



Clinical trial results:

A Phase 2 Multi-Center, Historically-Controlled Study of Dasatinib Added to Standard Chemotherapy in Pediatric Patients with Newly Diagnosed Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia

Summary

EudraCT number	2011-001123-20
Trial protocol	IT GB Outside EU/EEA
Global end of trial date	

Results information

Result version number	v1
This version publication date	10 June 2018
First version publication date	10 June 2018

Trial information

Trial identification

Sponsor protocol code	CA180-372
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000567-PIP09-05
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?	Yes

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	28 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 May 2017
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the 3-year efficacy based on EFS of dasatinib plus chemotherapy with external historical controls, in hierarchical order, as follows: - Superiority over chemotherapy alone of AIEOP-BFM 2000 - Non-inferiority to continuous imatinib plus chemotherapy of the amended EsPhALL trial - Superiority over continuous imatinib plus chemotherapy of the amended EsPhALL trial

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 April 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	Italy: 13
Country: Number of subjects enrolled	United States: 78
Worldwide total number of subjects	109
EEA total number of subjects	26

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)	4
Children (2-11 years)	70

Adolescents (12-17 years)	35
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 109 subjects were enrolled and 106 subjects were treated with dasatinib (82 subjects received dasatinib in the tablet form exclusively and 24 subjects received either tablet and/or PFOS).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Tablet Only

Arm description:

For children and adolescents capable of swallowing tablets, dasatinib tablets in strengths of 5 mg, 20 mg, and 50 mg, were given to cover the anticipated dose range.

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

Dosage and administration details:

Tablets in strengths of 5 mg, 20 mg, and 50 mg, were given to cover the anticipated dose range of 60 mg/m² daily.

Arm title	PFOS Used
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Arm description:

If necessary for administration in young children not able to swallow tablets, dasatinib was dispersed as Powder For Oral Suspension (PFOS) at a dose of 60 mg/m² daily in 100% preservative-free juice.

Arm type	Experimental
Investigational medicinal product name	Dasatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for oral solution
Routes of administration	Oral use

Dosage and administration details:

Powder for Oral Solution dispersed at dose of 60 mg/m² daily. The PFOS bottle was constituted with 77 mL purified water or Sterile Water for Injection to give a total volume of 99 mL with a 10 mg/mL suspension.

Number of subjects in period 1 ^[1]	Tablet Only	PFOS Used
Started	82	24
Completed	78	22
Not completed	4	2
Death	4	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total of 109 subjects were enrolled and 106 subjects were treated with dasatinib (82 subjects received dasatinib in the tablet form exclusively and 24 subjects received either tablet and/or PFOS).

Baseline characteristics

Reporting groups

Reporting group title	Tablet Only
Reporting group description:	
For children and adolescents capable of swallowing tablets, dasatinib tablets in strengths of 5 mg, 20 mg, and 50 mg, were given to cover the anticipated dose range.	
Reporting group title	PFOS Used
Reporting group description:	
If necessary for administration in young children not able to swallow tablets, dasatinib was dispersed as Powder For Oral Suspension (PFOS) at a dose of 60 mg/m ² daily in 100% preservative-free juice.	

Reporting group values	Tablet Only	PFOS Used	Total
Number of subjects	82	24	106
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	4	4
Children (2-11 years)	48	19	67
Adolescents (12-17 years)	34	1	35
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	10.33	5.73	
standard deviation	± 4.160	± 3.612	-
Sex: Female, Male			
Units: Subjects			
Female	37	12	49
Male	45	12	57
Race			
Units: Subjects			
White	66	19	85
Black or African American	9	4	13
Asian	5	0	5
American Indian or Alaska Native	0	1	1
Native Hawaiian or Other Pacific Islander	1	0	1
Other	1	0	1
BCR-ABL Transcript			
Units: Subjects			
P190	60	15	75
P210	11	5	16
Not Available	11	4	15

Subject analysis sets

Subject analysis set title	All Treated Subjects
Subject analysis set type	Intention-to-treat
Subject analysis set description: All subjects receiving at least one dose of study treatment (tablet or PFOS)	

Reporting group values	All Treated Subjects		
Number of subjects	106		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	4		
Children (2-11 years)	67		
Adolescents (12-17 years)	35		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age Continuous			
Units: years			
arithmetic mean			
standard deviation	±		
Sex: Female, Male			
Units: Subjects			
Female			
Male			
Race			
Units: Subjects			
White			
Black or African American			
Asian			
American Indian or Alaska Native			
Native Hawaiian or Other Pacific Islander			
Other			
BCR-ABL Transcript			
Units: Subjects			
P190			
P210			
Not Available			

End points

End points reporting groups

Reporting group title	Tablet Only
Reporting group description: For children and adolescents capable of swallowing tablets, dasatinib tablets in strengths of 5 mg, 20 mg, and 50 mg, were given to cover the anticipated dose range.	
Reporting group title	PFOS Used
Reporting group description: If necessary for administration in young children not able to swallow tablets, dasatinib was dispersed as Powder For Oral Suspension (PFOS) at a dose of 60 mg/m ² daily in 100% preservative-free juice.	
Subject analysis set title	All Treated Subjects
Subject analysis set type	Intention-to-treat
Subject analysis set description: All subjects receiving at least one dose of study treatment (tablet or PFOS)	

Primary: 3-year Event-free survival (EFS) Rate

End point title	3-year Event-free survival (EFS) Rate
End point description: EFS is defined as the time from the starting date of dasatinib until an event. In the primary analysis, the 3-year EFS response rate is defined as the number of subjects without event after 3 years since the start of dasatinib divided by the number of treated subjects and expressed as a percentage. Events for EFS are defined as ANY first one of the following: · Lack of complete response in bone marrow · Relapse at any site · Development of second malignant neoplasm · Death from any cause	
End point type	Primary
End point timeframe: 3 years	

End point values	Tablet Only	PFOS Used	All Treated Subjects	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	82	24	106	
Units: Percentage				
number (confidence interval 90%)	65.9 (56.3 to 74.5)	66.7 (47.9 to 82.2)	66.0 (57.7 to 73.7)	

Statistical analyses

Statistical analysis title	Binomial EFS rate difference vs. AIEOP-BFM 2000
Statistical analysis description: Difference in 3-year binomial EFS rate in all treated subjects (dasatinib plus chemotherapy) vs. chemotherapy alone in AIEOP-BFM 2000 historical control	
Comparison groups	Tablet Only v PFOS Used

Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.032 ^[1]
Method	Chi-squared
Parameter estimate	Estimate of Difference
Point estimate	16.86
Confidence interval	
level	90 %
sides	2-sided
lower limit	3.9
upper limit	29.8

Notes:

[1] - Superiority test versus AIEOP-BFM 2000

Statistical analysis title	Binomial EFS rate difference vs. EsPhALL Trial
Statistical analysis description:	
Difference in 3-year binomial EFS rate for all treated subjects (dasatinib plus chemotherapy) vs. continuous imatinib plus chemotherapy in the Amended EsPhALL Trial Historical Control	
Comparison groups	Tablet Only v PFOS Used
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.271 ^[2]
Method	Chi-squared
Parameter estimate	Estimate of difference
Point estimate	6.91
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.3
upper limit	17.2

Notes:

[2] - Superiority test versus EsPhALL

Secondary: 3-year EFS rate (K-M estimate)

End point title	3-year EFS rate (K-M estimate)
End point description:	
Overall estimation of the EFS of dasatinib plus chemotherapy was performed utilizing the Kaplan-Meier (KM) Product Limit method. The 3-year EFS rates were computed with the corresponding 95% CI's using Greenwood's formula. Analyses of EFS included KM plots with number of patients at risk. Subjects who neither relapse nor die or who are lost to follow-up were censored on the date of their last bone marrow, CSF assessment or physical exam, whichever occurred last.	
End point type	Secondary
End point timeframe:	
3 years	

End point values	Tablet Only	PFOS Used	All Treated Subjects	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	82	24	106	
Units: Percentage				
number (confidence interval 95%)	65.1 (53.6 to 74.4)	66.7 (44.3 to 81.7)	65.5 (55.5 to 73.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (K-M Estimate) Rate at 3 years

End point title	Overall Survival (K-M Estimate) Rate at 3 years
End point description:	
Overall survival is defined as time from the first day of dasatinib treatment until the time of death. Subjects who have not died or who are lost to follow-up will be censored on the last date the subject is known to be alive. The rate of OS at 3 years was expressed as a percentage of all treated subjects.	
End point type	Secondary
End point timeframe:	
3 years	

End point values	Tablet Only	PFOS Used	All Treated Subjects	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	82	24	106	
Units: percentage				
number (confidence interval 95%)	92.6 (84.3 to 96.6)	87.5 (66.1 to 95.8)	91.5 (84.2 to 95.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Remission Rate

End point title	Complete Remission Rate
End point description:	
CR rate is defined as the proportion of subjects achieving a complete remission, i.e. < 5% lymphoblasts in bone marrow and in CSF, with no evidence of other extramedullary disease, and expressed as a percentage. Complete remission will be assessed at the end of Induction IA, end of induction IB and end of HR3 for all treated subjects.	
End point type	Secondary
End point timeframe:	
Approximately 3 years	

End point values	Tablet Only	PFOS Used	All Treated Subjects	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	82	24	106	
Units: percentage				
number (not applicable)				
End of Induction period (period IA)	64.6	66.7	65.1	
End of Induction period (period IB)	87.8	91.7	88.7	
End of Consolidation period	93.9	91.7	93.4	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with Minimal Residual Disease based on Ig/TCR method

End point title	Percentage of subjects with Minimal Residual Disease based on Ig/TCR method
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End point description:

The number of subjects with MRD at the end of the Induction 1B and Consolidation periods was divided by the number of treated subjects and expressed as a percentage.

End point type	Secondary
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End point timeframe:

Approximately 3 years

End point values	Tablet Only	PFOS Used	All Treated Subjects	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	82	24	106	
Units: percentage				
number (confidence interval 95%)				
MRD-negative, end of Induction IB period	53.7 (42.30 to 64.75)	50.0 (29.12 to 70.88)	52.8 (42.89 to 62.60)	
MRD-negative, end of Consolidation	74.4 (63.56 to 83.40)	62.5 (40.59 to 81.20)	71.7 (62.12 to 80.02)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with AEs or drug related death

End point title	Number of subjects with AEs or drug related death
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End point description:	
The number of subjects with any AE or with study drug-related death was reported for each arm.	
End point type	Secondary
End point timeframe:	
Approximately 3 years	

End point values	Tablet Only	PFOS Used	All Treated Subjects	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	82	24	106	
Units: subjects				
AEs	82	24	106	
Drug Related Death	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with BCR-ABL Mutations at time of disease progression

End point title	Number of subjects with BCR-ABL Mutations at time of disease progression
End point description:	
The number of Ph+ ALL subjects with BCR-ABL Mutations at Disease Progression or Relapse was reported for each arm.	
End point type	Secondary
End point timeframe:	
Approximately 3 years	

End point values	Tablet Only	PFOS Used	All Treated Subjects	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	25	6	106	
Units: subjects				
Number of subjects with mutations	2	0	2	
Number of subjects with no mutations	17	3	20	
Not Reported	6	3	9	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Grade 3-4 hematology laboratory abnormalities

End point title	Number of subjects with Grade 3-4 hematology laboratory abnormalities
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End point description:

The number of subjects experiencing Grade 3 or 4 hematology laboratory abnormalities was reported by arm.

End point type	Secondary
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End point timeframe:

Approximately 3 years

End point values	Tablet Only	PFOS Used	All Treated Subjects	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	82	24	106	
Units: subjects				
Leukocytes	77	23	100	
Absolute Neutrophil Count	79	24	103	
Platelet Count	72	21	93	
Hemoglobin	67	21	88	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Grade 3-4 liver function laboratory abnormalities

End point title	Number of subjects with Grade 3-4 liver function laboratory abnormalities
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End point description:

The number of subjects experiencing Grade 3 or 4 liver function laboratory abnormalities was reported by arm.

End point type	Secondary
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End point timeframe:

Approximately 3 years

End point values	Tablet Only	PFOS Used	All Treated Subjects	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	82	24	106	
Units: subjects				
ALT	38	15	53	
AST	21	7	28	
Total bilirubin	9	0	9	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Grade 3-4 kidney function abnormalities

End point title	Number of subjects with Grade 3-4 kidney function abnormalities
End point description: The number of subjects experiencing Grade 3 or 4 kidney function laboratory abnormalities was reported by arm.	
End point type	Secondary
End point timeframe: Approximately 3 years	

End point values	Tablet Only	PFOS Used	All Treated Subjects	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	82	24	106	
Units: subjects				
BUN/Urea >ULN	33	7	40	
Serum Creatinine	2	0	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Grade 3-4 serum chemistry abnormalities

End point title	Number of subjects with Grade 3-4 serum chemistry abnormalities
End point description: The number of subjects with grade 3-4 serum chemistry laboratory abnormalities was presented for each arm.	
End point type	Secondary
End point timeframe: Approximately 3 years	

End point values	Tablet Only	PFOS Used	All Treated Subjects	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	82	24	106	
Units: subjects				
HC03<LLN (All Grade)	27	11	38	
HC03>ULN (All Grade)	24	1	25	
LDH>ULN (All Grade)	63	18	81	
Sodium	15	3	18	
Potassium	33	10	43	
Chloride (low) < LLN	20	2	22	
Chloride(high) > ULN	29	11	40	
Magnesium (low)	1	0	1	
Phosphorus	9	4	13	
Calcium (low)	15	3	18	
Uric Acid	0	1	1	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All serious and non-serious adverse events were reported from first dose up to 30 days after last dose

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	Tablet Only
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Reporting group description:

Subjects who were capable of swallowing tablets received treatment orally Dasatinib 60 milligram per meter square (mg/m²) once daily and subjects who were not able to swallow tablets received treatment as dispersed tablets in 100 percent (%) preservative free juice up to 27 months along with Associazione Italiana di Ematologia Pediatrica-Berlin-Frankfurt-Muenster Acute Lymphoblastic Leukemia (AIEOP-BFM ALL) 2000 chemotherapy regimen.

Reporting group title	PFOS Used
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Reporting group description:

Total of 24 subjects, 16 received Dasatinib 60 mg/m² once daily orally as both the tablet and as a suspension from Powder for oral suspension (PFOS), 8 subjects who were not able to swallow tablets received the treatment as PFOS only up to 27 months along with AIEOP-BFM ALL 2000 chemotherapy regimen.

Serious adverse events	Tablet Only	PFOS Used	
Total subjects affected by serious adverse events			
subjects affected / exposed	79 / 82 (96.34%)	22 / 24 (91.67%)	
number of deaths (all causes)	3	2	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia			
subjects affected / exposed	0 / 82 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Astrocytoma			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukaemia recurrent			

subjects affected / exposed	0 / 82 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Embolism			
subjects affected / exposed	3 / 82 (3.66%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	4 / 82 (4.88%)	3 / 24 (12.50%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	15 / 82 (18.29%)	7 / 24 (29.17%)	
occurrences causally related to treatment / all	1 / 20	1 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related thrombosis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised oedema			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Mucosal inflammation			
subjects affected / exposed	11 / 82 (13.41%)	7 / 24 (29.17%)	
occurrences causally related to treatment / all	2 / 14	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Cardiac chest pain			
subjects affected / exposed	2 / 82 (2.44%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 82 (1.22%)	2 / 24 (8.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	39 / 82 (47.56%)	13 / 24 (54.17%)	
occurrences causally related to treatment / all	8 / 104	6 / 26	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	7 / 82 (8.54%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	6 / 82 (7.32%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast			

disorders			
Oedema genital			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chylothorax			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	6 / 82 (7.32%)	2 / 24 (8.33%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	4 / 82 (4.88%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	2 / 82 (2.44%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	5 / 82 (6.10%)	2 / 24 (8.33%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	8 / 82 (9.76%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	3 / 9	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pleuritic pain			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	3 / 82 (3.66%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stridor			
subjects affected / exposed	0 / 82 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 82 (1.22%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Personality change			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Aspartate aminotransferase increased			
subjects affected / exposed	2 / 82 (2.44%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	2 / 82 (2.44%)	3 / 24 (12.50%)	
occurrences causally related to treatment / all	1 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	2 / 82 (2.44%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	7 / 82 (8.54%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood culture positive			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug clearance decreased			
subjects affected / exposed	1 / 82 (1.22%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovirus test positive			
subjects affected / exposed	0 / 82 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	8 / 82 (9.76%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	7 / 11	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			

subjects affected / exposed	7 / 82 (8.54%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin i increased			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urine output decreased			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral test			
subjects affected / exposed	1 / 82 (1.22%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	3 / 82 (3.66%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	5 / 82 (6.10%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	1 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count increased			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Allergic transfusion reaction			

subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic transfusion reaction			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	2 / 82 (2.44%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 82 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transfusion reaction			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic fracture			
subjects affected / exposed	1 / 82 (1.22%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access complication			
subjects affected / exposed	1 / 82 (1.22%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			

subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 82 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	3 / 82 (3.66%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 82 (1.22%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			

subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	2 / 82 (2.44%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paresis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	6 / 82 (7.32%)	2 / 24 (8.33%)	
occurrences causally related to treatment / all	0 / 6	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukoencephalopathy			
subjects affected / exposed	2 / 82 (2.44%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			

subjects affected / exposed	0 / 82 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	2 / 82 (2.44%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	3 / 82 (3.66%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	4 / 82 (4.88%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	12 / 82 (14.63%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	5 / 18	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile bone marrow aplasia			

subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	61 / 82 (74.39%)	20 / 24 (83.33%)	
occurrences causally related to treatment / all	33 / 217	8 / 60	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic anaemia			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	3 / 82 (3.66%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	4 / 5	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphatic disorder			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	20 / 82 (24.39%)	5 / 24 (20.83%)	
occurrences causally related to treatment / all	12 / 33	6 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	3 / 82 (3.66%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	9 / 82 (10.98%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	7 / 15	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Hypoacusis			

subjects affected / exposed	0 / 82 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Photophobia			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vision blurred			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	10 / 82 (12.20%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	1 / 13	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal haemorrhage			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	2 / 82 (2.44%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	8 / 82 (9.76%)	2 / 24 (8.33%)	
occurrences causally related to treatment / all	5 / 10	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			

subjects affected / exposed	2 / 82 (2.44%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	15 / 82 (18.29%)	6 / 24 (25.00%)	
occurrences causally related to treatment / all	5 / 24	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea haemorrhagic			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Enterocolitis			
subjects affected / exposed	2 / 82 (2.44%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	0 / 82 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal necrosis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 82 (1.22%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal ulcer			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	3 / 82 (3.66%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	2 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	4 / 82 (4.88%)	2 / 24 (8.33%)	
occurrences causally related to treatment / all	2 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			

subjects affected / exposed	6 / 82 (7.32%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 82 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	14 / 82 (17.07%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 17	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			

subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	13 / 82 (15.85%)	3 / 24 (12.50%)	
occurrences causally related to treatment / all	2 / 18	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis toxic			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venoocclusive liver disease			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	0 / 82 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	3 / 82 (3.66%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash macular			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash generalised			

subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	9 / 82 (10.98%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	1 / 9	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder spasm			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis noninfective			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			

subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 82 (2.44%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	2 / 82 (2.44%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	2 / 82 (2.44%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	2 / 82 (2.44%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Myalgia			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	4 / 82 (4.88%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in jaw			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 82 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal infection			
subjects affected / exposed	2 / 82 (2.44%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	11 / 82 (13.41%)	3 / 24 (12.50%)	
occurrences causally related to treatment / all	0 / 18	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	1 / 82 (1.22%)	2 / 24 (8.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchitis			

subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida infection			
subjects affected / exposed	3 / 82 (3.66%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida pneumonia			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	3 / 82 (3.66%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis of male external genital organ			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridial infection			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	6 / 82 (7.32%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	2 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			

subjects affected / exposed	6 / 82 (7.32%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 8	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coccidioidomycosis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conjunctivitis			
subjects affected / exposed	3 / 82 (3.66%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	13 / 82 (15.85%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	1 / 14	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis bacterial			
subjects affected / exposed	1 / 82 (1.22%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			

subjects affected / exposed	2 / 82 (2.44%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 82 (1.22%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal sepsis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 82 (2.44%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic infection			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	2 / 82 (2.44%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 82 (1.22%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	3 / 82 (3.66%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella bacteraemia			
subjects affected / exposed	0 / 82 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	2 / 82 (2.44%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	2 / 82 (2.44%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	6 / 82 (7.32%)	4 / 24 (16.67%)	
occurrences causally related to treatment / all	0 / 6	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Mucosal infection			
subjects affected / exposed	2 / 82 (2.44%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nail bed infection			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nail infection			

subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			
subjects affected / exposed	0 / 82 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	3 / 82 (3.66%)	2 / 24 (8.33%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pasteurella infection			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic infection			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perineal cellulitis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			
subjects affected / exposed	0 / 82 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			

subjects affected / exposed	2 / 82 (2.44%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	2 / 82 (2.44%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	7 / 82 (8.54%)	3 / 24 (12.50%)	
occurrences causally related to treatment / all	1 / 8	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 82 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal bacteraemia			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash pustular			
subjects affected / exposed	1 / 82 (1.22%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			

subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	17 / 82 (20.73%)	3 / 24 (12.50%)	
occurrences causally related to treatment / all	6 / 26	1 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic embolus			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	5 / 82 (6.10%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	2 / 82 (2.44%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	4 / 82 (4.88%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	2 / 9	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic infection			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic candida			

subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic mycosis			
subjects affected / exposed	0 / 82 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 82 (3.66%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection enterococcal			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral diarrhoea			
subjects affected / exposed	0 / 82 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			

subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 82 (3.66%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	8 / 82 (9.76%)	3 / 24 (12.50%)	
occurrences causally related to treatment / all	3 / 14	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	2 / 82 (2.44%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	2 / 82 (2.44%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypernatraemia			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertriglyceridaemia			
subjects affected / exposed	1 / 82 (1.22%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	3 / 82 (3.66%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			

subjects affected / exposed	7 / 82 (8.54%)	2 / 24 (8.33%)	
occurrences causally related to treatment / all	2 / 7	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	7 / 82 (8.54%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	2 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	2 / 82 (2.44%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Tablet Only	PFOS Used	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	82 / 82 (100.00%)	24 / 24 (100.00%)	
Vascular disorders			
Flushing			
subjects affected / exposed	9 / 82 (10.98%)	1 / 24 (4.17%)	
occurrences (all)	12	1	
Haematoma			
subjects affected / exposed	4 / 82 (4.88%)	2 / 24 (8.33%)	
occurrences (all)	6	2	
Hypertension			
subjects affected / exposed	35 / 82 (42.68%)	6 / 24 (25.00%)	
occurrences (all)	65	13	
Hypotension			
subjects affected / exposed	23 / 82 (28.05%)	5 / 24 (20.83%)	
occurrences (all)	37	6	
Pallor			
subjects affected / exposed	7 / 82 (8.54%)	4 / 24 (16.67%)	
occurrences (all)	13	6	
General disorders and administration site conditions			

Asthenia		
subjects affected / exposed	11 / 82 (13.41%)	0 / 24 (0.00%)
occurrences (all)	19	0
Catheter site bruise		
subjects affected / exposed	0 / 82 (0.00%)	3 / 24 (12.50%)
occurrences (all)	0	3
Catheter site erythema		
subjects affected / exposed	3 / 82 (3.66%)	3 / 24 (12.50%)
occurrences (all)	3	4
Catheter site pain		
subjects affected / exposed	10 / 82 (12.20%)	4 / 24 (16.67%)
occurrences (all)	13	5
Face oedema		
subjects affected / exposed	7 / 82 (8.54%)	1 / 24 (4.17%)
occurrences (all)	10	1
Chills		
subjects affected / exposed	16 / 82 (19.51%)	4 / 24 (16.67%)
occurrences (all)	29	8
Fatigue		
subjects affected / exposed	45 / 82 (54.88%)	13 / 24 (54.17%)
occurrences (all)	121	26
Gait disturbance		
subjects affected / exposed	6 / 82 (7.32%)	4 / 24 (16.67%)
occurrences (all)	7	8
Influenza like illness		
subjects affected / exposed	6 / 82 (7.32%)	0 / 24 (0.00%)
occurrences (all)	7	0
Malaise		
subjects affected / exposed	7 / 82 (8.54%)	0 / 24 (0.00%)
occurrences (all)	8	0
Mucosal inflammation		
subjects affected / exposed	43 / 82 (52.44%)	8 / 24 (33.33%)
occurrences (all)	68	13
Non-Cardiac chest pain		
subjects affected / exposed	15 / 82 (18.29%)	3 / 24 (12.50%)
occurrences (all)	23	7

Oedema			
subjects affected / exposed	9 / 82 (10.98%)	1 / 24 (4.17%)	
occurrences (all)	9	1	
Oedema peripheral			
subjects affected / exposed	16 / 82 (19.51%)	1 / 24 (4.17%)	
occurrences (all)	31	1	
Pain			
subjects affected / exposed	25 / 82 (30.49%)	3 / 24 (12.50%)	
occurrences (all)	38	7	
Pyrexia			
subjects affected / exposed	58 / 82 (70.73%)	21 / 24 (87.50%)	
occurrences (all)	234	55	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 82 (1.22%)	3 / 24 (12.50%)	
occurrences (all)	1	3	
Drug hypersensitivity			
subjects affected / exposed	14 / 82 (17.07%)	3 / 24 (12.50%)	
occurrences (all)	18	3	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	5 / 82 (6.10%)	3 / 24 (12.50%)	
occurrences (all)	6	3	
Dyspnoea			
subjects affected / exposed	14 / 82 (17.07%)	4 / 24 (16.67%)	
occurrences (all)	22	4	
Cough			
subjects affected / exposed	63 / 82 (76.83%)	15 / 24 (62.50%)	
occurrences (all)	197	40	
Epistaxis			
subjects affected / exposed	24 / 82 (29.27%)	3 / 24 (12.50%)	
occurrences (all)	42	5	
Hypoxia			
subjects affected / exposed	11 / 82 (13.41%)	4 / 24 (16.67%)	
occurrences (all)	12	8	
Nasal congestion			

subjects affected / exposed	24 / 82 (29.27%)	4 / 24 (16.67%)	
occurrences (all)	48	4	
Oropharyngeal pain			
subjects affected / exposed	31 / 82 (37.80%)	4 / 24 (16.67%)	
occurrences (all)	55	11	
Pleural effusion			
subjects affected / exposed	13 / 82 (15.85%)	3 / 24 (12.50%)	
occurrences (all)	15	3	
Productive cough			
subjects affected / exposed	6 / 82 (7.32%)	2 / 24 (8.33%)	
occurrences (all)	11	2	
Respiratory tract congestion			
subjects affected / exposed	8 / 82 (9.76%)	2 / 24 (8.33%)	
occurrences (all)	13	3	
Rhinitis allergic			
subjects affected / exposed	8 / 82 (9.76%)	0 / 24 (0.00%)	
occurrences (all)	9	0	
Rhinorrhoea			
subjects affected / exposed	24 / 82 (29.27%)	13 / 24 (54.17%)	
occurrences (all)	56	18	
Tachypnoea			
subjects affected / exposed	9 / 82 (10.98%)	2 / 24 (8.33%)	
occurrences (all)	10	3	
Sneezing			
subjects affected / exposed	5 / 82 (6.10%)	2 / 24 (8.33%)	
occurrences (all)	5	2	
Wheezing			
subjects affected / exposed	12 / 82 (14.63%)	1 / 24 (4.17%)	
occurrences (all)	14	2	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	11 / 82 (13.41%)	4 / 24 (16.67%)	
occurrences (all)	15	12	
Agitation			
subjects affected / exposed	6 / 82 (7.32%)	4 / 24 (16.67%)	
occurrences (all)	7	13	

Depression			
subjects affected / exposed	13 / 82 (15.85%)	3 / 24 (12.50%)	
occurrences (all)	16	3	
Insomnia			
subjects affected / exposed	13 / 82 (15.85%)	3 / 24 (12.50%)	
occurrences (all)	17	3	
Hallucination			
subjects affected / exposed	2 / 82 (2.44%)	2 / 24 (8.33%)	
occurrences (all)	2	2	
Irritability			
subjects affected / exposed	7 / 82 (8.54%)	5 / 24 (20.83%)	
occurrences (all)	9	7	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	29 / 82 (35.37%)	13 / 24 (54.17%)	
occurrences (all)	88	32	
Amylase increased			
subjects affected / exposed	2 / 82 (2.44%)	2 / 24 (8.33%)	
occurrences (all)	6	2	
Aspartate aminotransferase increased			
subjects affected / exposed	23 / 82 (28.05%)	12 / 24 (50.00%)	
occurrences (all)	57	19	
Blood bilirubin increased			
subjects affected / exposed	11 / 82 (13.41%)	1 / 24 (4.17%)	
occurrences (all)	12	1	
Blood creatinine increased			
subjects affected / exposed	7 / 82 (8.54%)	2 / 24 (8.33%)	
occurrences (all)	10	2	
Cardiac murmur			
subjects affected / exposed	11 / 82 (13.41%)	1 / 24 (4.17%)	
occurrences (all)	25	1	
Gamma-Glutamyltransferase increased			
subjects affected / exposed	5 / 82 (6.10%)	2 / 24 (8.33%)	
occurrences (all)	8	3	
Electrocardiogram qt prolonged			

subjects affected / exposed	6 / 82 (7.32%)	0 / 24 (0.00%)	
occurrences (all)	14	0	
Lipase increased			
subjects affected / exposed	2 / 82 (2.44%)	2 / 24 (8.33%)	
occurrences (all)	2	3	
Lymphocyte count decreased			
subjects affected / exposed	5 / 82 (6.10%)	3 / 24 (12.50%)	
occurrences (all)	38	17	
Neutrophil count decreased			
subjects affected / exposed	31 / 82 (37.80%)	10 / 24 (41.67%)	
occurrences (all)	170	51	
Platelet count decreased			
subjects affected / exposed	29 / 82 (35.37%)	10 / 24 (41.67%)	
occurrences (all)	176	53	
Weight increased			
subjects affected / exposed	9 / 82 (10.98%)	2 / 24 (8.33%)	
occurrences (all)	21	2	
Weight decreased			
subjects affected / exposed	22 / 82 (26.83%)	4 / 24 (16.67%)	
occurrences (all)	29	4	
White blood cell count decreased			
subjects affected / exposed	16 / 82 (19.51%)	5 / 24 (20.83%)	
occurrences (all)	79	40	
Injury, poisoning and procedural complications			
Allergic transfusion reaction			
subjects affected / exposed	10 / 82 (12.20%)	3 / 24 (12.50%)	
occurrences (all)	11	7	
Anal injury			
subjects affected / exposed	1 / 82 (1.22%)	2 / 24 (8.33%)	
occurrences (all)	1	2	
Arthropod bite			
subjects affected / exposed	4 / 82 (4.88%)	2 / 24 (8.33%)	
occurrences (all)	4	3	
Contusion			

subjects affected / exposed	24 / 82 (29.27%)	8 / 24 (33.33%)	
occurrences (all)	46	12	
Skin abrasion			
subjects affected / exposed	6 / 82 (7.32%)	2 / 24 (8.33%)	
occurrences (all)	8	2	
Sunburn			
subjects affected / exposed	5 / 82 (6.10%)	2 / 24 (8.33%)	
occurrences (all)	5	2	
Transfusion reaction			
subjects affected / exposed	6 / 82 (7.32%)	0 / 24 (0.00%)	
occurrences (all)	10	0	
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	6 / 82 (7.32%)	0 / 24 (0.00%)	
occurrences (all)	6	0	
Sinus bradycardia			
subjects affected / exposed	5 / 82 (6.10%)	0 / 24 (0.00%)	
occurrences (all)	6	0	
Sinus tachycardia			
subjects affected / exposed	16 / 82 (19.51%)	3 / 24 (12.50%)	
occurrences (all)	25	4	
Tachycardia			
subjects affected / exposed	25 / 82 (30.49%)	10 / 24 (41.67%)	
occurrences (all)	50	30	
Nervous system disorders			
Ataxia			
subjects affected / exposed	2 / 82 (2.44%)	2 / 24 (8.33%)	
occurrences (all)	2	3	
Dizziness			
subjects affected / exposed	14 / 82 (17.07%)	0 / 24 (0.00%)	
occurrences (all)	30	0	
Lethargy			
subjects affected / exposed	6 / 82 (7.32%)	1 / 24 (4.17%)	
occurrences (all)	11	2	
Headache			

subjects affected / exposed	60 / 82 (73.17%)	10 / 24 (41.67%)	
occurrences (all)	218	24	
Neuropathy peripheral			
subjects affected / exposed	5 / 82 (6.10%)	1 / 24 (4.17%)	
occurrences (all)	10	2	
Peripheral motor neuropathy			
subjects affected / exposed	11 / 82 (13.41%)	1 / 24 (4.17%)	
occurrences (all)	16	1	
Peripheral sensory neuropathy			
subjects affected / exposed	12 / 82 (14.63%)	1 / 24 (4.17%)	
occurrences (all)	14	1	
Somnolence			
subjects affected / exposed	5 / 82 (6.10%)	0 / 24 (0.00%)	
occurrences (all)	6	0	
Tremor			
subjects affected / exposed	7 / 82 (8.54%)	1 / 24 (4.17%)	
occurrences (all)	7	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	66 / 82 (80.49%)	17 / 24 (70.83%)	
occurrences (all)	556	131	
Febrile neutropenia			
subjects affected / exposed	30 / 82 (36.59%)	7 / 24 (29.17%)	
occurrences (all)	53	9	
Leukopenia			
subjects affected / exposed	9 / 82 (10.98%)	3 / 24 (12.50%)	
occurrences (all)	23	9	
Neutropenia			
subjects affected / exposed	35 / 82 (42.68%)	8 / 24 (33.33%)	
occurrences (all)	111	34	
Thrombocytopenia			
subjects affected / exposed	40 / 82 (48.78%)	10 / 24 (41.67%)	
occurrences (all)	281	47	
Ear and labyrinth disorders			
Ear pain			

subjects affected / exposed occurrences (all)	21 / 82 (25.61%) 33	4 / 24 (16.67%) 11	
Eye disorders			
Eye discharge			
subjects affected / exposed	0 / 82 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Eye pain			
subjects affected / exposed	6 / 82 (7.32%)	2 / 24 (8.33%)	
occurrences (all)	7	2	
Ocular hyperaemia			
subjects affected / exposed	4 / 82 (4.88%)	3 / 24 (12.50%)	
occurrences (all)	4	4	
Periorbital oedema			
subjects affected / exposed	6 / 82 (7.32%)	3 / 24 (12.50%)	
occurrences (all)	9	3	
Vision blurred			
subjects affected / exposed	14 / 82 (17.07%)	1 / 24 (4.17%)	
occurrences (all)	17	1	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	8 / 82 (9.76%)	3 / 24 (12.50%)	
occurrences (all)	10	7	
Abdominal pain			
subjects affected / exposed	57 / 82 (69.51%)	16 / 24 (66.67%)	
occurrences (all)	188	41	
Abdominal pain upper			
subjects affected / exposed	17 / 82 (20.73%)	2 / 24 (8.33%)	
occurrences (all)	33	2	
Anal fissure			
subjects affected / exposed	5 / 82 (6.10%)	0 / 24 (0.00%)	
occurrences (all)	5	0	
Anal inflammation			
subjects affected / exposed	4 / 82 (4.88%)	3 / 24 (12.50%)	
occurrences (all)	4	4	
Ascites			

subjects affected / exposed	5 / 82 (6.10%)	0 / 24 (0.00%)
occurrences (all)	7	0
Colitis		
subjects affected / exposed	11 / 82 (13.41%)	2 / 24 (8.33%)
occurrences (all)	15	2
Constipation		
subjects affected / exposed	46 / 82 (56.10%)	12 / 24 (50.00%)
occurrences (all)	105	24
Diarrhoea		
subjects affected / exposed	62 / 82 (75.61%)	13 / 24 (54.17%)
occurrences (all)	187	48
Dyspepsia		
subjects affected / exposed	6 / 82 (7.32%)	1 / 24 (4.17%)
occurrences (all)	9	1
Dyschezia		
subjects affected / exposed	0 / 82 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	2
Enteritis		
subjects affected / exposed	0 / 82 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	2
Haematochezia		
subjects affected / exposed	12 / 82 (14.63%)	2 / 24 (8.33%)
occurrences (all)	24	2
Mouth ulceration		
subjects affected / exposed	5 / 82 (6.10%)	3 / 24 (12.50%)
occurrences (all)	7	3
Nausea		
subjects affected / exposed	69 / 82 (84.15%)	12 / 24 (50.00%)
occurrences (all)	267	50
Oral pain		
subjects affected / exposed	24 / 82 (29.27%)	3 / 24 (12.50%)
occurrences (all)	35	5
Proctalgia		
subjects affected / exposed	13 / 82 (15.85%)	2 / 24 (8.33%)
occurrences (all)	18	3
Proctitis		

subjects affected / exposed	3 / 82 (3.66%)	2 / 24 (8.33%)	
occurrences (all)	3	2	
Rectal haemorrhage			
subjects affected / exposed	5 / 82 (6.10%)	0 / 24 (0.00%)	
occurrences (all)	7	0	
Stomatitis			
subjects affected / exposed	41 / 82 (50.00%)	8 / 24 (33.33%)	
occurrences (all)	86	13	
Toothache			
subjects affected / exposed	8 / 82 (9.76%)	1 / 24 (4.17%)	
occurrences (all)	11	1	
Vomiting			
subjects affected / exposed	66 / 82 (80.49%)	17 / 24 (70.83%)	
occurrences (all)	341	79	
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	5 / 82 (6.10%)	0 / 24 (0.00%)	
occurrences (all)	12	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	19 / 82 (23.17%)	2 / 24 (8.33%)	
occurrences (all)	20	3	
Dermatitis diaper			
subjects affected / exposed	1 / 82 (1.22%)	4 / 24 (16.67%)	
occurrences (all)	1	5	
Dermatitis acneiform			
subjects affected / exposed	9 / 82 (10.98%)	0 / 24 (0.00%)	
occurrences (all)	14	0	
Dry skin			
subjects affected / exposed	16 / 82 (19.51%)	3 / 24 (12.50%)	
occurrences (all)	23	3	
Eczema			
subjects affected / exposed	2 / 82 (2.44%)	2 / 24 (8.33%)	
occurrences (all)	2	2	
Ecchymosis			

subjects affected / exposed	4 / 82 (4.88%)	3 / 24 (12.50%)
occurrences (all)	6	7
Erythema		
subjects affected / exposed	18 / 82 (21.95%)	4 / 24 (16.67%)
occurrences (all)	26	5
Hyperhidrosis		
subjects affected / exposed	5 / 82 (6.10%)	0 / 24 (0.00%)
occurrences (all)	5	0
Ingrowing nail		
subjects affected / exposed	5 / 82 (6.10%)	0 / 24 (0.00%)
occurrences (all)	5	0
Pain of skin		
subjects affected / exposed	5 / 82 (6.10%)	1 / 24 (4.17%)
occurrences (all)	5	1
Petechiae		
subjects affected / exposed	14 / 82 (17.07%)	3 / 24 (12.50%)
occurrences (all)	24	3
Pruritus		
subjects affected / exposed	21 / 82 (25.61%)	6 / 24 (25.00%)
occurrences (all)	28	11
Rash		
subjects affected / exposed	37 / 82 (45.12%)	11 / 24 (45.83%)
occurrences (all)	84	28
Rash papular		
subjects affected / exposed	6 / 82 (7.32%)	2 / 24 (8.33%)
occurrences (all)	6	2
Rash maculo-papular		
subjects affected / exposed	16 / 82 (19.51%)	5 / 24 (20.83%)
occurrences (all)	27	11
Swelling face		
subjects affected / exposed	8 / 82 (9.76%)	1 / 24 (4.17%)
occurrences (all)	8	1
Urticaria		
subjects affected / exposed	7 / 82 (8.54%)	2 / 24 (8.33%)
occurrences (all)	9	2
Renal and urinary disorders		

Dysuria			
subjects affected / exposed	8 / 82 (9.76%)	4 / 24 (16.67%)	
occurrences (all)	10	6	
Urinary retention			
subjects affected / exposed	5 / 82 (6.10%)	1 / 24 (4.17%)	
occurrences (all)	8	1	
Haematuria			
subjects affected / exposed	11 / 82 (13.41%)	2 / 24 (8.33%)	
occurrences (all)	14	2	
Urinary tract pain			
subjects affected / exposed	1 / 82 (1.22%)	2 / 24 (8.33%)	
occurrences (all)	1	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	33 / 82 (40.24%)	5 / 24 (20.83%)	
occurrences (all)	73	18	
Back pain			
subjects affected / exposed	40 / 82 (48.78%)	8 / 24 (33.33%)	
occurrences (all)	97	18	
Bone pain			
subjects affected / exposed	18 / 82 (21.95%)	4 / 24 (16.67%)	
occurrences (all)	35	5	
Muscle spasms			
subjects affected / exposed	3 / 82 (3.66%)	2 / 24 (8.33%)	
occurrences (all)	3	2	
Muscular weakness			
subjects affected / exposed	14 / 82 (17.07%)	7 / 24 (29.17%)	
occurrences (all)	18	10	
Musculoskeletal chest pain			
subjects affected / exposed	8 / 82 (9.76%)	0 / 24 (0.00%)	
occurrences (all)	15	0	
Musculoskeletal pain			
subjects affected / exposed	13 / 82 (15.85%)	2 / 24 (8.33%)	
occurrences (all)	17	2	
Myalgia			

subjects affected / exposed	12 / 82 (14.63%)	3 / 24 (12.50%)	
occurrences (all)	23	6	
Neck pain			
subjects affected / exposed	8 / 82 (9.76%)	1 / 24 (4.17%)	
occurrences (all)	13	2	
Osteonecrosis			
subjects affected / exposed	7 / 82 (8.54%)	0 / 24 (0.00%)	
occurrences (all)	8	0	
Pain in extremity			
subjects affected / exposed	51 / 82 (62.20%)	12 / 24 (50.00%)	
occurrences (all)	151	25	
Pain in jaw			
subjects affected / exposed	17 / 82 (20.73%)	1 / 24 (4.17%)	
occurrences (all)	27	3	
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 82 (2.44%)	2 / 24 (8.33%)	
occurrences (all)	3	2	
Catheter site infection			
subjects affected / exposed	1 / 82 (1.22%)	2 / 24 (8.33%)	
occurrences (all)	1	3	
Candida infection			
subjects affected / exposed	11 / 82 (13.41%)	0 / 24 (0.00%)	
occurrences (all)	18	0	
Cellulitis			
subjects affected / exposed	9 / 82 (10.98%)	1 / 24 (4.17%)	
occurrences (all)	9	1	
Clostridium difficile colitis			
subjects affected / exposed	9 / 82 (10.98%)	2 / 24 (8.33%)	
occurrences (all)	11	2	
Conjunctivitis			
subjects affected / exposed	12 / 82 (14.63%)	0 / 24 (0.00%)	
occurrences (all)	15	0	
Clostridium difficile infection			
subjects affected / exposed	6 / 82 (7.32%)	2 / 24 (8.33%)	
occurrences (all)	7	2	

Device related infection		
subjects affected / exposed	6 / 82 (7.32%)	1 / 24 (4.17%)
occurrences (all)	7	1
Ear infection		
subjects affected / exposed	7 / 82 (8.54%)	0 / 24 (0.00%)
occurrences (all)	7	0
Enterocolitis bacterial		
subjects affected / exposed	0 / 82 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	3
Enterocolitis infectious		
subjects affected / exposed	9 / 82 (10.98%)	1 / 24 (4.17%)
occurrences (all)	11	1
Influenza		
subjects affected / exposed	7 / 82 (8.54%)	0 / 24 (0.00%)
occurrences (all)	7	0
Lung infection		
subjects affected / exposed	6 / 82 (7.32%)	2 / 24 (8.33%)
occurrences (all)	6	2
Mucosal infection		
subjects affected / exposed	5 / 82 (6.10%)	0 / 24 (0.00%)
occurrences (all)	5	0
Oral candidiasis		
subjects affected / exposed	14 / 82 (17.07%)	0 / 24 (0.00%)
occurrences (all)	22	0
Otitis media		
subjects affected / exposed	10 / 82 (12.20%)	1 / 24 (4.17%)
occurrences (all)	12	3
Paronychia		
subjects affected / exposed	3 / 82 (3.66%)	2 / 24 (8.33%)
occurrences (all)	4	3
Pharyngitis		
subjects affected / exposed	9 / 82 (10.98%)	1 / 24 (4.17%)
occurrences (all)	10	1
Pneumonia		
subjects affected / exposed	5 / 82 (6.10%)	1 / 24 (4.17%)
occurrences (all)	5	1

Rhinitis			
subjects affected / exposed	11 / 82 (13.41%)	0 / 24 (0.00%)	
occurrences (all)	18	0	
Rhinovirus infection			
subjects affected / exposed	6 / 82 (7.32%)	1 / 24 (4.17%)	
occurrences (all)	6	1	
Sepsis			
subjects affected / exposed	5 / 82 (6.10%)	2 / 24 (8.33%)	
occurrences (all)	6	2	
Skin infection			
subjects affected / exposed	11 / 82 (13.41%)	1 / 24 (4.17%)	
occurrences (all)	13	2	
Sinusitis			
subjects affected / exposed	17 / 82 (20.73%)	1 / 24 (4.17%)	
occurrences (all)	25	1	
Upper respiratory tract infection			
subjects affected / exposed	29 / 82 (35.37%)	10 / 24 (41.67%)	
occurrences (all)	45	14	
Urinary tract infection			
subjects affected / exposed	12 / 82 (14.63%)	2 / 24 (8.33%)	
occurrences (all)	13	4	
Viral upper respiratory tract infection			
subjects affected / exposed	6 / 82 (7.32%)	3 / 24 (12.50%)	
occurrences (all)	7	4	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	12 / 82 (14.63%)	2 / 24 (8.33%)	
occurrences (all)	16	2	
Decreased appetite			
subjects affected / exposed	31 / 82 (37.80%)	9 / 24 (37.50%)	
occurrences (all)	65	22	
Fluid overload			
subjects affected / exposed	5 / 82 (6.10%)	0 / 24 (0.00%)	
occurrences (all)	5	0	
Hyperglycaemia			

subjects affected / exposed	17 / 82 (20.73%)	6 / 24 (25.00%)
occurrences (all)	20	10
Hypertriglyceridaemia		
subjects affected / exposed	3 / 82 (3.66%)	2 / 24 (8.33%)
occurrences (all)	3	2
Hypoalbuminaemia		
subjects affected / exposed	25 / 82 (30.49%)	9 / 24 (37.50%)
occurrences (all)	38	10
Hypocalcaemia		
subjects affected / exposed	25 / 82 (30.49%)	5 / 24 (20.83%)
occurrences (all)	50	8
Hypoglycaemia		
subjects affected / exposed	2 / 82 (2.44%)	2 / 24 (8.33%)
occurrences (all)	3	2
Hypokalaemia		
subjects affected / exposed	41 / 82 (50.00%)	9 / 24 (37.50%)
occurrences (all)	118	22
Hyponatraemia		
subjects affected / exposed	19 / 82 (23.17%)	4 / 24 (16.67%)
occurrences (all)	26	9
Hypomagnesaemia		
subjects affected / exposed	14 / 82 (17.07%)	5 / 24 (20.83%)
occurrences (all)	26	10
Hypophosphataemia		
subjects affected / exposed	17 / 82 (20.73%)	6 / 24 (25.00%)
occurrences (all)	26	9

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 September 2011	The following amendment was developed to incorporate two key changes including: 1) Changing the statistical design of the trial to allow comparison to historical external controls. Specifically, the 3-year event free survival (EFS) of dasatinib plus chemotherapy will be compared to the 3-year EFS of chemotherapy alone from the Associazione Italiana di Ematologia Pediatrica - Berlin-Frankfurt-Muenster ALL 2000 (AIEOP BFM 2000) trial and the 3-year EFS of imatinib plus chemotherapy from the European intergroup Study on post induction treatment of Philadelphia positive Acute Lymphoblastic Leukemia (EsPhALL). This analysis will improve the ability to interpret the safety and efficacy of dasatinib added to chemotherapy among other treatment options for this pediatric leukemia. 2) Incorporating additional supportive care options for chemotherapy to accommodate the standard of care at sites in the United Kingdom (UK). Additionally, typographical errors were also corrected.
07 December 2012	The key purposes of this amendment are to incorporate the following key changes: 1) Introduce a new pediatric formulation of dasatinib. 2) Address lack of availability of native-asparaginase in the United States and allow use of Peg-Asparaginase upfront in such instances as well as provide more detailed instruction for dose modifications of the various asparaginase formulations. 3) Indicate that the BCR-ABL mutation status will be reported for baseline and at time of progression as a secondary objective instead of as an exploratory objective. 4) Allow Philadelphia chromosome positivity from peripheral blood to be acceptable for study entry. 5) Expand the window for screening activities to 21 days. 6) Modify the definition of high risk group and low/standard risk group in response to Induction 1A treatment. 7) Provides for clarifications, fixes inconsistencies across sections of the protocol and corrects various typographical errors.
31 July 2013	The key purposes of this amendment are to incorporate the following key changes: 1) Increase the number of treated subjects from 75 to at least 75 and up to 90. 2) Modify language regarding pregnancy prevention. 3) Incorporate recommendations for subject management and supportive care during High Risk (HR) Blocks 1-3. 4) Provides for clarifications, fixes inconsistencies across sections of the protocol and corrects various typographical errors.
28 October 2013	The key purposes of this amendment are to incorporate the following changes: 1) Add mandatory supportive care measures during the 3 High Risk Blocks 2) Provide updates to the WOCBP language to harmonize this language with the current BMS directives for WOCBP.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported