



Clinical trial results:

A Phase 3 randomized, double-blind study of induction (daunorubicin/cytarabine) and consolidation (high-dose cytarabine) chemotherapy + midostaurin (PKC412) or placebo in newly diagnosed patients <60 years of age with FLT3-mutated acute myeloid leukemia

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.

Summary

EudraCT number	2006-006852-37
Trial protocol	DE ES AT CZ NL SK HU BE IT FR GB
Global end of trial date	26 March 2022

Results information

Result version number	v1 (current)
This version publication date	09 April 2023
First version publication date	09 April 2023

Trial information

Trial identification

Sponsor protocol code	CPKC412A2301
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00651261
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.emain@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111, novartis.emain@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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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	26 March 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 March 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to determine if the addition of midostaurin to daunorubicin/cytarabine induction, high-dose cytarabine consolidation, and continuation therapy improved long-term overall survival (OS) in mutant fms-like tyrosine inase 3 (FLT3)-AML patients.

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	08 May 2008
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	Australia: 2
Country: Number of subjects enrolled	Austria: 12
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	Czechia: 11
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 305
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Italy: 105
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Slovakia: 4
Country: Number of subjects enrolled	Spain: 22
Country: Number of subjects enrolled	United States: 223

Worldwide total number of subjects	717
EEA total number of subjects	479

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)	717
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were enrolled across 13 countries at 177 study centers.

Pre-assignment

Screening details:

This study comprised of 3 phases: Induction, Consolidation and Continuation phase. The randomization was stratified by FLT3 mutation status.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Induction and Consolidation Chemotherapy Plus Midostaurin

Arm description:

Patients received daunorubicin 60 mg/m² by IV push days 1-3 plus cytarabine 200 mg/m² IV days 1-7, and midostaurin 50 mg orally twice daily days 8-21. Participants achieving remission received four 28 day cycles of high dose cytarabine (3000 mg/m²) days 1, 3, & 5 and midostaurin at 50 mg orally twice daily days 8-14. Maintenance therapy was given to participants who continued in remission for 12 28-day cycles of midostaurin 50 mg orally twice daily.

Arm type	Experimental
Investigational medicinal product name	Midostaurin
Investigational medicinal product code	PKC412
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Induction Phase: 50 mg bid on Days 8-21

Consolidation Phase: 50 mg orally bid on Days 8-21

Continuation Phase: 50 mg bid orally on Days 1-28) for up to 12 cycles of 28 days.

Investigational medicinal product name	Daunorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Induction Phase: Daunorubicin 60 mg/m²/day by iv push or short infusion on Days 1–3 for up to 2 cycles

Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Induction Phase: Cytarabine 200 mg/m²/day continuous iv infusion on Days 1-7

Consolidation Phase: high dose cytarabine (3000 mg/m² iv every 12 hours on Days 1, 3, and 5) for up to 4 cycles

Arm title	Induction and Consolidation Chemotherapy Plus Placebo
Arm description:	
Patients received daunorubicin 60 mg/m ² by IV push days 1-3 plus cytarabine 200 mg/m ² IV days 1-7, and placebo 50 mg orally twice daily days 8-21. Participants achieving remission received four 28 day cycles of high dose cytarabine (3000 mg/m ²) days 1, 3, & 5 and placebo at 50 mg orally twice daily days 8-14. Maintenance therapy was given to participants who continued in remission for 12 28-day cycles of placebo 50 mg orally twice daily.	
Arm type	Placebo
Investigational medicinal product name	Matching Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use
Dosage and administration details:	
Matching placebo was administered orally via a bid regimen	
Investigational medicinal product name	Daunorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Induction Phase: Daunorubicin 60 mg/m ² /day by iv push or short infusion on Days 1–3 for up to 2 cycles	
Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Induction Phase: Cytarabine 200 mg/m ² /day continuous iv infusion on Days 1-7	
Consolidation Phase: high dose cytarabine (3000 mg/m ² iv every 12 hours on Days 1, 3, and 5) for up to 4 cycles	

Number of subjects in period 1	Induction and Consolidation Chemotherapy Plus Midostaurin	Induction and Consolidation Chemotherapy Plus Placebo
Started	360	357
Completed	69	52
Not completed	291	305
Pt off-treatment for other complicating disease	3	2
Consent withdrawn by subject	22	40
Disease progression	58	58
Adverse Event	32	22
Death	18	18
Other	44	55
Alternative therapy	109	107
Untreated	5	3

Baseline characteristics

Reporting groups

Reporting group title	Induction and Consolidation Chemotherapy Plus Midostaurin
Reporting group description:	
Patients received daunorubicin 60 mg/m ² by IV push days 1-3 plus cytarabine 200 mg/m ² IV days 1-7, and midostaurin 50 mg orally twice daily days 8-21. Participants achieving remission received four 28 day cycles of high dose cytarabine (3000 mg/m ²) days 1, 3, & 5 and midostaurin at 50 mg orally twice daily days 8-14. Maintenance therapy was given to participants who continued in remission for 12 28-day cycles of midostaurin 50 mg orally twice daily.	
Reporting group title	Induction and Consolidation Chemotherapy Plus Placebo
Reporting group description:	
Patients received daunorubicin 60 mg/m ² by IV push days 1-3 plus cytarabine 200 mg/m ² IV days 1-7, and placebo 50 mg orally twice daily days 8-21. Participants achieving remission received four 28 day cycles of high dose cytarabine (3000 mg/m ²) days 1, 3, & 5 and placebo at 50 mg orally twice daily days 8-14. Maintenance therapy was given to participants who continued in remission for 12 28-day cycles of placebo 50 mg orally twice daily.	

Reporting group values	Induction and Consolidation Chemotherapy Plus Midostaurin	Induction and Consolidation Chemotherapy Plus Placebo	Total
Number of subjects	360	357	717
Age Categorical Units: Subjects			

Age Continuous Units: years median full range (min-max)	47.0 19 to 59	48.0 18 to 60	-
Gender Categorical Units: Subjects			
Female	186	212	398
Male	174	145	319
FLT3 mutational subtype			
Mutations in the gene encoding the trans-membrane tyrosine kinase FLT3. FLT3 internal tandem duplications (ITD) mutation which results in a duplication between 3 and greater than 100 amino acids most commonly located in the juxtamembrane region. Tyrosine kinase domain (TKD) point mutations are the remainder of those with FLT3 mutations. FLT3 testing was done centrally.			
Units: Subjects			
TKD (No ITD)	81	81	162
ITD Allelic ratio <0.7	171	170	341
ITD Allelic ratio ≥0.7	108	106	214
Race Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	8	5	13
Black or African American	8	9	17
White	147	128	275
More than one race	2	1	3
Unknown or Not Reported	195	213	408

End points

End points reporting groups

Reporting group title	Induction and Consolidation Chemotherapy Plus Midostaurin
Reporting group description:	
Patients received daunorubicin 60 mg/m ² by IV push days 1-3 plus cytarabine 200 mg/m ² IV days 1-7, and midostaurin 50 mg orally twice daily days 8-21. Participants achieving remission received four 28 day cycles of high dose cytarabine (3000 mg/m ²) days 1, 3, & 5 and midostaurin at 50 mg orally twice daily days 8-14. Maintenance therapy was given to participants who continued in remission for 12 28-day cycles of midostaurin 50 mg orally twice daily.	
Reporting group title	Induction and Consolidation Chemotherapy Plus Placebo
Reporting group description:	
Patients received daunorubicin 60 mg/m ² by IV push days 1-3 plus cytarabine 200 mg/m ² IV days 1-7, and placebo 50 mg orally twice daily days 8-21. Participants achieving remission received four 28 day cycles of high dose cytarabine (3000 mg/m ²) days 1, 3, & 5 and placebo at 50 mg orally twice daily days 8-14. Maintenance therapy was given to participants who continued in remission for 12 28-day cycles of placebo 50 mg orally twice daily.	

Primary: Overall survival (OS) - Non-censored at the time of Stem Cell Transplantation (SCT)

End point title	Overall survival (OS) - Non-censored at the time of Stem Cell Transplantation (SCT)
End point description:	
Overall survival (OS) was defined as the time interval from randomization to death from any cause. The median OS with 95% CI was estimated using the Kaplan-Meier method.	
End point type	Primary
End point timeframe:	
Up to 10 years	

End point values	Induction and Consolidation Chemotherapy Plus Midostaurin	Induction and Consolidation Chemotherapy Plus Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	360	357		
Units: months				
median (confidence interval 95%)	67.71 (31.54 to 109.7)	25.59 (18.53 to 42.87)		

Statistical analyses

Statistical analysis title	Midostaurin vs. Placebo for OS (non-censoring)
Comparison groups	Induction and Consolidation Chemotherapy Plus Midostaurin v Induction and Consolidation Chemotherapy Plus Placebo

Number of subjects included in analysis	717
Analysis specification	Pre-specified
Analysis type	superiority
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1

Secondary: Overall Survival - Censored at the time of SCT

End point title	Overall Survival - Censored at the time of SCT
End point description:	
Overall survival (OS) was defined as the time interval from randomization to death from any cause. Any participants who received a stem cell transplant were censored at the time of transplant. The median OS with 95% CI was estimated using the Kaplan-Meier method.	
End point type	Secondary
End point timeframe:	
Up to 10 years	

End point values	Induction and Consolidation Chemotherapy Plus Midostaurin	Induction and Consolidation Chemotherapy Plus Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	360	357		
Units: months				
median (confidence interval 95%)	999 (104.8 to 999)	99 (27.43 to 999)		

Statistical analyses

Statistical analysis title	Midostaurin vs. Placebo (Censored)
Comparison groups	Induction and Consolidation Chemotherapy Plus Midostaurin v Induction and Consolidation Chemotherapy Plus Placebo
Number of subjects included in analysis	717
Analysis specification	Pre-specified
Analysis type	superiority
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	1.07

Secondary: Event free survival (EFS) - non-censored for SCT (Key Secondary endpoint)

End point title	Event free survival (EFS) - non-censored for SCT (Key Secondary endpoint)
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End point description:

Event free survival (EFS) was defined as the time from randomization until the earliest qualifying event, including: failure to obtain a complete response (CR) on or before 60 days of initiation of protocol therapy; relapse; or death from any cause. Patients alive and event free at the time of analysis were censored on the date of last clinical assessment. The median EFS with 95% CI was estimated using the Kaplan-Meier method. Due to a higher than expected transplant rate, EFS was promoted to be a key secondary endpoint.

End point type	Secondary
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End point timeframe:

Up to 10 years

End point values	Induction and Consolidation Chemotherapy Plus Midostaurin	Induction and Consolidation Chemotherapy Plus Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	360	357		
Units: months				
median (confidence interval 95%)	8.25 (5.45 to 11.07)	2.99 (1.91 to 5.91)		

Statistical analyses

Statistical analysis title	Midostaurin vs. Placebo - EFS
Comparison groups	Induction and Consolidation Chemotherapy Plus Midostaurin v Induction and Consolidation Chemotherapy Plus Placebo
Number of subjects included in analysis	717
Analysis specification	Pre-specified
Analysis type	superiority
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	0.94

Secondary: Complete Response Rate (CRR)

End point title	Complete Response Rate (CRR)
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End point description:

Percentage of participants who achieved a complete response (CR). A CR was defined as normalization of blood counts and a marrow showing less than 5% blasts occurring on or before day 60.

End point type	Secondary
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End point timeframe:

Induction therapy (up to 60 days)

End point values	Induction and Consolidation Chemotherapy Plus Midostaurin	Induction and Consolidation Chemotherapy Plus Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	360	357		
Units: Percentage of Subjects				
number (not applicable)	58.9	53.5		

Statistical analyses

Statistical analysis title	Midostaurin vs. Placebo (CRR)
Comparison groups	Induction and Consolidation Chemotherapy Plus Midostaurin v Induction and Consolidation Chemotherapy Plus Placebo
Number of subjects included in analysis	717
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.073 ^[1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.13

Notes:

[1] - One-sided p-value calculated using Cochran-Mantel-Haenszel test for two proportions adjusted for the FLT3 randomization stratum

Secondary: Disease-free Survival (DFS) - non-censored at the time of SCT

End point title	Disease-free Survival (DFS) - non-censored at the time of SCT
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End point description:

Disease free survival (DFS) is defined as the time from documentation of first clinical response (CR) at any time to the first of relapse or death from any cause in participants who achieved a CR.

End point type	Secondary
End point timeframe:	
Up to 10 years	

End point values	Induction and Consolidation Chemotherapy Plus Midostaurin	Induction and Consolidation Chemotherapy Plus Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	360	357		
Units: months				
median (confidence interval 95%)	26.74 (19.78 to 92.81)	15.51 (11.33 to 23.46)		

Statistical analyses

Statistical analysis title	Midostaurin vs. Placebo (DFS)
Comparison groups	Induction and Consolidation Chemotherapy Plus Midostaurin v Induction and Consolidation Chemotherapy Plus Placebo
Number of subjects included in analysis	717
Analysis specification	Pre-specified
Analysis type	superiority
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	0.95

Secondary: Disease-free Survival (DFS) Rate one year after completing the planned continuation phase

End point title	Disease-free Survival (DFS) Rate one year after completing the planned continuation phase
End point description:	
DFS was modified to reflect time from end of continuation to relapse/death from any cause. DFS was assessed for all patients having a CR within 60 days of treatment initiation, and who had completed continuation therapy (i.e. had taken study drug for a minimum of 335 days) and were still in CR. The outcome is presented as an estimated probability without an event at 1 year after completing continuation therapy for subjects.	
End point type	Secondary
End point timeframe:	
one year after completion of continuation therapy	

End point values	Induction and Consolidation Chemotherapy Plus Midostaurin	Induction and Consolidation Chemotherapy Plus Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	41		
Units: rate				
number (confidence interval 95%)	0.74 (0.61 to 0.84)	0.90 (0.76 to 0.96)		

Statistical analyses

Statistical analysis title	Midostaurin vs Placebo (FFS rate)
Comparison groups	Induction and Consolidation Chemotherapy Plus Midostaurin v Induction and Consolidation Chemotherapy Plus Placebo
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	3.22

Secondary: Stem cell transplantation (SCT) rates - Overall

End point title	Stem cell transplantation (SCT) rates - Overall
End point description:	Stem cell transplantation rates is defined as to compare the SCT rates whether they are similar in the two treatment groups
End point type	Secondary
End point timeframe:	
Up to 10 years	

End point values	Induction and Consolidation Chemotherapy Plus Midostaurin	Induction and Consolidation Chemotherapy Plus Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	360	357		
Units: Percentage of Subjects				
number (not applicable)	60.8	55.5		

Statistical analyses

Statistical analysis title	Midostaurin vs. Placebo (SCT)
Comparison groups	Induction and Consolidation Chemotherapy Plus Midostaurin v Induction and Consolidation Chemotherapy Plus Placebo
Number of subjects included in analysis	717
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in proportions
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.13

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Only Adverse Events (AEs) occurring after the date of the first study drug intake and up to 30 days after the last study drug intake are reported up to a maximum duration of 10 years.

* In North America, 13 expected AEs had all grades collected. For all

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
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Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Induction and Consolidation Chemotherapy Plus Midostaurin
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Reporting group description:

Patients received daunorubicin 60 mg/m² by IV push days 1-3 plus cytarabine 200 mg/m² IV days 1-7, and midostaurin 50 mg orally twice daily days 8-21. Participants achieving remission received four 28 day cycles of high dose cytarabine (3000 mg/m²) days 1, 3, & 5 and midostaurin at 50 mg orally twice daily days 8-14. Maintenance therapy was given to participants who continued in remission for 12 28-day cycles of midostaurin 50 mg orally twice daily.

Reporting group title	ALL Subjects
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Reporting group description:

This includes all subjects who participated in the trial.

Reporting group title	Induction and Consolidation Chemotherapy Plus Placebo
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Reporting group description:

Patients received daunorubicin 60 mg/m² by IV push days 1-3 plus cytarabine 200 mg/m² IV days 1-7, and placebo 50 mg orally twice daily days 8-21. Participants achieving remission received four 28 day cycles of high dose cytarabine (3000 mg/m²) days 1, 3, & 5 and placebo at 50 mg orally twice daily days 8-14. Maintenance therapy was given to participants who continued in remission for 12 28-day cycles of placebo 50 mg orally twice daily.

Serious adverse events	Induction and Consolidation Chemotherapy Plus Midostaurin	ALL Subjects	Induction and Consolidation Chemotherapy Plus Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	172 / 345 (49.86%)	346 / 680 (50.88%)	174 / 335 (51.94%)
number of deaths (all causes)	15	36	21
number of deaths resulting from adverse events	9	16	7
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma of liver			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Colon cancer metastatic			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cancer pain			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Testicular neoplasm			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelodysplastic syndrome			
subjects affected / exposed	1 / 345 (0.29%)	2 / 680 (0.29%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	2 / 345 (0.58%)	4 / 680 (0.59%)	2 / 335 (0.60%)
occurrences causally related to treatment / all	0 / 2	1 / 4	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phlebitis superficial			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			

subjects affected / exposed	16 / 345 (4.64%)	20 / 680 (2.94%)	4 / 335 (1.19%)
occurrences causally related to treatment / all	6 / 17	8 / 21	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	1 / 345 (0.29%)	3 / 680 (0.44%)	2 / 335 (0.60%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Oophorectomy			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Catheter site erythema			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	7 / 345 (2.03%)	13 / 680 (1.91%)	6 / 335 (1.79%)
occurrences causally related to treatment / all	6 / 8	15 / 17	9 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	1 / 345 (0.29%)	3 / 680 (0.44%)	2 / 335 (0.60%)
occurrences causally related to treatment / all	0 / 1	2 / 3	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Influenza like illness			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	1 / 345 (0.29%)	2 / 680 (0.29%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 1	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multi-organ failure			
subjects affected / exposed	2 / 345 (0.58%)	6 / 680 (0.88%)	4 / 335 (1.19%)
occurrences causally related to treatment / all	2 / 2	4 / 6	2 / 4
deaths causally related to treatment / all	2 / 2	4 / 5	2 / 3
Localised oedema			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injection site reaction			
subjects affected / exposed	1 / 345 (0.29%)	3 / 680 (0.44%)	2 / 335 (0.60%)
occurrences causally related to treatment / all	1 / 1	1 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis in device			
subjects affected / exposed	3 / 345 (0.87%)	4 / 680 (0.59%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	1 / 3	1 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Pyrexia			
subjects affected / exposed	9 / 345 (2.61%)	19 / 680 (2.79%)	10 / 335 (2.99%)
occurrences causally related to treatment / all	3 / 14	5 / 24	2 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			

subjects affected / exposed	2 / 345 (0.58%)	3 / 680 (0.44%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	3 / 3	4 / 4	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Unevaluable event			
subjects affected / exposed	1 / 345 (0.29%)	2 / 680 (0.29%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 345 (0.00%)	4 / 680 (0.59%)	4 / 335 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactic reaction			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Uterine haemorrhage			
subjects affected / exposed	2 / 345 (0.58%)	4 / 680 (0.59%)	2 / 335 (0.60%)
occurrences causally related to treatment / all	2 / 2	4 / 4	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menorrhagia			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal haemorrhage			
subjects affected / exposed	3 / 345 (0.87%)	4 / 680 (0.59%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	1 / 4	1 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal inflammation			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspiration			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchospasm			
subjects affected / exposed	2 / 345 (0.58%)	2 / 680 (0.29%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	7 / 345 (2.03%)	10 / 680 (1.47%)	3 / 335 (0.90%)
occurrences causally related to treatment / all	3 / 7	5 / 10	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory distress syndrome			
subjects affected / exposed	8 / 345 (2.32%)	11 / 680 (1.62%)	3 / 335 (0.90%)
occurrences causally related to treatment / all	2 / 8	4 / 11	2 / 3
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Pleural effusion			
subjects affected / exposed	2 / 345 (0.58%)	2 / 680 (0.29%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pharyngeal inflammation			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal pain			
subjects affected / exposed	1 / 345 (0.29%)	3 / 680 (0.44%)	2 / 335 (0.60%)
occurrences causally related to treatment / all	0 / 1	2 / 4	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal oedema			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	15 / 345 (4.35%)	27 / 680 (3.97%)	12 / 335 (3.58%)
occurrences causally related to treatment / all	8 / 17	14 / 30	6 / 13
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiccups			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	3 / 345 (0.87%)	5 / 680 (0.74%)	2 / 335 (0.60%)
occurrences causally related to treatment / all	1 / 3	1 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	7 / 345 (2.03%)	7 / 680 (1.03%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	3 / 7	3 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			

subjects affected / exposed	2 / 345 (0.58%)	3 / 680 (0.44%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	1 / 2	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary toxicity			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary mass			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	1 / 345 (0.29%)	2 / 680 (0.29%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary alveolar haemorrhage			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	3 / 345 (0.87%)	3 / 680 (0.44%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract haemorrhage			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachypnoea			

subjects affected / exposed	2 / 345 (0.58%)	2 / 680 (0.29%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhinitis allergic			
subjects affected / exposed	1 / 345 (0.29%)	2 / 680 (0.29%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	1 / 1	4 / 4	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Restlessness			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Agitation			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
C-reactive protein increased			
subjects affected / exposed	2 / 345 (0.58%)	3 / 680 (0.44%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	2 / 2	3 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Blood fibrinogen increased			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	2 / 345 (0.58%)	4 / 680 (0.59%)	2 / 335 (0.60%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	2 / 345 (0.58%)	4 / 680 (0.59%)	2 / 335 (0.60%)
occurrences causally related to treatment / all	0 / 2	2 / 4	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 345 (0.29%)	3 / 680 (0.44%)	2 / 335 (0.60%)
occurrences causally related to treatment / all	1 / 1	2 / 3	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	9 / 345 (2.61%)	10 / 680 (1.47%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	9 / 10	9 / 11	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase increased			
subjects affected / exposed	10 / 345 (2.90%)	14 / 680 (2.06%)	4 / 335 (1.19%)
occurrences causally related to treatment / all	9 / 11	11 / 15	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipase increased			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	29 / 345 (8.41%)	62 / 680 (9.12%)	33 / 335 (9.85%)
occurrences causally related to treatment / all	20 / 30	49 / 67	29 / 37
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			

subjects affected / exposed	24 / 345 (6.96%)	52 / 680 (7.65%)	28 / 335 (8.36%)
occurrences causally related to treatment / all	16 / 25	40 / 58	24 / 33
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prothrombin time prolonged			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin decreased			
subjects affected / exposed	12 / 345 (3.48%)	21 / 680 (3.09%)	9 / 335 (2.69%)
occurrences causally related to treatment / all	7 / 12	15 / 22	8 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 345 (0.29%)	5 / 680 (0.74%)	4 / 335 (1.19%)
occurrences causally related to treatment / all	1 / 1	4 / 6	3 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram QT prolonged			
subjects affected / exposed	8 / 345 (2.32%)	17 / 680 (2.50%)	9 / 335 (2.69%)
occurrences causally related to treatment / all	8 / 8	15 / 17	7 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin T increased			
subjects affected / exposed	2 / 345 (0.58%)	3 / 680 (0.44%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	1 / 2	2 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CD4 lymphocytes decreased			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			

Jaw fracture			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical vertebral fracture			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural bile leak			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiation mucositis			
subjects affected / exposed	1 / 345 (0.29%)	6 / 680 (0.88%)	5 / 335 (1.49%)
occurrences causally related to treatment / all	1 / 1	3 / 6	2 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post-traumatic pain			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Epidermolysis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 345 (0.87%)	3 / 680 (0.44%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	2 / 4	2 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Atrial flutter			
subjects affected / exposed	2 / 345 (0.58%)	4 / 680 (0.59%)	2 / 335 (0.60%)
occurrences causally related to treatment / all	1 / 2	2 / 4	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 345 (0.29%)	2 / 680 (0.29%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular dysfunction			
subjects affected / exposed	6 / 345 (1.74%)	8 / 680 (1.18%)	2 / 335 (0.60%)
occurrences causally related to treatment / all	5 / 6	7 / 8	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular failure			
subjects affected / exposed	1 / 345 (0.29%)	2 / 680 (0.29%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			

subjects affected / exposed	2 / 345 (0.58%)	3 / 680 (0.44%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Myocardial infarction			
subjects affected / exposed	2 / 345 (0.58%)	3 / 680 (0.44%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	2 / 2	2 / 3	0 / 1
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Pericardial effusion			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 345 (0.00%)	2 / 680 (0.29%)	2 / 335 (0.60%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus tachycardia			
subjects affected / exposed	3 / 345 (0.87%)	7 / 680 (1.03%)	4 / 335 (1.19%)
occurrences causally related to treatment / all	2 / 3	7 / 8	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus bradycardia			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			

subjects affected / exposed	3 / 345 (0.87%)	3 / 680 (0.44%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aphasia			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	4 / 345 (1.16%)	7 / 680 (1.03%)	3 / 335 (0.90%)
occurrences causally related to treatment / all	3 / 4	5 / 7	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 345 (0.29%)	3 / 680 (0.44%)	2 / 335 (0.60%)
occurrences causally related to treatment / all	1 / 1	2 / 3	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	1 / 345 (0.29%)	2 / 680 (0.29%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	2 / 345 (0.58%)	6 / 680 (0.88%)	4 / 335 (1.19%)
occurrences causally related to treatment / all	1 / 2	3 / 6	2 / 4
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Cerebrovascular accident			

subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 345 (0.00%)	2 / 680 (0.29%)	2 / 335 (0.60%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuroleptic malignant syndrome			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiplegia			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 345 (0.29%)	4 / 680 (0.59%)	3 / 335 (0.90%)
occurrences causally related to treatment / all	1 / 1	1 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone marrow failure			

subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coagulopathy			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenitis			
subjects affected / exposed	1 / 345 (0.29%)	2 / 680 (0.29%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 1	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenopathy			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (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
Lymphopenia			
subjects affected / exposed	2 / 345 (0.58%)	7 / 680 (1.03%)	5 / 335 (1.49%)
occurrences causally related to treatment / all	1 / 2	4 / 7	3 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	9 / 345 (2.61%)	16 / 680 (2.35%)	7 / 335 (2.09%)
occurrences causally related to treatment / all	7 / 9	13 / 17	6 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune thrombocytopenic purpura			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	53 / 345 (15.36%)	106 / 680 (15.59%)	53 / 335 (15.82%)
occurrences causally related to treatment / all	33 / 70	70 / 134	37 / 64
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic haematoma			

subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic infarction			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
External ear pain			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deafness			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Eyelid oedema			
subjects affected / exposed	2 / 345 (0.58%)	2 / 680 (0.29%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye pain			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periorbital oedema			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	4 / 345 (1.16%)	10 / 680 (1.47%)	6 / 335 (1.79%)
occurrences causally related to treatment / all	1 / 5	5 / 11	4 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal ulcer			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anorectal discomfort			
subjects affected / exposed	2 / 345 (0.58%)	2 / 680 (0.29%)	0 / 335 (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
Colitis			
subjects affected / exposed	11 / 345 (3.19%)	21 / 680 (3.09%)	10 / 335 (2.99%)
occurrences causally related to treatment / all	6 / 11	10 / 21	4 / 10
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Constipation			
subjects affected / exposed	3 / 345 (0.87%)	5 / 680 (0.74%)	2 / 335 (0.60%)
occurrences causally related to treatment / all	0 / 3	1 / 5	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dental caries			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	7 / 345 (2.03%)	17 / 680 (2.50%)	10 / 335 (2.99%)
occurrences causally related to treatment / all	6 / 9	12 / 19	6 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			

subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eruclation			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal necrosis			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	2 / 345 (0.58%)	2 / 680 (0.29%)	0 / 335 (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
Ileus paralytic			
subjects affected / exposed	2 / 345 (0.58%)	6 / 680 (0.88%)	4 / 335 (1.19%)
occurrences causally related to treatment / all	1 / 2	4 / 6	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 345 (0.00%)	2 / 680 (0.29%)	2 / 335 (0.60%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			

subjects affected / exposed	0 / 345 (0.00%)	2 / 680 (0.29%)	2 / 335 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Large intestinal haemorrhage			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intra-abdominal haemorrhage			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	5 / 345 (1.45%)	11 / 680 (1.62%)	6 / 335 (1.79%)
occurrences causally related to treatment / all	6 / 8	11 / 14	5 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proctalgia			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral pain			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal ulcer			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic colitis			
subjects affected / exposed	0 / 345 (0.00%)	2 / 680 (0.29%)	2 / 335 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			

subjects affected / exposed	1 / 345 (0.29%)	3 / 680 (0.44%)	2 / 335 (0.60%)
occurrences causally related to treatment / all	1 / 1	1 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salivary gland disorder			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal haemorrhage			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	4 / 345 (1.16%)	10 / 680 (1.47%)	6 / 335 (1.79%)
occurrences causally related to treatment / all	7 / 8	13 / 16	6 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 345 (0.58%)	2 / 680 (0.29%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toothache			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	6 / 345 (1.74%)	11 / 680 (1.62%)	5 / 335 (1.49%)
occurrences causally related to treatment / all	3 / 6	7 / 11	4 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 345 (0.00%)	2 / 680 (0.29%)	2 / 335 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder disorder			

subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	1 / 345 (0.29%)	2 / 680 (0.29%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	2 / 345 (0.58%)	7 / 680 (1.03%)	5 / 335 (1.49%)
occurrences causally related to treatment / all	2 / 2	5 / 7	3 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatotoxicity			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis exfoliative			
subjects affected / exposed	11 / 345 (3.19%)	15 / 680 (2.21%)	4 / 335 (1.19%)
occurrences causally related to treatment / all	9 / 13	12 / 17	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain of skin			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	2 / 345 (0.58%)	2 / 680 (0.29%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperhidrosis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Exfoliative rash			

subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dry skin			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Petechiae			
subjects affected / exposed	1 / 345 (0.29%)	2 / 680 (0.29%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 1	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pruritus			
subjects affected / exposed	3 / 345 (0.87%)	3 / 680 (0.44%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	2 / 3	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 345 (0.58%)	3 / 680 (0.44%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	1 / 2	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	8 / 345 (2.32%)	10 / 680 (1.47%)	2 / 335 (0.60%)
occurrences causally related to treatment / all	3 / 8	3 / 10	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal haemorrhage			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric obstruction			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urogenital haemorrhage			

subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral pain			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary bladder haemorrhage			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Diabetes insipidus			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 345 (0.29%)	3 / 680 (0.44%)	2 / 335 (0.60%)
occurrences causally related to treatment / all	0 / 2	1 / 4	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gouty arthritis			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Back pain			
subjects affected / exposed	2 / 345 (0.58%)	4 / 680 (0.59%)	2 / 335 (0.60%)
occurrences causally related to treatment / all	0 / 2	1 / 4	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis			
subjects affected / exposed	0 / 345 (0.00%)	2 / 680 (0.29%)	2 / 335 (0.60%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovitis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint effusion			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Trismus			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			

Abdominal infection			
subjects affected / exposed	1 / 345 (0.29%)	2 / 680 (0.29%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenoviral hepatitis			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acarodermatitis			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			
subjects affected / exposed	2 / 345 (0.58%)	2 / 680 (0.29%)	0 / 335 (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
Anal infection			
subjects affected / exposed	2 / 345 (0.58%)	5 / 680 (0.74%)	3 / 335 (0.90%)
occurrences causally related to treatment / all	1 / 2	2 / 5	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 345 (0.00%)	2 / 680 (0.29%)	2 / 335 (0.60%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis bacterial			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Candida infection			

subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical pneumonia			
subjects affected / exposed	1 / 345 (0.29%)	2 / 680 (0.29%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	1 / 345 (0.29%)	2 / 680 (0.29%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 345 (0.29%)	3 / 680 (0.44%)	2 / 335 (0.60%)
occurrences causally related to treatment / all	0 / 1	1 / 3	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopulmonary aspergillosis			
subjects affected / exposed	2 / 345 (0.58%)	5 / 680 (0.74%)	3 / 335 (0.90%)
occurrences causally related to treatment / all	2 / 2	3 / 5	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	2 / 345 (0.58%)	4 / 680 (0.59%)	2 / 335 (0.60%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	25 / 345 (7.25%)	38 / 680 (5.59%)	13 / 335 (3.88%)
occurrences causally related to treatment / all	10 / 28	15 / 42	5 / 14
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related sepsis			
subjects affected / exposed	1 / 345 (0.29%)	5 / 680 (0.74%)	4 / 335 (1.19%)
occurrences causally related to treatment / all	0 / 1	2 / 6	2 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			

subjects affected / exposed	6 / 345 (1.74%)	10 / 680 (1.47%)	4 / 335 (1.19%)
occurrences causally related to treatment / all	2 / 6	4 / 11	2 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridial infection			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium colitis			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterococcal infection			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis necroticans			
subjects affected / exposed	2 / 345 (0.58%)	2 / 680 (0.29%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 345 (0.29%)	2 / 680 (0.29%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia bacteraemia			

subjects affected / exposed	1 / 345 (0.29%)	2 / 680 (0.29%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis Escherichia coli			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	2 / 345 (0.58%)	2 / 680 (0.29%)	0 / 335 (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
Furuncle			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia infection			
subjects affected / exposed	1 / 345 (0.29%)	4 / 680 (0.59%)	3 / 335 (0.90%)
occurrences causally related to treatment / all	1 / 1	3 / 4	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic infection fungal			
subjects affected / exposed	1 / 345 (0.29%)	2 / 680 (0.29%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	1 / 1	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic infection			
subjects affected / exposed	1 / 345 (0.29%)	2 / 680 (0.29%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 1	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis norovirus			

subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes simplex			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious colitis			
subjects affected / exposed	2 / 345 (0.58%)	3 / 680 (0.44%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	2 / 2	3 / 3	1 / 1
deaths causally related to treatment / all	1 / 1	2 / 2	1 / 1
Infection			
subjects affected / exposed	8 / 345 (2.32%)	11 / 680 (1.62%)	3 / 335 (0.90%)
occurrences causally related to treatment / all	3 / 8	5 / 11	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incision site infection			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	2 / 345 (0.58%)	4 / 680 (0.59%)	2 / 335 (0.60%)
occurrences causally related to treatment / all	2 / 2	2 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lip infection			
subjects affected / exposed	1 / 345 (0.29%)	4 / 680 (0.59%)	3 / 335 (0.90%)
occurrences causally related to treatment / all	1 / 1	2 / 5	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nail infection			

subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic infection			
subjects affected / exposed	12 / 345 (3.48%)	18 / 680 (2.65%)	6 / 335 (1.79%)
occurrences causally related to treatment / all	5 / 12	8 / 18	3 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis externa			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral fungal infection			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Opportunistic infection			
subjects affected / exposed	2 / 345 (0.58%)	5 / 680 (0.74%)	3 / 335 (0.90%)
occurrences causally related to treatment / all	0 / 2	2 / 5	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Neutropenic sepsis			
subjects affected / exposed	10 / 345 (2.90%)	11 / 680 (1.62%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	4 / 10	5 / 11	1 / 1
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Osteomyelitis			
subjects affected / exposed	1 / 345 (0.29%)	2 / 680 (0.29%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	1 / 1	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paronychia			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parotitis			

subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periorbital cellulitis			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perirectal abscess			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	1 / 345 (0.29%)	3 / 680 (0.44%)	2 / 335 (0.60%)
occurrences causally related to treatment / all	1 / 1	1 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	27 / 345 (7.83%)	55 / 680 (8.09%)	28 / 335 (8.36%)
occurrences causally related to treatment / all	13 / 30	26 / 60	13 / 30
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia fungal			
subjects affected / exposed	0 / 345 (0.00%)	2 / 680 (0.29%)	2 / 335 (0.60%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural infection			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	19 / 345 (5.51%)	37 / 680 (5.44%)	18 / 335 (5.37%)
occurrences causally related to treatment / all	14 / 22	27 / 41	13 / 19
deaths causally related to treatment / all	2 / 3	4 / 7	2 / 4
Rhinitis			

subjects affected / exposed	1 / 345 (0.29%)	2 / 680 (0.29%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 1	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic infection			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	1 / 345 (0.29%)	3 / 680 (0.44%)	2 / 335 (0.60%)
occurrences causally related to treatment / all	0 / 1	1 / 3	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	2 / 345 (0.58%)	2 / 680 (0.29%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 345 (0.29%)	2 / 680 (0.29%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	1 / 1	1 / 2	0 / 1
Pulmonary sepsis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic infection fungal			
subjects affected / exposed	2 / 345 (0.58%)	2 / 680 (0.29%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection bacterial			

subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	7 / 345 (2.03%)	16 / 680 (2.35%)	9 / 335 (2.69%)
occurrences causally related to treatment / all	2 / 8	7 / 19	5 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	2 / 345 (0.58%)	2 / 680 (0.29%)	0 / 335 (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
Tooth infection			
subjects affected / exposed	1 / 345 (0.29%)	3 / 680 (0.44%)	2 / 335 (0.60%)
occurrences causally related to treatment / all	1 / 1	4 / 4	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	2 / 345 (0.58%)	2 / 680 (0.29%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal infection			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	2 / 345 (0.58%)	3 / 680 (0.44%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	2 / 2	3 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vulval abscess			

subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	0 / 345 (0.00%)	4 / 680 (0.59%)	4 / 335 (1.19%)
occurrences causally related to treatment / all	0 / 0	4 / 5	4 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	1 / 345 (0.29%)	2 / 680 (0.29%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercholesterolaemia			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	5 / 345 (1.45%)	8 / 680 (1.18%)	3 / 335 (0.90%)
occurrences causally related to treatment / all	3 / 6	3 / 9	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertriglyceridaemia			

subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypernatraemia			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypermagnesaemia			
subjects affected / exposed	0 / 345 (0.00%)	1 / 680 (0.15%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperuricaemia			
subjects affected / exposed	1 / 345 (0.29%)	1 / 680 (0.15%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	8 / 345 (2.32%)	13 / 680 (1.91%)	5 / 335 (1.49%)
occurrences causally related to treatment / all	1 / 8	2 / 13	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	1 / 345 (0.29%)	2 / 680 (0.29%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 1	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoalbuminaemia			
subjects affected / exposed	1 / 345 (0.29%)	2 / 680 (0.29%)	1 / 335 (0.30%)
occurrences causally related to treatment / all	0 / 1	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomagnesaemia			

subjects affected / exposed	3 / 345 (0.87%)	3 / 680 (0.44%)	0 / 335 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	2 / 345 (0.58%)	4 / 680 (0.59%)	2 / 335 (0.60%)
occurrences causally related to treatment / all	0 / 2	1 / 4	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophosphataemia			
subjects affected / exposed	2 / 345 (0.58%)	6 / 680 (0.88%)	4 / 335 (1.19%)
occurrences causally related to treatment / all	1 / 2	3 / 6	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Induction and Consolidation Chemotherapy Plus Midostaurin	ALL Subjects	Induction and Consolidation Chemotherapy Plus Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	344 / 345 (99.71%)	679 / 680 (99.85%)	335 / 335 (100.00%)
Vascular disorders			
Hypotension			
subjects affected / exposed	39 / 345 (11.30%)	81 / 680 (11.91%)	42 / 335 (12.54%)
occurrences (all)	40	86	46
Hypertension			
subjects affected / exposed	24 / 345 (6.96%)	43 / 680 (6.32%)	19 / 335 (5.67%)
occurrences (all)	26	46	20
Haematoma			
subjects affected / exposed	38 / 345 (11.01%)	76 / 680 (11.18%)	38 / 335 (11.34%)
occurrences (all)	44	86	42
Phlebitis superficial			
subjects affected / exposed	17 / 345 (4.93%)	38 / 680 (5.59%)	21 / 335 (6.27%)
occurrences (all)	18	39	21
General disorders and administration site conditions			
Fatigue			

subjects affected / exposed	245 / 345 (71.01%)	481 / 680 (70.74%)	236 / 335 (70.45%)
occurrences (all)	337	651	314
Chills			
subjects affected / exposed	39 / 345 (11.30%)	72 / 680 (10.59%)	33 / 335 (9.85%)
occurrences (all)	42	78	36
Chest pain			
subjects affected / exposed	15 / 345 (4.35%)	33 / 680 (4.85%)	18 / 335 (5.37%)
occurrences (all)	18	37	19
Injection site reaction			
subjects affected / exposed	25 / 345 (7.25%)	51 / 680 (7.50%)	26 / 335 (7.76%)
occurrences (all)	27	59	32
Pyrexia			
subjects affected / exposed	86 / 345 (24.93%)	167 / 680 (24.56%)	81 / 335 (24.18%)
occurrences (all)	103	197	94
Oedema peripheral			
subjects affected / exposed	56 / 345 (16.23%)	118 / 680 (17.35%)	62 / 335 (18.51%)
occurrences (all)	62	136	74
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	37 / 345 (10.72%)	67 / 680 (9.85%)	30 / 335 (8.96%)
occurrences (all)	39	73	34
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	15 / 345 (4.35%)	36 / 680 (5.29%)	21 / 335 (6.27%)
occurrences (all)	16	39	23
Respiratory, thoracic and mediastinal disorders			
Laryngeal pain			
subjects affected / exposed	33 / 345 (9.57%)	61 / 680 (8.97%)	28 / 335 (8.36%)
occurrences (all)	37	69	32
Hypoxia			
subjects affected / exposed	11 / 345 (3.19%)	30 / 680 (4.41%)	19 / 335 (5.67%)
occurrences (all)	11	30	19
Epistaxis			
subjects affected / exposed	71 / 345 (20.58%)	129 / 680 (18.97%)	58 / 335 (17.31%)
occurrences (all)	79	147	68
Dyspnoea			

subjects affected / exposed occurrences (all)	37 / 345 (10.72%) 40	73 / 680 (10.74%) 78	36 / 335 (10.75%) 38
Cough subjects affected / exposed occurrences (all)	53 / 345 (15.36%) 66	107 / 680 (15.74%) 126	54 / 335 (16.12%) 60
Pneumonitis subjects affected / exposed occurrences (all)	18 / 345 (5.22%) 19	45 / 680 (6.62%) 46	27 / 335 (8.06%) 27
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	21 / 345 (6.09%) 23	48 / 680 (7.06%) 57	27 / 335 (8.06%) 34
Insomnia subjects affected / exposed occurrences (all)	36 / 345 (10.43%) 44	60 / 680 (8.82%) 74	24 / 335 (7.16%) 30
Depression subjects affected / exposed occurrences (all)	15 / 345 (4.35%) 17	44 / 680 (6.47%) 49	29 / 335 (8.66%) 32
Investigations Blood creatinine increased subjects affected / exposed occurrences (all)	24 / 345 (6.96%) 26	47 / 680 (6.91%) 52	23 / 335 (6.87%) 26
Blood bilirubin increased subjects affected / exposed occurrences (all)	33 / 345 (9.57%) 36	75 / 680 (11.03%) 85	42 / 335 (12.54%) 49
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	37 / 345 (10.72%) 45	77 / 680 (11.32%) 90	40 / 335 (11.94%) 45
C-reactive protein increased subjects affected / exposed occurrences (all)	22 / 345 (6.38%) 26	52 / 680 (7.65%) 63	30 / 335 (8.96%) 37
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	102 / 345 (29.57%) 147	199 / 680 (29.26%) 264	97 / 335 (28.96%) 117
Activated partial thromboplastin time prolonged			

subjects affected / exposed	34 / 345 (9.86%)	61 / 680 (8.97%)	27 / 335 (8.06%)
occurrences (all)	35	64	29
Aspartate aminotransferase increased			
subjects affected / exposed	76 / 345 (22.03%)	149 / 680 (21.91%)	73 / 335 (21.79%)
occurrences (all)	105	194	89
Electrocardiogram QT prolonged			
subjects affected / exposed	51 / 345 (14.78%)	90 / 680 (13.24%)	39 / 335 (11.64%)
occurrences (all)	71	118	47
Gamma-glutamyltransferase increased			
subjects affected / exposed	36 / 345 (10.43%)	78 / 680 (11.47%)	42 / 335 (12.54%)
occurrences (all)	43	89	46
Haemoglobin decreased			
subjects affected / exposed	334 / 345 (96.81%)	656 / 680 (96.47%)	322 / 335 (96.12%)
occurrences (all)	388	749	361
Neutrophil count decreased			
subjects affected / exposed	319 / 345 (92.46%)	626 / 680 (92.06%)	307 / 335 (91.64%)
occurrences (all)	376	719	343
Platelet count decreased			
subjects affected / exposed	328 / 345 (95.07%)	640 / 680 (94.12%)	312 / 335 (93.13%)
occurrences (all)	403	774	371
Weight decreased			
subjects affected / exposed	11 / 345 (3.19%)	28 / 680 (4.12%)	17 / 335 (5.07%)
occurrences (all)	11	28	17
Weight increased			
subjects affected / exposed	18 / 345 (5.22%)	26 / 680 (3.82%)	8 / 335 (2.39%)
occurrences (all)	18	26	8
Injury, poisoning and procedural complications			
Radiation mucositis			
subjects affected / exposed	132 / 345 (38.26%)	261 / 680 (38.38%)	129 / 335 (38.51%)
occurrences (all)	156	310	154
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	25 / 345 (7.25%)	53 / 680 (7.79%)	28 / 335 (8.36%)
occurrences (all)	26	58	32
Nervous system disorders			

Headache			
subjects affected / exposed	121 / 345 (35.07%)	227 / 680 (33.38%)	106 / 335 (31.64%)
occurrences (all)	165	297	132
Dysgeusia			
subjects affected / exposed	9 / 345 (2.61%)	26 / 680 (3.82%)	17 / 335 (5.07%)
occurrences (all)	9	27	18
Dizziness			
subjects affected / exposed	53 / 345 (15.36%)	103 / 680 (15.15%)	50 / 335 (14.93%)
occurrences (all)	60	115	55
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	254 / 345 (73.62%)	506 / 680 (74.41%)	252 / 335 (75.22%)
occurrences (all)	310	613	303
Leukopenia			
subjects affected / exposed	94 / 345 (27.25%)	193 / 680 (28.38%)	99 / 335 (29.55%)
occurrences (all)	114	225	111
Lymphopenia			
subjects affected / exposed	73 / 345 (21.16%)	149 / 680 (21.91%)	76 / 335 (22.69%)
occurrences (all)	97	182	85
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	14 / 345 (4.06%)	31 / 680 (4.56%)	17 / 335 (5.07%)
occurrences (all)	16	35	19
Vomiting			
subjects affected / exposed	209 / 345 (60.58%)	397 / 680 (58.38%)	188 / 335 (56.12%)
occurrences (all)	278	512	234
Diarrhoea			
subjects affected / exposed	260 / 345 (75.36%)	508 / 680 (74.71%)	248 / 335 (74.03%)
occurrences (all)	349	645	296
Dyspepsia			
subjects affected / exposed	25 / 345 (7.25%)	47 / 680 (6.91%)	22 / 335 (6.57%)
occurrences (all)	27	51	24
Dysphagia			
subjects affected / exposed	13 / 345 (3.77%)	32 / 680 (4.71%)	19 / 335 (5.67%)
occurrences (all)	14	34	20
Haemorrhoids			

subjects affected / exposed	35 / 345 (10.14%)	62 / 680 (9.12%)	27 / 335 (8.06%)
occurrences (all)	36	64	28
Mouth haemorrhage			
subjects affected / exposed	16 / 345 (4.64%)	37 / 680 (5.44%)	21 / 335 (6.27%)
occurrences (all)	16	43	27
Nausea			
subjects affected / exposed	282 / 345 (81.74%)	525 / 680 (77.21%)	243 / 335 (72.54%)
occurrences (all)	393	715	322
Stomatitis			
subjects affected / exposed	59 / 345 (17.10%)	94 / 680 (13.82%)	35 / 335 (10.45%)
occurrences (all)	65	104	39
Abdominal pain upper			
subjects affected / exposed	38 / 345 (11.01%)	74 / 680 (10.88%)	36 / 335 (10.75%)
occurrences (all)	43	81	38
Abdominal pain			
subjects affected / exposed	71 / 345 (20.58%)	158 / 680 (23.24%)	87 / 335 (25.97%)
occurrences (all)	81	178	97
Constipation			
subjects affected / exposed	59 / 345 (17.10%)	128 / 680 (18.82%)	69 / 335 (20.60%)
occurrences (all)	69	144	75
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	40 / 345 (11.59%)	82 / 680 (12.06%)	42 / 335 (12.54%)
occurrences (all)	48	95	47
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	31 / 345 (8.99%)	71 / 680 (10.44%)	40 / 335 (11.94%)
occurrences (all)	34	78	44
Hyperhidrosis			
subjects affected / exposed	36 / 345 (10.43%)	57 / 680 (8.38%)	21 / 335 (6.27%)
occurrences (all)	43	69	26
Dermatitis exfoliative			
subjects affected / exposed	218 / 345 (63.19%)	440 / 680 (64.71%)	222 / 335 (66.27%)
occurrences (all)	269	544	275
Petechiae			

subjects affected / exposed occurrences (all)	88 / 345 (25.51%) 102	156 / 680 (22.94%) 180	68 / 335 (20.30%) 78
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	21 / 345 (6.09%)	32 / 680 (4.71%)	11 / 335 (3.28%)
occurrences (all)	23	34	11
Arthralgia			
subjects affected / exposed	39 / 345 (11.30%)	57 / 680 (8.38%)	18 / 335 (5.37%)
occurrences (all)	44	70	26
Back pain			
subjects affected / exposed	58 / 345 (16.81%)	100 / 680 (14.71%)	42 / 335 (12.54%)
occurrences (all)	67	118	51
Bone pain			
subjects affected / exposed	24 / 345 (6.96%)	47 / 680 (6.91%)	23 / 335 (6.87%)
occurrences (all)	29	56	27
Myalgia			
subjects affected / exposed	19 / 345 (5.51%)	38 / 680 (5.59%)	19 / 335 (5.67%)
occurrences (all)	24	45	21
Pain in extremity			
subjects affected / exposed	32 / 345 (9.28%)	56 / 680 (8.24%)	24 / 335 (7.16%)
occurrences (all)	38	66	28
Infections and infestations			
Neutropenic infection			
subjects affected / exposed	11 / 345 (3.19%)	28 / 680 (4.12%)	17 / 335 (5.07%)
occurrences (all)	11	28	17
Nasopharyngitis			
subjects affected / exposed	20 / 345 (5.80%)	35 / 680 (5.15%)	15 / 335 (4.48%)
occurrences (all)	28	45	17
Device related infection			
subjects affected / exposed	53 / 345 (15.36%)	93 / 680 (13.68%)	40 / 335 (11.94%)
occurrences (all)	61	105	44
Conjunctivitis			
subjects affected / exposed	22 / 345 (6.38%)	39 / 680 (5.74%)	17 / 335 (5.07%)
occurrences (all)	22	42	20
Oral herpes			

subjects affected / exposed	14 / 345 (4.06%)	31 / 680 (4.56%)	17 / 335 (5.07%)
occurrences (all)	15	37	22
Pneumonia			
subjects affected / exposed	28 / 345 (8.12%)	60 / 680 (8.82%)	32 / 335 (9.55%)
occurrences (all)	29	63	34
Urinary tract infection			
subjects affected / exposed	16 / 345 (4.64%)	42 / 680 (6.18%)	26 / 335 (7.76%)
occurrences (all)	16	43	27
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	45 / 345 (13.04%)	103 / 680 (15.15%)	58 / 335 (17.31%)
occurrences (all)	50	116	66
Hypocalcaemia			
subjects affected / exposed	69 / 345 (20.00%)	136 / 680 (20.00%)	67 / 335 (20.00%)
occurrences (all)	79	155	76
Hypoalbuminaemia			
subjects affected / exposed	66 / 345 (19.13%)	129 / 680 (18.97%)	63 / 335 (18.81%)
occurrences (all)	81	150	69
Hyperuricaemia			
subjects affected / exposed	22 / 345 (6.38%)	38 / 680 (5.59%)	16 / 335 (4.78%)
occurrences (all)	29	50	21
Hyperglycaemia			
subjects affected / exposed	75 / 345 (21.74%)	139 / 680 (20.44%)	64 / 335 (19.10%)
occurrences (all)	109	195	86
Hypokalaemia			
subjects affected / exposed	92 / 345 (26.67%)	191 / 680 (28.09%)	99 / 335 (29.55%)
occurrences (all)	110	224	114
Hypomagnesaemia			
subjects affected / exposed	36 / 345 (10.43%)	76 / 680 (11.18%)	40 / 335 (11.94%)
occurrences (all)	37	84	47
Hypophosphataemia			
subjects affected / exposed	28 / 345 (8.12%)	62 / 680 (9.12%)	34 / 335 (10.15%)
occurrences (all)	34	74	40
Hyponatraemia			
subjects affected / exposed	60 / 345 (17.39%)	120 / 680 (17.65%)	60 / 335 (17.91%)
occurrences (all)	66	131	65

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 February 2009	Clarification of eligibility criterion for patients with neurologic symptoms; Changes in dose modification required in cases of QTc prolongation between 470 ms and 500 ms; Added dose modification requirement for cases of \geq grade-2 neurotoxicity due to high-dose cytarabine
01 April 2009	Change in dosing regimen for midostaurin/placebo continuation therapy from 14 days of each 28 day cycle to continuous daily dosing, continuing for 12 cycles, along with clarifying rationale; Adding dose modification requirement for cases of QTc prolongation; Clarifying dose modification requirements for nonhematologic toxicities of grade 3/4 severity; Change in prohibited ancillary therapy (i.e. use of aprepitant was not permitted)
01 December 2009	Changes in reporting of AEs for NNA sites as well as for their expedited reporting requirements; Addition of collection of concomitant medications; Revised information regarding drug accountability, storage and stability, and unblinding of midostaurin; Revision on statistical analyses to be performed for secondary endpoints; Revision on requirement for bone marrow aspiration during remission induction stage and response assessments.
15 December 2010	At the time of protocol version 1, the transplantation option was estimated to be available for about 15% of the population eligible for the study. This rate of withdrawal from study treatment for patients in first CR was factored into the estimate of sample size. At Amendment 4, based on blinded data from the study to date, 25% of all randomized patients were expected to have received an SCT. The sample size and power justification were therefore revised and justification for amending statistical considerations was added to reflect revised sample size; Addition of a new secondary objective to compare the OS in the two groups using an analysis in which patient who receive an SCT are censored at the time of transplantation.
15 May 2011	Revision of response assessment to include time requirement for bone marrow aspiration after recovery of ANC and platelet count to document complete response
15 September 2011	Changes in AE reporting for NA and NNA sites
15 November 2011	Update in administrative procedure for the unblinding of patients
05 May 2013	Editorial / Administrative changes
15 February 2015	Editorial / Administrative changes
15 June 2015	The protocol was amended to perform the final confirmatory analysis with a DCO of 01-Apr-2015 without waiting for the originally targeted 509 OS events to occur; The secondary endpoint EFS was promoted to a key secondary endpoint to be tested in a hierarchical manner if the OS endpoint is significant. In addition, the SCT rate was added as a secondary efficacy endpoint.

27 December 2018	Data submission for this study will now be performed using Medidata Rave; Adverse event reporting have been updated to reflect the use of CTCAE version 5.0 for serious adverse event reporting; Administrative changes
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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.

<p>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.</p>
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Notes: