Clinical trial results:
GRAVITAS-301: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Itacitinib or Placebo in Combination With Corticosteroids for the Treatment of First-Line Acute Graft-Versus-Host Disease

Summary

EudraCT number	2017-000538-78
Trial protocol	HU CZ GB BE AT PT ES NL GR FI IT
Global end of trial date	13 July 2020

Results information

Result version number	v1 (current)
This version publication date	29 July 2021
First version publication date	29 July 2021

Trial information

Trial identification

Sponsor protocol code	INCB 39110-301

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Incyte
Sponsor organisation address	1801 Augustine Cutoff drive, Wilmington, United States, 19803
Public contact	Study Director, Incyte Corporation, 3022744765 18554633463, globalmedinfo@incyte.com
Scientific contact	Study Director, Incyte Corporation, 3022744765 18554633463, globalmedinfo@incyte.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 July 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate itacitinib or placebo in combination with corticosteroids as first-line treatment of participants with Grade II to IV acute graft-versus-host disease (aGVHD).

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	19 July 2017
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: 4
Country: Number of subjects enrolled	Austria: 9
Country: Number of subjects enrolled	Belgium: 22
Country: Number of subjects enrolled	Czechia: 1
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	France: 22
Country: Number of subjects enrolled	Germany: 21
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Israel: 13
Country: Number of subjects enrolled	Italy: 37
Country: Number of subjects enrolled	New Zealand: 2
Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	Portugal: 15
Country: Number of subjects enrolled	Korea, Republic of: 4
Country: Number of subjects enrolled	Spain: 75
Country: Number of subjects enrolled	Switzerland: 7
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	United States: 186

Worldwide total number of subjects	439
EEA total number of subjects	218

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)	336
From 65 to 84 years	103
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 128 investigative sites in 19 different countries.

Pre-assignment

Screening details:

A total of 498 participants were screened for this study, of which 59 participants were screen failures and 439 participants were randomized to treatment.

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	Itacitinib plus Corticosteroids

Arm description:

Itacitinib was administered at a starting dose of 200 mg orally once daily QD (2 × 100 mg tablets) in combination with steroids i.e. methylprednisolone 2 mg/kg IV daily (or prednisone equivalent) or at a dose that is appropriate for the severity of the disease.

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

Dosage and administration details:

Itacitinib was be administered orally at a starting dose of 200 mg once daily.

Arm title	Placebo plus Corticosteroids

Arm description:

Matching placebo was administered orally once daily QD in combination with steroids i.e. methylprednisolone 2 mg/kg IV daily (or prednisone equivalent) or at a dose that is appropriate for the severity of the disease.

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

Dosage and administration details:

Placebo was administered orally at a starting dose of 200 mg once daily.

Number of subjects in period 1	Itacitinib plus Corticosteroids	Placebo plus Corticosteroids
Started	219	220
Completed	0	0
Not completed	219	220
Adverse event, serious fatal	65	67
Consent withdrawn by subject	16	17
Physician decision	1	2
Unknown	7	3
EOS missing- COVID-19 site monitoring restrictions	5	3
Study Terminated by Sponsor	122	127
Lost to follow-up	3	1

Baseline characteristics

Reporting groups	
Reporting group title	Itacitinib plus Corticosteroids
Reporting group description:	
Itacitinib was administered at a starting dose of 200 mg orally once daily QD (2 × 100 mg tablets) in combination with steroids i.e. methylprednisolone 2 mg/kg IV daily (or prednisone equivalent) or at a dose that is appropriate for the severity of the disease.	
Reporting group title	Placebo plus Corticosteroids
Reporting group description:	
Matching placebo was administered orally once daily QD in combination with steroids i.e. methylprednisolone 2 mg/kg IV daily (or prednisone equivalent) or at a dose that is appropriate for the severity of the disease.	

Reporting group values	Itacitinib plus Corticosteroids	Placebo plus Corticosteroids	Total
Number of subjects	219	220	439
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	166	170	336
From 65-84 years	53	50	103
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	53.6	54.0	
standard deviation	± 13.53	± 12.96	-
Sex: Female, Male Units: Participants			
Female	82	91	173
Male	137	129	266
Race/Ethnicity Units: Subjects			
Hispanic or Latino	17	22	39
Not Hispanic or Latino	167	169	336
Not Reported	17	14	31
Unknown	12	9	21
Other	6	5	11
missing	0	1	1
Race/Ethnicity Units: Subjects			
White/Caucasian	196	194	390
Black/African-American	8	5	13
Asian	4	4	8

American-Indian/Alaska Native	0	2	2
missing	1	4	5
Other	10	11	21

End points

End points reporting groups

Reporting group title	Itacitinib plus Corticosteroids
Reporting group description:	
Itacitinib was administered at a starting dose of 200 mg orally once daily QD (2 × 100 mg tablets) in combination with steroids i.e. methylprednisolone 2 mg/kg IV daily (or prednisone equivalent) or at a dose that is appropriate for the severity of the disease.	
Reporting group title	Placebo plus Corticosteroids
Reporting group description:	
Matching placebo was administered orally once daily QD in combination with steroids i.e. methylprednisolone 2 mg/kg IV daily (or prednisone equivalent) or at a dose that is appropriate for the severity of the disease.	

Primary: Overall response rate based on Center for International Blood and Marrow Transplant Research (CIBMTR) response index

End point title	Overall response rate based on Center for International Blood and Marrow Transplant Research (CIBMTR) response index
End point description:	
Defined as the percentage of participants demonstrating a complete response (CR), very good partial response (VGPR), or partial response (PR).	
End point type	Primary
End point timeframe:	
Day 28	

End point values	Itacitinib plus Corticosteroids	Placebo plus Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219	220		
Units: Percentage of Participants				
number (confidence interval 95%)	74.0 (67.6 to 79.7)	66.4 (59.7 to 72.6)		

Statistical analyses

Statistical analysis title	Stratified CMH
Statistical analysis description:	
binomial distribution	
Comparison groups	Itacitinib plus Corticosteroids v Placebo plus Corticosteroids
Number of subjects included in analysis	439
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0782 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.45

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.959
upper limit	2.204

Notes:

[1] - Not adjusted for multiplicity with interim and final analyses

Secondary: Nonrelapse mortality

End point title	Nonrelapse mortality

End point description:

Defined as the percentage of participants who died due to causes other than malignancy relapse.

End point type	Secondary

End point timeframe:

Month 6,9,12 and 24

End point values	Itacitinib plus Corticosteroids	Placebo plus Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219	220		
Units: participants				
6 Months	36	37		
9 Months	46	45		
12 Months	51	52		
24 Months	56	52		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response

End point title	Duration of response

End point description:

Defined as the interval from first response until GVHD progression or death.

End point type	Secondary

End point timeframe:

Baseline through 30-35 days after end of treatment, total particpation expected to average 24 months

End point values	Itacitinib plus Corticosteroids	Placebo plus Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219	220		
Units: days				
median (confidence interval 95%)	587 (513 to 999999999)	99.999999 (9.9999999 to 99999999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of itacitinib when administered in combination with corticosteroids

End point title	Cmax of itacitinib when administered in combination with corticosteroids[2]

End point description:

Defined as maximum observed plasma concentration.

End point type	Secondary

End point timeframe:

Protocol-defined timepoints up to Day 28

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK Parameters were not analyzed for placebo group

End point values	Itacitinib plus Corticosteroids			
Subject group type	Reporting group			
Number of subjects analysed	162			
Units: nM				
arithmetic mean (standard deviation)	796 (± 642)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmin of itacitinib when administered in combination with corticosteroids

End point title	Cmin of itacitinib when administered in combination with corticosteroids[3]

End point description:

Defined as minimum observed plasma concentration.

End point type	Secondary

End point timeframe:

Protocol-defined timepoints up to Day 28

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK Parameters were not analyzed for placebo group

End point values	Itacitinib plus Corticosteroids			
Subject group type	Reporting group			
Number of subjects analysed	62			
Units: nM				
arithmetic mean (standard deviation)	72.5 (± 121)			

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax of itacitinib when administered in combination with corticosteroids

End point title	Tmax of itacitinib when administered in combination with corticosteroids[4]

End point description:

Defined as time to maximum plasma concentration.

End point type	Secondary

End point timeframe:

Protocol-defined timepoints up to Day 28

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK Parameters were not analyzed for placebo group

End point values	Itacitinib plus Corticosteroids			
Subject group type	Reporting group			
Number of subjects analysed	62			
Units: hrs				
median (full range (min-max))	2.1 (0.83 to 5.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: AUC of itacitinib when administered in combination with corticosteroids

End point title	AUC of itacitinib when administered in combination with corticosteroids[5]

End point description:

Defined as area under the concentration-time curve.

End point type	Secondary

End point timeframe:

Protocol-defined timepoints up to Day 28

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK Parameters were not analyzed for placebo group

End point values	Itacitinib plus Corticosteroids			
Subject group type	Reporting group			
Number of subjects analysed	62			
Units: nM*h				
arithmetic mean (standard deviation)	6720 (± 6210)			

Statistical analyses

No statistical analyses for this end point

Secondary: CL/F of itacitinib when administered in combination with corticosteroids

End point title	CL/F of itacitinib when administered in combination with corticosteroids[6]

End point description:

Defined as oral dose clearance.

End point type	Secondary

End point timeframe:

Protocol-defined timepoints up to Day 28

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK Parameters were not analyzed for placebo group

End point values	Itacitinib plus Corticosteroids			
Subject group type	Reporting group			
Number of subjects analysed	62			
Units: L/h				
arithmetic mean (standard deviation)	104 (± 76.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to response

End point title	Time to response

End point description:

Defined as the interval from treatment initiation to first response

End point type	Secondary

End point timeframe:

End of Study, total particpation expected to average 24 months

End point values	Itacitinib plus Corticosteroids	Placebo plus Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	185		
Units: days				
arithmetic mean (standard deviation)	9.9 (± 6.25)	10.1 (± 5.37)		

Statistical analyses

No statistical analyses for this end point

Secondary: Relapse rate of malignant and nonmalignant hematologic disease

End point title	Relapse rate of malignant and nonmalignant hematologic disease

End point description:

Defined as the proportion of subjects whose underlying hematologic disease relapses

End point type	Secondary

End point timeframe:

Randomization through end of Study, study duration expected to average 24 months

End point values	Itacitinib plus Corticosteroids	Placebo plus Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	217	220		
Units: percentage				
number (not applicable)	12.4	11.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Malignancy relapse-related mortality rate

End point title	Malignancy relapse-related mortality rate

End point description:

Defined as the proportion of subjects whose malignancy relapses and has a fatal outcome.

End point type	Secondary

End point timeframe:

Randomization through end of Study, study duration expected to average 24 months

End point values	Itacitinib plus Corticosteroids	Placebo plus Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219	220		
Units: percentage				
number (not applicable)	6.4	7.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Failure-free survival

End point title	Failure-free survival

End point description:

defined as the proportion of subjects who are still alive, have not relapsed, have not required additional therapy for aGVHD, and have not demonstrated signs or symptoms of chronic graft-versus-host disease (cGVHD)

End point type	Secondary

End point timeframe:

6 months from randomization

End point values	Itacitinib plus Corticosteroids	Placebo plus Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219	220		
Units: proportion of participants				
number (not applicable)	44.29	44.00		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

Defined as the interval from study enrollment to death due to any cause.

End point type	Secondary

End point timeframe:

End of Study up to approximately 24 months

End point values	Itacitinib plus Corticosteroids	Placebo plus Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219	220		
Units: days				
median (full range (min-max))	365 (1 to 867)	348.5 (1 to 827)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment-emergent adverse events with INCB39110

End point title	Number of treatment-emergent adverse events with INCB39110

End point description:

Adverse events reported for the first time or worsening of a pre-existing event after the first dose of study treatment

End point type	Secondary

End point timeframe:

30-35 days after end of treatment, approximately 24 months

End point values	Itacitinib plus Corticosteroids	Placebo plus Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	215	216		
Units: participants	208	214		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence rate of secondary graft failure

End point title	Incidence rate of secondary graft failure

End point description:

Defined as > 95% recipient cells any time after engraftment with no signs of relapse, OR retransplantation because of secondary neutropenia (< 0.5 × 109/L) and/or thrombocytopenia (< 20 × 109/L) within 2 months of transplantion

End point type	Secondary

End point timeframe:

Randomization through end of Study, study duration expected to average 24 months

End point values	Itacitinib plus Corticosteroids	Placebo plus Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219	220		
Units: participants	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: proportion of subjects who discontinue corticosteroids

End point title	proportion of subjects who discontinue corticosteroids

End point description:

Average and cumulative corticosteroid dose usage will be calculated and proportion of subjects discontinuing corticosteroids will be tabulated

End point type	Secondary

End point timeframe:

Days 28, 56, 100, and 180

End point values	Itacitinib plus Corticosteroids	Placebo plus Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	215	216		
Units: participants				
Day 28	3	3		
Day 56	16	11		
Day 100	39	45		
Day 180	39	45		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects who discontinue immunosuppressive medications

End point title	Proportion of subjects who discontinue immunosuppressive medications

End point description:

Summary statistics of subjects discontinuing immunosuppressive medications will be calculated

End point type	Secondary

End point timeframe:

Days 56 and 100

End point values	Itacitinib plus Corticosteroids	Placebo plus Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219	220		
Units: participants				
Day 56	12	10		
Day 100	11	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence rate of aGVHD flares

End point title	Incidence rate of aGVHD flares

End point description:

End point type	Secondary

End point timeframe:

up to day 100

End point values	Itacitinib plus Corticosteroids	Placebo plus Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219	220		
Units: participants	42	48		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence rate of cGVHD

End point title	Incidence rate of cGVHD

End point description:

End point type	Secondary

End point timeframe:

Days 180 and 365

End point values	Itacitinib plus Corticosteroids	Placebo plus Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	59		
Units: participants				
Day 180	25	36		
Day 365	41	57		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate

End point title	Objective Response Rate

End point description:

End point type	Secondary

End point timeframe:

Days 14, 56 and 100

End point values	Itacitinib plus Corticosteroids	Placebo plus Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219	220		
Units: participants				
Day 14	170	160		
Day 56	138	124		
Day 100	92	96		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
30-35 days after end of treatment, approximately 24 months	
Adverse event reporting additional description:	
AE additional description	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22

Reporting groups	
Reporting group title	Itacitinib plus Corticosteroids
Reporting group description:	
Itacitinib was administered at a starting dose of 200 mg orally once daily QD (2 × 100 mg tablets) in combination with steroids i.e. methylprednisolone 2 mg/kg IV daily (or prednisone equivalent) or at a dose that is appropriate for the severity of the disease.	
Reporting group title	Total
Reporting group description:	
Total	
Reporting group title	Placebo plus Corticosteroids
Reporting group description:	
Matching placebo was administered orally once daily QD in combination with steroids i.e. methylprednisolone 2 mg/kg IV daily (or prednisone equivalent) or at a dose that is appropriate for the severity of the disease.	

Serious adverse events	Itacitinib plus Corticosteroids	Total	Placebo plus Corticosteroids
Total subjects affected by serious adverse events			
subjects affected / exposed	133 / 215 (61.86%)	264 / 431 (61.25%)	131 / 216 (60.65%)
number of deaths (all causes)	69	138	69
number of deaths resulting from adverse events	22	54	32
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Chronic lymphocytic leukaemia recurrent			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Malignant neoplasm progression			

subjects affected / exposed	2 / 215 (0.93%)	4 / 431 (0.93%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 2
Myelodysplastic syndrome			
subjects affected / exposed	0 / 215 (0.00%)	2 / 431 (0.46%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Myeloid leukaemia			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Nasal cavity cancer			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post transplant lymphoproliferative disorder			
subjects affected / exposed	1 / 215 (0.47%)	2 / 431 (0.46%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 1	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
T-cell lymphoma recurrent			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Acute myeloid leukaemia recurrent			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Blast cell crisis			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukaemia recurrent			

subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 215 (0.47%)	3 / 431 (0.70%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Microangiopathy			
subjects affected / exposed	1 / 215 (0.47%)	2 / 431 (0.46%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Shock			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
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			
Asthenia			
subjects affected / exposed	2 / 215 (0.93%)	4 / 431 (0.93%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	2 / 215 (0.93%)	2 / 431 (0.46%)	0 / 216 (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
General physical health deterioration			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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

Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 215 (0.47%)	3 / 431 (0.70%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 1
Oedema			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Pyrexia			
subjects affected / exposed	15 / 215 (6.98%)	25 / 431 (5.80%)	10 / 216 (4.63%)
occurrences causally related to treatment / all	5 / 19	6 / 29	1 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Acute graft versus host disease			
subjects affected / exposed	1 / 215 (0.47%)	4 / 431 (0.93%)	3 / 216 (1.39%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 2
Acute graft versus host disease in skin			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Graft versus host disease			
subjects affected / exposed	1 / 215 (0.47%)	4 / 431 (0.93%)	3 / 216 (1.39%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 3	0 / 2
Graft versus host disease in gastrointestinal tract			
subjects affected / exposed	3 / 215 (1.40%)	9 / 431 (2.09%)	6 / 216 (2.78%)
occurrences causally related to treatment / all	0 / 3	0 / 9	0 / 6
deaths causally related to treatment / all	0 / 1	0 / 3	0 / 2

Graft versus host disease in lung			
subjects affected / exposed	0 / 215 (0.00%)	2 / 431 (0.46%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Acute graft versus host disease in intestine			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Reproductive system and breast disorders			
Testicular pain			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
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, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 215 (0.47%)	2 / 431 (0.46%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Acute respiratory failure			
subjects affected / exposed	0 / 215 (0.00%)	2 / 431 (0.46%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea exertional			

subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
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	1 / 215 (0.47%)	2 / 431 (0.46%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemothorax			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Hypoxia			
subjects affected / exposed	1 / 215 (0.47%)	2 / 431 (0.46%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 1	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obliterative bronchiolitis			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Organising pneumonia			
subjects affected / exposed	1 / 215 (0.47%)	2 / 431 (0.46%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic pain			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Pneumonitis			
subjects affected / exposed	1 / 215 (0.47%)	2 / 431 (0.46%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Pulmonary embolism			

subjects affected / exposed	2 / 215 (0.93%)	4 / 431 (0.93%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	1 / 2	1 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	3 / 215 (1.40%)	8 / 431 (1.86%)	5 / 216 (2.31%)
occurrences causally related to treatment / all	0 / 3	0 / 8	0 / 5
deaths causally related to treatment / all	0 / 1	0 / 3	0 / 2
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Haemoptysis			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Pneumothorax			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary alveolar haemorrhage			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
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 distress			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 215 (0.47%)	3 / 431 (0.70%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	1 / 1	1 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			

subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Substance-induced psychotic disorder			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 215 (0.47%)	2 / 431 (0.46%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 215 (0.47%)	2 / 431 (0.46%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood fibrinogen decreased			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Liver function test increased			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	1 / 215 (0.47%)	2 / 431 (0.46%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			

subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Blood bilirubin increased			
subjects affected / exposed	1 / 215 (0.47%)	2 / 431 (0.46%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium test positive			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram T wave abnormal			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Enterococcus test positive			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Klebsiella test positive			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotavirus test positive			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			

subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Extradural haematoma			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Fall			
subjects affected / exposed	1 / 215 (0.47%)	4 / 431 (0.93%)	3 / 216 (1.39%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Wrist fracture			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Head injury			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin laceration			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Toxicity to various agents			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transplant dysfunction			

subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Transplant failure			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
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			
Bartter's syndrome			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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 disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 215 (0.47%)	2 / 431 (0.46%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Cardiac arrest			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cardiac failure congestive			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Myocardial infarction			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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

Nervous system disorders			
Encephalopathy			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lethargy			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Limbic encephalitis			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurotoxicity			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral motor neuropathy			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Presyncope			
subjects affected / exposed	1 / 215 (0.47%)	3 / 431 (0.70%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Syncope			
subjects affected / exposed	4 / 215 (1.86%)	5 / 431 (1.16%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	1 / 4	1 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic encephalopathy			
subjects affected / exposed	1 / 215 (0.47%)	2 / 431 (0.46%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Altered state of consciousness			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	1 / 215 (0.47%)	2 / 431 (0.46%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 1
Cerebrovascular accident			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic coma			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyneuropathy			
subjects affected / exposed	0 / 215 (0.00%)	2 / 431 (0.46%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal subdural haematoma			

subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status epilepticus			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 215 (1.40%)	5 / 431 (1.16%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	1 / 3	1 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bicytopenia			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Febrile neutropenia			
subjects affected / exposed	7 / 215 (3.26%)	15 / 431 (3.48%)	8 / 216 (3.70%)
occurrences causally related to treatment / all	2 / 8	5 / 18	3 / 10
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Hypofibrinogenaemia			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Leukopenia			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Microangiopathic haemolytic anaemia			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			

subjects affected / exposed	3 / 215 (1.40%)	6 / 431 (1.39%)	3 / 216 (1.39%)
occurrences causally related to treatment / all	1 / 3	2 / 6	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	4 / 215 (1.86%)	4 / 431 (0.93%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	3 / 5	3 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	3 / 215 (1.40%)	9 / 431 (2.09%)	6 / 216 (2.78%)
occurrences causally related to treatment / all	2 / 3	8 / 9	6 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombotic microangiopathy			
subjects affected / exposed	3 / 215 (1.40%)	6 / 431 (1.39%)	3 / 216 (1.39%)
occurrences causally related to treatment / all	0 / 3	1 / 6	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Agranulocytosis			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Haemolysis			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Eye disorders			

Photophobia			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 215 (0.93%)	7 / 431 (1.62%)	5 / 216 (2.31%)
occurrences causally related to treatment / all	0 / 2	0 / 7	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	10 / 215 (4.65%)	23 / 431 (5.34%)	13 / 216 (6.02%)
occurrences causally related to treatment / all	0 / 11	3 / 26	3 / 15
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticular perforation			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Gastritis erosive			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Haemoperitoneum			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Ileus			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal haemorrhage			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Lower gastrointestinal haemorrhage			

subjects affected / exposed	1 / 215 (0.47%)	2 / 431 (0.46%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	2 / 215 (0.93%)	3 / 431 (0.70%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 2	1 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 215 (0.47%)	2 / 431 (0.46%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumatosis intestinalis			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
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	3 / 215 (1.40%)	7 / 431 (1.62%)	4 / 216 (1.85%)
occurrences causally related to treatment / all	0 / 3	1 / 7	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal haemorrhage			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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 inflammation			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Intestinal ischaemia			

subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Small intestinal obstruction			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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 / 215 (0.47%)	2 / 431 (0.46%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 1
Venoocclusive liver disease			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Ecchymosis			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			

subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	8 / 215 (3.72%)	13 / 431 (3.02%)	5 / 216 (2.31%)
occurrences causally related to treatment / all	0 / 8	0 / 13	0 / 5
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Cystitis haemorrhagic			
subjects affected / exposed	4 / 215 (1.86%)	4 / 431 (0.93%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysuria			
subjects affected / exposed	1 / 215 (0.47%)	2 / 431 (0.46%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Bullous oedema of the bladder			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Musculoskeletal and connective tissue disorders			

Muscular weakness			
subjects affected / exposed	2 / 215 (0.93%)	3 / 431 (0.70%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myopathy			
subjects affected / exposed	3 / 215 (1.40%)	5 / 431 (1.16%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	0 / 3	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 215 (0.47%)	2 / 431 (0.46%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue necrosis			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Amyotrophy			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	1 / 215 (0.47%)	2 / 431 (0.46%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute sinusitis			

subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenovirus infection			
subjects affected / exposed	3 / 215 (1.40%)	4 / 431 (0.93%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	1 / 3	1 / 4	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 1
Aspergillus infection			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
BK virus infection			
subjects affected / exposed	1 / 215 (0.47%)	2 / 431 (0.46%)	1 / 216 (0.46%)
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	0 / 215 (0.00%)	4 / 431 (0.93%)	4 / 216 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial sepsis			
subjects affected / exposed	0 / 215 (0.00%)	2 / 431 (0.46%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Bronchitis			
subjects affected / exposed	1 / 215 (0.47%)	3 / 431 (0.70%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopulmonary aspergillosis			
subjects affected / exposed	3 / 215 (1.40%)	4 / 431 (0.93%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	2 / 3	3 / 4	1 / 1
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Campylobacter infection			

subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral toxoplasmosis			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Cholecystitis infective			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 215 (0.00%)	2 / 431 (0.46%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	0 / 215 (0.00%)	2 / 431 (0.46%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Cytomegalovirus infection			
subjects affected / exposed	2 / 215 (0.93%)	5 / 431 (1.16%)	3 / 216 (1.39%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus infection reactivation			
subjects affected / exposed	6 / 215 (2.79%)	7 / 431 (1.62%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	1 / 6	1 / 8	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus viraemia			

subjects affected / exposed	5 / 215 (2.33%)	10 / 431 (2.32%)	5 / 216 (2.31%)
occurrences causally related to treatment / all	3 / 5	7 / 10	4 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 215 (0.47%)	2 / 431 (0.46%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalitis			
subjects affected / exposed	0 / 215 (0.00%)	2 / 431 (0.46%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Enterovirus infection			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epstein-Barr virus infection reactivation			
subjects affected / exposed	1 / 215 (0.47%)	2 / 431 (0.46%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	1 / 1	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia infection			
subjects affected / exposed	1 / 215 (0.47%)	2 / 431 (0.46%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Escherichia sepsis			
subjects affected / exposed	2 / 215 (0.93%)	4 / 431 (0.93%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	0 / 2	1 / 4	1 / 2
deaths causally related to treatment / all	0 / 1	1 / 2	1 / 1
Fungal infection			
subjects affected / exposed	1 / 215 (0.47%)	2 / 431 (0.46%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis norovirus			

subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
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 rotavirus			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Gastrointestinal infection			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
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 zoster			
subjects affected / exposed	1 / 215 (0.47%)	2 / 431 (0.46%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
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			
subjects affected / exposed	1 / 215 (0.47%)	4 / 431 (0.93%)	3 / 216 (1.39%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Lower respiratory tract infection fungal			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucormycosis			
subjects affected / exposed	1 / 215 (0.47%)	2 / 431 (0.46%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 1
Neutropenic sepsis			

subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Ophthalmic herpes zoster			
subjects affected / exposed	2 / 215 (0.93%)	2 / 431 (0.46%)	0 / 216 (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
Oral candidiasis			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
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 herpes			
subjects affected / exposed	2 / 215 (0.93%)	2 / 431 (0.46%)	0 / 216 (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
Pneumonia			
subjects affected / exposed	11 / 215 (5.12%)	24 / 431 (5.57%)	13 / 216 (6.02%)
occurrences causally related to treatment / all	2 / 12	6 / 27	4 / 15
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 3
Pneumonia bacterial			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia cytomegaloviral			
subjects affected / exposed	1 / 215 (0.47%)	2 / 431 (0.46%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia influenzal			
subjects affected / exposed	2 / 215 (0.93%)	2 / 431 (0.46%)	0 / 216 (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
Pneumonia necrotising			

subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Pneumonia pneumococcal			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pseudomonal			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonal sepsis			
subjects affected / exposed	2 / 215 (0.93%)	2 / 431 (0.46%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Pseudomonas infection			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 215 (0.47%)	2 / 431 (0.46%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 1	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
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 fungal			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Rhinovirus infection			

subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
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	5 / 215 (2.33%)	11 / 431 (2.55%)	6 / 216 (2.78%)
occurrences causally related to treatment / all	0 / 5	1 / 11	1 / 6
deaths causally related to treatment / all	0 / 3	1 / 6	1 / 3
Septic shock			
subjects affected / exposed	2 / 215 (0.93%)	8 / 431 (1.86%)	6 / 216 (2.78%)
occurrences causally related to treatment / all	0 / 2	1 / 8	1 / 6
deaths causally related to treatment / all	0 / 1	0 / 4	0 / 3
Sinusitis			
subjects affected / exposed	1 / 215 (0.47%)	2 / 431 (0.46%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 1	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 215 (0.47%)	5 / 431 (1.16%)	4 / 216 (1.85%)
occurrences causally related to treatment / all	0 / 1	3 / 5	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxoplasmosis			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
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	3 / 215 (1.40%)	4 / 431 (0.93%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	1 / 4	1 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella zoster virus infection			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral diarrhoea			

subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral haemorrhagic cystitis			
subjects affected / exposed	3 / 215 (1.40%)	3 / 431 (0.70%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	1 / 3	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenoviral hepatitis			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Arthritis bacterial			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronavirus infection			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus colitis			

subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated aspergillosis			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Enterococcal bacteraemia			
subjects affected / exposed	0 / 215 (0.00%)	3 / 431 (0.70%)	3 / 216 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epstein-Barr virus infection			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Escherichia bacteraemia			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fungal sepsis			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Gastrointestinal candidiasis			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Klebsiella sepsis			
subjects affected / exposed	1 / 215 (0.47%)	2 / 431 (0.46%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningoencephalitis herpetic			

subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Osteomyelitis			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parainfluenzae virus infection			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Peritonitis			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Pseudomonal bacteraemia			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
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 syndrome			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis aspergillus			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Sinusitis fungal			

subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Streptococcal urinary tract infection			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Urosepsis			
subjects affected / exposed	0 / 215 (0.00%)	1 / 431 (0.23%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular device infection			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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			
Cachexia			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Dehydration			
subjects affected / exposed	1 / 215 (0.47%)	3 / 431 (0.70%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	2 / 215 (0.93%)	4 / 431 (0.93%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercholesterolaemia			

subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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	4 / 215 (1.86%)	9 / 431 (2.09%)	5 / 216 (2.31%)
occurrences causally related to treatment / all	0 / 4	0 / 9	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	2 / 215 (0.93%)	5 / 431 (1.16%)	3 / 216 (1.39%)
occurrences causally related to treatment / all	0 / 2	1 / 5	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertriglyceridaemia			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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	2 / 215 (0.93%)	2 / 431 (0.46%)	0 / 216 (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
Malnutrition			
subjects affected / exposed	0 / 215 (0.00%)	2 / 431 (0.46%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Metabolic acidosis			
subjects affected / exposed	1 / 215 (0.47%)	1 / 431 (0.23%)	0 / 216 (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
Steroid diabetes			
subjects affected / exposed	2 / 215 (0.93%)	2 / 431 (0.46%)	0 / 216 (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

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

Non-serious adverse events	Itacitinib plus Corticosteroids	Total	Placebo plus Corticosteroids
Total subjects affected by non-serious adverse events			
subjects affected / exposed	207 / 215 (96.28%)	413 / 431 (95.82%)	206 / 216 (95.37%)
Vascular disorders			
Hypertension			
subjects affected / exposed	46 / 215 (21.40%)	77 / 431 (17.87%)	31 / 216 (14.35%)
occurrences (all)	52	87	35
Hypotension			
subjects affected / exposed	16 / 215 (7.44%)	27 / 431 (6.26%)	11 / 216 (5.09%)
occurrences (all)	16	27	11
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	12 / 215 (5.58%)	31 / 431 (7.19%)	19 / 216 (8.80%)
occurrences (all)	15	34	19
Fatigue			
subjects affected / exposed	28 / 215 (13.02%)	65 / 431 (15.08%)	37 / 216 (17.13%)
occurrences (all)	32	86	54
Oedema			
subjects affected / exposed	7 / 215 (3.26%)	23 / 431 (5.34%)	16 / 216 (7.41%)
occurrences (all)	7	23	16
Oedema peripheral			
subjects affected / exposed	53 / 215 (24.65%)	106 / 431 (24.59%)	53 / 216 (24.54%)
occurrences (all)	55	116	61
Pyrexia			
subjects affected / exposed	34 / 215 (15.81%)	65 / 431 (15.08%)	31 / 216 (14.35%)
occurrences (all)	44	82	38
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	32 / 215 (14.88%)	74 / 431 (17.17%)	42 / 216 (19.44%)
occurrences (all)	35	89	54
Dyspnoea			
subjects affected / exposed	28 / 215 (13.02%)	43 / 431 (9.98%)	15 / 216 (6.94%)
occurrences (all)	31	50	19

Rhinorrhoea			
subjects affected / exposed	6 / 215 (2.79%)	20 / 431 (4.64%)	14 / 216 (6.48%)
occurrences (all)	6	21	15
Epistaxis			
subjects affected / exposed	9 / 215 (4.19%)	20 / 431 (4.64%)	11 / 216 (5.09%)
occurrences (all)	9	20	11
Psychiatric disorders			
Insomnia			
subjects affected / exposed	22 / 215 (10.23%)	47 / 431 (10.90%)	25 / 216 (11.57%)
occurrences (all)	23	49	26
Anxiety			
subjects affected / exposed	17 / 215 (7.91%)	30 / 431 (6.96%)	13 / 216 (6.02%)
occurrences (all)	17	30	13
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	30 / 215 (13.95%)	51 / 431 (11.83%)	21 / 216 (9.72%)
occurrences (all)	39	62	23
Aspartate aminotransferase increased			
subjects affected / exposed	23 / 215 (10.70%)	36 / 431 (8.35%)	13 / 216 (6.02%)
occurrences (all)	37	55	18
Blood alkaline phosphatase increased			
subjects affected / exposed	12 / 215 (5.58%)	28 / 431 (6.50%)	16 / 216 (7.41%)
occurrences (all)	14	33	19
Blood cholesterol increased			
subjects affected / exposed	16 / 215 (7.44%)	27 / 431 (6.26%)	11 / 216 (5.09%)
occurrences (all)	19	32	13
Blood creatinine increased			
subjects affected / exposed	25 / 215 (11.63%)	44 / 431 (10.21%)	19 / 216 (8.80%)
occurrences (all)	27	47	20
Gamma-glutamyltransferase increased			
subjects affected / exposed	11 / 215 (5.12%)	18 / 431 (4.18%)	7 / 216 (3.24%)
occurrences (all)	11	19	8
Platelet count decreased			
subjects affected / exposed	38 / 215 (17.67%)	60 / 431 (13.92%)	22 / 216 (10.19%)
occurrences (all)	45	70	25
Neutrophil count decreased			

subjects affected / exposed	15 / 215 (6.98%)	24 / 431 (5.57%)	9 / 216 (4.17%)
occurrences (all)	18	29	11
Weight decreased			
subjects affected / exposed	11 / 215 (5.12%)	19 / 431 (4.41%)	8 / 216 (3.70%)
occurrences (all)	11	21	10
White blood cell count decreased			
subjects affected / exposed	12 / 215 (5.58%)	22 / 431 (5.10%)	10 / 216 (4.63%)
occurrences (all)	18	29	11
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	20 / 215 (9.30%)	41 / 431 (9.51%)	21 / 216 (9.72%)
occurrences (all)	22	45	23
Nervous system disorders			
Dizziness			
subjects affected / exposed	23 / 215 (10.70%)	40 / 431 (9.28%)	17 / 216 (7.87%)
occurrences (all)	24	43	19
Headache			
subjects affected / exposed	20 / 215 (9.30%)	52 / 431 (12.06%)	32 / 216 (14.81%)
occurrences (all)	21	60	39
Tremor			
subjects affected / exposed	27 / 215 (12.56%)	46 / 431 (10.67%)	19 / 216 (8.80%)
occurrences (all)	28	49	21
Dysgeusia			
subjects affected / exposed	11 / 215 (5.12%)	13 / 431 (3.02%)	2 / 216 (0.93%)
occurrences (all)	12	15	3
Neuropathy peripheral			
subjects affected / exposed	6 / 215 (2.79%)	17 / 431 (3.94%)	11 / 216 (5.09%)
occurrences (all)	6	17	11
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	63 / 215 (29.30%)	117 / 431 (27.15%)	54 / 216 (25.00%)
occurrences (all)	80	146	66
Neutropenia			
subjects affected / exposed	36 / 215 (16.74%)	76 / 431 (17.63%)	40 / 216 (18.52%)
occurrences (all)	57	116	59
Thrombocytopenia			

subjects affected / exposed	73 / 215 (33.95%)	142 / 431 (32.95%)	69 / 216 (31.94%)
occurrences (all)	87	164	77
Leukopenia			
subjects affected / exposed	6 / 215 (2.79%)	17 / 431 (3.94%)	11 / 216 (5.09%)
occurrences (all)	8	22	14
Pancytopenia			
subjects affected / exposed	11 / 215 (5.12%)	17 / 431 (3.94%)	6 / 216 (2.78%)
occurrences (all)	11	17	6
Eye disorders			
Dry eye			
subjects affected / exposed	18 / 215 (8.37%)	35 / 431 (8.12%)	17 / 216 (7.87%)
occurrences (all)	18	37	19
Vision blurred			
subjects affected / exposed	7 / 215 (3.26%)	19 / 431 (4.41%)	12 / 216 (5.56%)
occurrences (all)	7	20	13
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	26 / 215 (12.09%)	52 / 431 (12.06%)	26 / 216 (12.04%)
occurrences (all)	32	60	28
Constipation			
subjects affected / exposed	25 / 215 (11.63%)	46 / 431 (10.67%)	21 / 216 (9.72%)
occurrences (all)	27	49	22
Diarrhoea			
subjects affected / exposed	42 / 215 (19.53%)	85 / 431 (19.72%)	43 / 216 (19.91%)
occurrences (all)	48	108	60
Dry mouth			
subjects affected / exposed	14 / 215 (6.51%)	32 / 431 (7.42%)	18 / 216 (8.33%)
occurrences (all)	15	39	24
Nausea			
subjects affected / exposed	38 / 215 (17.67%)	71 / 431 (16.47%)	33 / 216 (15.28%)
occurrences (all)	47	92	45
Vomiting			
subjects affected / exposed	23 / 215 (10.70%)	48 / 431 (11.14%)	25 / 216 (11.57%)
occurrences (all)	26	53	27
Dyspepsia			

subjects affected / exposed	10 / 215 (4.65%)	23 / 431 (5.34%)	13 / 216 (6.02%)
occurrences (all)	10	23	13
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	13 / 215 (6.05%)	30 / 431 (6.96%)	17 / 216 (7.87%)
occurrences (all)	14	38	24
Dry skin			
subjects affected / exposed	6 / 215 (2.79%)	18 / 431 (4.18%)	12 / 216 (5.56%)
occurrences (all)	6	22	16
Rash			
subjects affected / exposed	11 / 215 (5.12%)	14 / 431 (3.25%)	3 / 216 (1.39%)
occurrences (all)	11	14	3
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	11 / 215 (5.12%)	32 / 431 (7.42%)	21 / 216 (9.72%)
occurrences (all)	13	36	23
Dysuria			
subjects affected / exposed	17 / 215 (7.91%)	25 / 431 (5.80%)	8 / 216 (3.70%)
occurrences (all)	18	26	8
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	23 / 215 (10.70%)	41 / 431 (9.51%)	18 / 216 (8.33%)
occurrences (all)	24	43	19
Back pain			
subjects affected / exposed	17 / 215 (7.91%)	38 / 431 (8.82%)	21 / 216 (9.72%)
occurrences (all)	20	45	25
Muscular weakness			
subjects affected / exposed	23 / 215 (10.70%)	42 / 431 (9.74%)	19 / 216 (8.80%)
occurrences (all)	24	44	20
Pain in extremity			
subjects affected / exposed	14 / 215 (6.51%)	27 / 431 (6.26%)	13 / 216 (6.02%)
occurrences (all)	15	28	13
Infections and infestations			
Cytomegalovirus infection			
subjects affected / exposed	16 / 215 (7.44%)	26 / 431 (6.03%)	10 / 216 (4.63%)
occurrences (all)	20	32	12

Cytomegalovirus infection reactivation			
subjects affected / exposed	26 / 215 (12.09%)	50 / 431 (11.60%)	24 / 216 (11.11%)
occurrences (all)	35	61	26
Cytomegalovirus viraemia			
subjects affected / exposed	34 / 215 (15.81%)	60 / 431 (13.92%)	26 / 216 (12.04%)
occurrences (all)	38	68	30
Upper respiratory tract infection			
subjects affected / exposed	17 / 215 (7.91%)	34 / 431 (7.89%)	17 / 216 (7.87%)
occurrences (all)	25	44	19
Urinary tract infection			
subjects affected / exposed	15 / 215 (6.98%)	32 / 431 (7.42%)	17 / 216 (7.87%)
occurrences (all)	15	34	19
Epstein-Barr virus infection reactivation			
subjects affected / exposed	11 / 215 (5.12%)	17 / 431 (3.94%)	6 / 216 (2.78%)
occurrences (all)	11	17	6
Nasopharyngitis			
subjects affected / exposed	7 / 215 (3.26%)	18 / 431 (4.18%)	11 / 216 (5.09%)
occurrences (all)	8	20	12
Oral candidiasis			
subjects affected / exposed	11 / 215 (5.12%)	22 / 431 (5.10%)	11 / 216 (5.09%)
occurrences (all)	13	24	11
Pneumonia			
subjects affected / exposed	5 / 215 (2.33%)	16 / 431 (3.71%)	11 / 216 (5.09%)
occurrences (all)	6	17	11
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	24 / 215 (11.16%)	47 / 431 (10.90%)	23 / 216 (10.65%)
occurrences (all)	26	52	26
Hyperglycaemia			
subjects affected / exposed	47 / 215 (21.86%)	97 / 431 (22.51%)	50 / 216 (23.15%)
occurrences (all)	56	113	57
Hyperkalaemia			
subjects affected / exposed	9 / 215 (4.19%)	25 / 431 (5.80%)	16 / 216 (7.41%)
occurrences (all)	11	34	23
Hypertriglyceridaemia			

subjects affected / exposed	31 / 215 (14.42%)	58 / 431 (13.46%)	27 / 216 (12.50%)
occurrences (all)	33	67	34
Hypoalbuminaemia			
subjects affected / exposed	12 / 215 (5.58%)	35 / 431 (8.12%)	23 / 216 (10.65%)
occurrences (all)	13	39	26
Hypocalcaemia			
subjects affected / exposed	16 / 215 (7.44%)	36 / 431 (8.35%)	20 / 216 (9.26%)
occurrences (all)	17	38	21
Hypokalaemia			
subjects affected / exposed	40 / 215 (18.60%)	75 / 431 (17.40%)	35 / 216 (16.20%)
occurrences (all)	51	94	43
Hypomagnesaemia			
subjects affected / exposed	27 / 215 (12.56%)	48 / 431 (11.14%)	21 / 216 (9.72%)
occurrences (all)	46	74	28
Hyponatraemia			
subjects affected / exposed	16 / 215 (7.44%)	38 / 431 (8.82%)	22 / 216 (10.19%)
occurrences (all)	27	54	27
Hypophosphataemia			
subjects affected / exposed	14 / 215 (6.51%)	25 / 431 (5.80%)	11 / 216 (5.09%)
occurrences (all)	18	31	13

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 May 2017	The primary purpose of this amendment is to address regulatory feedback provided after finalization of the original Protocol that relates to appropriate birth control measures that are aligned with Health Canada guidelines.
16 June 2017	The primary purpose of this amendment is to address regulatory feedback provided after finalization of the original Protocol that aligns eligibility and study conduct to Voluntary Harmonisation Procedure (VHP) recommendations and additional feedback from other agencies.
07 May 2018	The primary purpose of this amendment is to include an additional interim analysis for efficacy, reduce PK sampling schedule after the first interim analysis, provide clarification on eligibility requirements and study procedures.
13 August 2018	The primary purpose of this amendment is to clarify the population and procedural requirements for study subjects to enter the re-treatment phase.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported