affected / exposed	52 / 836 (6.22%)		
occurrences (all)	132		
Haemorrhoids			
subjects affected / exposed	46 / 836 (5.50%)		
occurrences (all)	108		
Nausea			
subjects affected / exposed	267 / 836 (31.94%)		
occurrences (all)	990		
Toothache			
subjects affected / exposed	42 / 836 (5.02%)		
occurrences (all)	98		
Vomiting			
subjects affected / exposed	184 / 836 (22.01%)		
occurrences (all)	758		
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	111 / 836 (13.28%)		
occurrences (all)	456		

Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	120 / 836 (14.35%)		
occurrences (all)	270		
Dry skin			
subjects affected / exposed	91 / 836 (10.89%)		
occurrences (all)	230		
Eczema			
subjects affected / exposed	37 / 836 (4.43%)		
occurrences (all)	104		
Erythema			
subjects affected / exposed	43 / 836 (5.14%)		
occurrences (all)	96		
Hyperhidrosis			
subjects affected / exposed	33 / 836 (3.95%)		
occurrences (all)	82		
Night sweats			
subjects affected / exposed	36 / 836 (4.31%)		
occurrences (all)	92		
Pruritus			
subjects affected / exposed	137 / 836 (16.39%)		
occurrences (all)	386		
Rash			
subjects affected / exposed	291 / 836 (34.81%)		
occurrences (all)	1044		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	197 / 836 (23.56%)		
occurrences (all)	558		
Back pain			
subjects affected / exposed	183 / 836 (21.89%)		
occurrences (all)	550		
Bone pain			
subjects affected / exposed	66 / 836 (7.89%)		
occurrences (all)	156		
Muscle spasms			

subjects affected / exposed	172 / 836 (20.57%)		
occurrences (all)	592		
Musculoskeletal pain			
subjects affected / exposed	89 / 836 (10.65%)		
occurrences (all)	240		
Myalgia			
subjects affected / exposed	168 / 836 (20.10%)		
occurrences (all)	464		
Neck pain			
subjects affected / exposed	38 / 836 (4.55%)		
occurrences (all)	86		
Pain in extremity			
subjects affected / exposed	146 / 836 (17.46%)		
occurrences (all)	438		
Infections and infestations			
Bronchitis			
subjects affected / exposed	73 / 836 (8.73%)		
occurrences (all)	232		
Conjunctivitis			
subjects affected / exposed	59 / 836 (7.06%)		
occurrences (all)	140		
Folliculitis			
subjects affected / exposed	35 / 836 (4.19%)		
occurrences (all)	100		
Gastroenteritis			
subjects affected / exposed	75 / 836 (8.97%)		
occurrences (all)	188		
Herpes zoster			
subjects affected / exposed	35 / 836 (4.19%)		
occurrences (all)	72		
Influenza			
subjects affected / exposed	132 / 836 (15.79%)		
occurrences (all)	426		
Nasopharyngitis			
subjects affected / exposed	213 / 836 (25.48%)		
occurrences (all)	1230		

Pharyngitis subjects affected / exposed occurrences (all)	48 / 836 (5.74%) 132		
Sinusitis subjects affected / exposed occurrences (all)	72 / 836 (8.61%) 248		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	167 / 836 (19.98%) 626		
Urinary tract infection subjects affected / exposed occurrences (all)	55 / 836 (6.58%) 202		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	63 / 836 (7.54%) 162		
Hypercholesterolaemia subjects affected / exposed occurrences (all)	75 / 836 (8.97%) 184		
Hyperglycaemia subjects affected / exposed occurrences (all)	64 / 836 (7.66%) 238		
Hyperlipidaemia subjects affected / exposed occurrences (all)	35 / 836 (4.19%) 88		
Hyperuricaemia subjects affected / exposed occurrences (all)	32 / 836 (3.83%) 82		
Hypokalaemia subjects affected / exposed occurrences (all)	45 / 836 (5.38%) 130		
Hypophosphataemia subjects affected / exposed occurrences (all)	150 / 836 (17.94%) 588		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 March 2007	Amendment 1 (released 20 weeks before first patient first visit on 31-Jul-2007) was a local, country-specific amendment for Japan. The modifications to the protocol were made in order to allow patients in Japan to participate in this global study. Specifically, this study clarified the tablet strength for imatinib and stated that PK parameters in Japanese patients would be investigated more thoroughly. This amendment also indicated that Japan would not be participating in the pharmacogenetic, pharmacogenomic, and biomarker portions of the study. Additionally, changes were made to align study procedures in data review/management and safety monitoring/reporting with Japanese standards of practice.
09 June 2007	Amendment 2 (released seven weeks before first patient first visit on 31-Jul-2007) was a global amendment to reflect newly available data in support of an alternate nilotinib lower dose and regimen (300 mg bid replaced 600 mg qd). This amendment re moved (1) the dose escalation in the nilotinib 300 mg bid arm and (2) the crossover regimens for all arms, while establishing an extension protocol (Protocol post-text supplement 4) to allow for continuation of therapy after patients had demonstrated lack of response to their assigned treatment regimen. Clarifications of the dose escalation in the imatinib arm and the use and definition of MMR in the clinical conduct of the study were also made. Statistically, the protocol was amended to include the following: "durable" MMR to be measured at 24 months, patients with missing data were to be considered as non-responders, confirmed responses for MMR, and the presentation of ≥ 4.5 log reduction in BCR-ABL transcripts.
29 November 2007	Amendment 3 (released on 29-Nov-2007 after 69 patients were enrolled into the study) was a global amendment. The major changes in this amendment included: -The dosage form of nilotinib (50 mg capsules) was replaced with 150 mg capsules in the nilotinib 300 mg treatment arm; - Clarifications were made to the dose reduction guidelines for study drug related non-hematological toxicities; - The restriction of using Erythropoiesis Stimulating Agents was removed from the protocol, the use of leukapheresis and hydroxyurea and/or anagrelide was to be permitted during the first month of treatment; - The frequency of the patients' reported outcome assessment was reduced; - The entrance criteria to the extension study were clarified; - The PCR committee was removed from the protocol. Additionally, the ECHO and ECG review processes were clarified as follows: (1). ECHOs were to be reviewed both locally and centrally. Study eligibility and all clinical decisions (including dose-adjustments) were to be based on local ECHO reads. Centrally read ECHO results were to be used for the data analyses; (2) the enrollment of patients had to be based on centrally assessed QTcF time. If one of the three serial ECGs prior to dosing on Day 1 of Cycle 1 showed a QTcF >450 ms by automated reading, an immediate manual central reading had to be requested by calling CRO. The patient was not to be dosed if the average of the manually read ECGs confirmed a QTcF >450 ms.

21 October 2008	Amendment 4 (released on 21-Oct-2008, following completion of enrolment on 30-Sep-2008, total 846 patients were enrolled into the study) was a global amendment. Some of th major changes in this amendment included: - Cardiac troponin was assessed whenever clinically indicated; - "No MMR at 18 months" and "loss of MMR at any time" were moved from the list of definitions of "treatment failures" to the list of definition of "suboptimal responses"; - "Evidence of clonal evolution" was deleted from the list of AP defining criteria; - The dose reduction guidelines for hypophosphatemia, pancreatitis and QTc prolongation were clarified; - For patients who achieved undetectable BCR-ABL by RQ-PCR due to variability in sample quality and blood cell counts, a repeat assay using more than 10 mL of blood may have been needed to determine whether a ≤ 0.01% and ≤ 0.0032% BCR-ABL/ABL% level was reached. Therefore, collection of 20 mL of blood from these patients for PCR analysis was permitted; - The measurement frequency of glucose, insulin, C-peptide, glycosylated hemoglobin A1c (HbA1c) and lipid panel was modified; - Time to event CRF page was removed from CRF binder since the information on this page can be derived from data collected; - The time points of mandatory manual differential counts were clarified; - The time points of evaluation of cytogenetic response were clarified, bone marrow aspirates and/or biopsies were to be performed at the end of every six cycles until Month 24; - Full PK blood samples could be drawn any day after Day 8 at protocol-defined time points; - The definition of a molecular or cytogenetic response duration, and the definition of loss of a molecular or cytogenetic response were clarified;
08 June 2009	Amendment 5 (released on 08-Jun-2009) was a local, country-specific amendment for Sweden. This amendment includes all changes introduced with global Amendment 4, except the "evidence of clonal evolution" which remains in the list of AP defining criteria upon request from the Swedish medical products agency. The amendments described above (all introduced before primary analysis database lock on 08-Oct-2009) are not considered to affect the interpretation of study results, as most changes were made to enhance safety monitoring. No changes were made to study end points; however, a sensitivity analysis was added to the planned analyses for progression to AP/BC including clonal evolution as a progression criterion
30 July 2010	Amendment 6 (released on 30-Jul-2010) was a global amendment. The purpose of this amendment was to: remove the comparison of MMR rates at 12 months between studies CAMN107A2303 and CSTI571K2301 from exploratory objectives, modify the decision algorithm for patients insufficiently responding to their assigned core study treatments, amend the schedule of cytogenetic bone marrow assessments, allow patients who have been dose escalated from imatinib 400 mg QD and did not tolerate 400 mg BID imatinib or reduced dose levels of 600 mg QD imatinib, further dose de-escalation to highest tolerable dose. Patients who do not tolerate 300 mg QD must discontinue treatment, removal of the prohibition on the concurrent use of nilotinib with warfarin or other coumarin derivatives, extend biomarker test sample collection beyond Cycle 12, add ECG with central reading after month 12, remove requirements of collecting pregnancy outcomes from female partners of male patients, integrate into the protocol clarifications from the RAP , implement additional changes in the extension protocol.
11 July 2011	Amendment 7 (released on 11-July-2011) was a global amendment. The purpose of this amendment was to: modify decision algorithm, combine safety analyses with the annual analyses of the study after the Month 24 analysis time point and to disband DMC if there are no significant new safety findings in the Month 36 analysis, remove PK sample collection at the end of core study visit or early discontinuation visit, to remove time-off data collection at cycle 36 and 48, remove treatment options in the event of early termination of nilotinib 300mg BID arm.

31 January 2012	Amendment 8 (released on 31-Jan-2012) was a global amendment and major changes included: - the duration of the study was extended to 10 calendar years from 15-Oct-2008: date when the last patient randomized to the core study received the first dose of study drug. Therefore, the end of study date or Last Patient Last Visit is projected to be 15-Oct-2018. All end-of-study evaluations for ongoing patients must be completed by this date. This includes survival information follow-up on those patients who have discontinued for reasons other than death. By the end of the study, all patients would have received at least 10 calendar years of treatment or discontinued from the study; - remove the option for patients treated with nilotinib in the core study and experiencing unsatisfactory therapeutic effect to enter the extension study to receive imatinib - the current visit frequency after End of Cycle 60 was revised from every 3 months to every six months for patients in MMR; - Bone marrow biopsy for cytogenetics was no longer required to evaluate response; - Vital sign parameters were reduced to assessments of blood pressure and body weight at each visit; cardiac safety monitoring and laboratory safety assessments were modified, collection of the SF-36 and Fact-Leu questionnaires was extended.
09 August 2013	Amendment 9 (released on 09-Aug-2013) was a global amendment. The purpose of this amendment was to 1) provide additional guidance for the management of ischemic vascular or ischemic cardiovascular events, 2) outlined acceptable contraception methods for female patients of childbearing potential and revised pregnancy testing and reporting processes and 3) clarified the use of commercial drug supply of imatinib and nilotinib.
03 November 2014	Amendment 10 (released on 03-Nov-2014) was a global amendment. The purpose of this amendment was to: - modify treatment guidelines for patients on the nilotinib 400 mg BID treatment arm in the context of ischemic cardio/vascular events - eliminate the Ischemic Vascular or Ischemic Cardiovascular AE Fax alert form - incorporate nilotinib program-wide language regarding monitoring and treatment of glucose and cholesterol as well as dose reduction guidelines - emphasize the importance of monitoring glucose levels in patients and - provide a harmonization on dose reductions guidelines across Novartis-sponsored Tasigna study protocols
18 April 2016	Amendment 11 (released on 18-Apr-2016) was a global amendment. The purpose of this amendment was to include hepatitis B virus testing as one of the study procedures, to identify study patients who may be at risk of hepatitis B virus reactivation. Reactivation of hepatitis B virus infection could occur in patients who were chronic carriers of this virus and were receiving a drug of the BCR-ABL TKI class such as nilotinib/imatinib. Some cases involving BCR-ABL TKI resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.
30 March 2017	Amendment 12 (released on 30-Mar-2017) was a global amendment. The main purpose for the amendment was: - To change the source of the Reference Safety Information for Glivec® (imatinib), Novartis has taken the decision to discontinue the use of the Investigator´s Brochure for Glivec® (imatinib), since Glivec has been on the market for more than 15 years (first registered in 2001) and has a well-established efficacy/safety profile. The Glivec IB version 19 (dated 21-Jun-2016) is the final IB for the compound. As of the dispatch of the Glivec DSUR 006 in July 2017, the latest approved national/regional product information (e.g. in the EU Summary of Product Characteristics) will serve as the reference safety information (RSI) for the compound. In addition, there is no further global clinical development planned for the compound. - After Cycle 60, all ECG assessments were to be performed and assessed locally. The reference to the central evaluation via vendor (eRT) has been removed from the toxicity guidelines for study drug-related non-hematologic toxicity.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Notes: