Clinical trial results:
A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Bendamustine and Rituximab for Previously Treated Chronic Lymphocytic Leukemia

Summary

EudraCT number	2011-006292-20
Trial protocol	GB BE ES IT PL CZ HU DE IE PT GR HR
Global end of trial date	10 June 2019

Results information

Result version number	v1 (current)
This version publication date	18 March 2020
First version publication date	18 March 2020

Trial information

Trial identification

Sponsor protocol code	GS-US-312-0115

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01569295
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, CA, United States, 94404
Public contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com
Scientific contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.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	10 June 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 June 2019
Global end of trial reached?	Yes
Global end of trial date	10 June 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the efficacy and safety of idelalisib in combination with bendamustine and rituximab in previously treated chronic lymphocytic leukemia (CLL) (Tugela).

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements. This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy:

Bendamustine and Rituximab

Evidence for comparator: -

Actual start date of recruitment	15 June 2012
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	Romania: 11
Country: Number of subjects enrolled	United States: 70
Country: Number of subjects enrolled	Russian Federation: 36
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Turkey: 12
Country: Number of subjects enrolled	Australia: 16
Country: Number of subjects enrolled	New Zealand: 6
Country: Number of subjects enrolled	Poland: 39
Country: Number of subjects enrolled	Portugal: 5
Country: Number of subjects enrolled	Spain: 32
Country: Number of subjects enrolled	United Kingdom: 56
Country: Number of subjects enrolled	Croatia: 14
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Czech Republic: 14
Country: Number of subjects enrolled	France: 27
Country: Number of subjects enrolled	Greece: 2

Country: Number of subjects enrolled	Hungary: 44
Country: Number of subjects enrolled	Ireland: 2
Country: Number of subjects enrolled	Italy: 17
Worldwide total number of subjects	416
EEA total number of subjects	273

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)	241
From 65 to 84 years	175
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at a total of 110 sites in Australia, New Zealand, Europe, Asia and North America. The first participant was screened on 15 June 2012. The last study visit occurred on 10 June 2019.

Pre-assignment

Screening details:

540 participants were screened.

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, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Idelalisib + Bendamustine + Rituximab

Arm description:

Idelalisib 150 mg tablet administered orally twice daily (until the earliest of participant withdrawal from study, definitive progression of CLL, intolerable toxicity, pregnancy, substantial noncompliance with study procedures, or study discontinuation) + rituximab 375 mg/m^2 on Day 1, then 500 mg/m^2 every 28 days administered intravenously for a total of 6 infusions + bendamustine 70 mg/mg^2/infusion on days 1 and 2 of each 28 day cycle, administered intravenously for a total of 6 cycles (12 infusions).

Arm type	Experimental
Investigational medicinal product name	Idelalisib
Investigational medicinal product code	GS-1101, CAL-101
Other name	Zydelig®
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

150 mg administered orally twice daily.

Investigational medicinal product name	Bendamustine
Investigational medicinal product code	
Other name	Treanda®
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

70 mg/mg^2/day on 2 consecutive days every 28 days administered intravenously for a maximum of 12 infusions.

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	MabThera, Rituxan®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

375 mg/m^2 on Day 1, then 500 mg/m^2 every 28 days administered intravenously for a maximum of 6 infusions.

Arm title	Placebo + Bendamustine + Rituximab

Arm description:

Placebo to match idelalisib administered orally twice daily + rituximab 375 mg/m^2 on Day 1, then 500 mg/ m^2 every 28 days administered intravenously for a total of 6 infusions + bendamustine 70 mg/m^2/infusion on days 1 and 2 of each 28 day cycle administered intravenously for a total of 6 cycles (12 infusions).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Tablet administered orally twice daily.

Investigational medicinal product name	Bendamustine
Investigational medicinal product code	
Other name	Treanda®
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

70 mg/mg^2/day on 2 consecutive days every 28 days administered intravenously for a maximum of 12 infusions.

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	MabThera, Rituxan®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

375 mg/m^2 on Day 1, then 500 mg/m^2 every 28 days administered intravenously for a maximum of 6 infusions.

Number of subjects in period 1	Idelalisib + Bendamustine + Rituximab	Placebo + Bendamustine + Rituximab
Started	207	209
Completed	0	0
Not completed	207	209
Physician decision	13	18
Non-Compliance with Study Drug	6	1
Other Anticancer/Experimental Therapy	2	2
Adverse event, non-fatal	39	14
Death	19	15
Other Reason not Specified	3	5
Progressive Disease	75	139
Withdrawal by Subject	25	12
Study Terminated by Sponsor	24	2
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Idelalisib + Bendamustine + Rituximab
Reporting group description:	
Idelalisib 150 mg tablet administered orally twice daily (until the earliest of participant withdrawal from study, definitive progression of CLL, intolerable toxicity, pregnancy, substantial noncompliance with study procedures, or study discontinuation) + rituximab 375 mg/m^2 on Day 1, then 500 mg/m^2 every 28 days administered intravenously for a total of 6 infusions + bendamustine 70 mg/mg^2/infusion on days 1 and 2 of each 28 day cycle, administered intravenously for a total of 6 cycles (12 infusions).	
Reporting group title	Placebo + Bendamustine + Rituximab
Reporting group description:	
Placebo to match idelalisib administered orally twice daily + rituximab 375 mg/m^2 on Day 1, then 500 mg/ m^2 every 28 days administered intravenously for a total of 6 infusions + bendamustine 70 mg/m^2/infusion on days 1 and 2 of each 28 day cycle administered intravenously for a total of 6 cycles (12 infusions).	

Reporting group values	Idelalisib + Bendamustine + Rituximab	Placebo + Bendamustine + Rituximab	Total
Number of subjects	207	209	416
Age categorical Units: Subjects			
Adults (18-64 years)	131	110	241
From 65-84 years	76	99	175
Age continuous Units: years			
arithmetic mean	62	63	
standard deviation	± 9.2	± 9.8	-
Gender categorical Units: Subjects			
Female	47	53	100
Male	160	156	316
Race/Ethnicity, Customized Units: Subjects			
White	187	190	377
Black or African American	6	4	10
Asian	2	1	3
Other	2	2	4
Not Permitted	10	12	22
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	4	5	9
Not Hispanic or Latino	191	188	379
Not Permitted	12	15	27
Missing	0	1	1
Region of Enrollment Units: Subjects			
Romania	5	6	11
Hungary	24	20	44
United States	37	33	70

Czech Republic	9	5	14
United Kingdom	27	29	56
Portugal	1	4	5
Russia	22	14	36
Spain	14	18	32
Greece	1	1	2
Canada	0	3	3
Turkey	6	6	12
Belgium	3	7	10
Ireland	1	1	2
Poland	17	22	39
Italy	10	7	17
Australia	8	8	16
France	13	14	27
Croatia	5	9	14
New Zealand	4	2	6

End points

End points reporting groups

Reporting group title	Idelalisib + Bendamustine + Rituximab

Reporting group description:

Idelalisib 150 mg tablet administered orally twice daily (until the earliest of participant withdrawal from study, definitive progression of CLL, intolerable toxicity, pregnancy, substantial noncompliance with study procedures, or study discontinuation) + rituximab 375 mg/m^2 on Day 1, then 500 mg/m^2 every 28 days administered intravenously for a total of 6 infusions + bendamustine 70 mg/mg^2/infusion on days 1 and 2 of each 28 day cycle, administered intravenously for a total of 6 cycles (12 infusions).

Reporting group title	Placebo + Bendamustine + Rituximab

Reporting group description:

Placebo to match idelalisib administered orally twice daily + rituximab 375 mg/m^2 on Day 1, then 500 mg/ m^2 every 28 days administered intravenously for a total of 6 infusions + bendamustine 70 mg/m^2/infusion on days 1 and 2 of each 28 day cycle administered intravenously for a total of 6 cycles (12 infusions).

Primary: Progression-Free Survival

End point title	Progression-Free Survival

End point description:

Progression-free survival (PFS) was defined as the interval from randomization to the earlier of the first documentation of definitive disease progression or death from any cause. PFS (months) = (minimum (date of disease progression, date of death) - date of randomization + 1)/30.4375. The intent-to-treat (ITT) Analysis Set included all participants randomised in the study regardless of whether study drug was administered and with treatment group designated according to initial randomisation.

End point type	Primary

End point timeframe:

Up to 84 months

End point values	Idelalisib + Bendamustine + Rituximab	Placebo + Bendamustine + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	209		
Units: months				
median (confidence interval 95%)	21.8 (16.5 to 27.8)	11.1 (8.9 to 11.1)		

Statistical analyses

Statistical analysis title	Idela+Bend+Ritux vs Placebo+Bend+Ritux

Statistical analysis description:

Idela= Idelalisib; Bend= Bendamustine; Ritux= Rituximab

Comparison groups	Idelalisib + Bendamustine + Rituximab v Placebo + Bendamustine + Rituximab

Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	0.45

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)

End point description:

ORR was the percentage of participants who achieved a complete response (CR), CR with incomplete marrow recovery (CRi,) or partial response (PR) and maintained the response for at least 12 weeks. CR was defined as no lymphadenopathy, hepatomegaly, splenomegaly; normal complete blood count; confirmed by bone marrow aspirate & biopsy.
PR was defined as >1 of the following criteria: a 50% decrease in peripheral blood lymphocytes, lymphadenopathy, liver size, spleen size; plus ≥ 1 of the following: ≥ 1500/µL absolute neutrophil count, > 100000/µL platelets, > 11.0 g/dL hemoglobin or 50% improvement for either of these parameters without transfusions or growth factors. CRi was defined as all criteria for CR met but with persistent anemia, thrombocytopenia, neutropenia or a hypocellular bone marrow. Participants in the ITT Analysis Set were analysed.

End point type	Secondary

End point timeframe:

Up to 84 months

End point values	Idelalisib + Bendamustine + Rituximab	Placebo + Bendamustine + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	209		
Units: percentage of participants				
number (confidence interval 95%)	70.0 (63.3 to 76.2)	45.5 (38.6 to 52.5)		

Statistical analyses

Statistical analysis title	Idela+Bend+Ritux vs Placebo+Bend+Ritux

Statistical analysis description:

Idela= Idelalisib; Bend= Bendamustine; Ritux= Rituximab

Comparison groups	Placebo + Bendamustine + Rituximab v Idelalisib + Bendamustine + Rituximab

Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	3.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.98
upper limit	4.62

Notes:

[1] - Odds ratio, p-value and 95% Confidence Interval (CI) were calculated from the CMH Chi-square test stratified by stratification factors in EDC (del17p/TP53, immunoglobulin heavy chain variable region (IgHV) mutation and disease status).

Secondary: Lymph Node Response Rate

End point title	Lymph Node Response Rate

End point description:

Lymph node response rate was defined as the percentage of participants who achieved a ≥ 50% decrease from baseline in the sum of the products of the greatest perpendicular diameters (SPD) of index lesions. Participants in the ITT Analysis Set with available data were analysed.

End point type	Secondary

End point timeframe:

Up to 84 months

End point values	Idelalisib + Bendamustine + Rituximab	Placebo + Bendamustine + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	192	197		
Units: percentage of participants				
number (confidence interval 95%)	96.9 (93.3 to 98.8)	60.9 (53.7 to 67.8)		

Statistical analyses

Statistical analysis title	Idela+Bend+Ritux vs Placebo+Bend+Ritux

Statistical analysis description:

Idela= Idelalisib; Bend= Bendamustine; Ritux= Rituximab

Comparison groups	Idelalisib + Bendamustine + Rituximab v Placebo + Bendamustine + Rituximab

Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	28.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.5
upper limit	79.02

Notes:

[2] - Odds ratio, p-value and 95% CI were calculated from the CMH Chi-square test stratified by stratification factors in EDC (del17p/TP53, IgHV mutation and disease status).

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival (OS) was defined as the interval from randomization to death from any cause. Overall survival (months) = (date of death - date of randomization + 1)/30.4375. Participants in the ITT Analysis Set were analysed. 99999= Upper CI was not reached due to low number of deaths by the time of study closure.

End point type	Secondary

End point timeframe:

Up to 84 months

End point values	Idelalisib + Bendamustine + Rituximab	Placebo + Bendamustine + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	209		
Units: months				
median (confidence interval 95%)	56.2 (40.1 to 99999)	42.6 (35.3 to 54.8)		

Statistical analyses

Statistical analysis title	Idela+Bend+Ritux vs Placebo+Bend+Ritux

Statistical analysis description:

Idela= Idelalisib; Bend= Bendamustine; Ritux= Rituximab

Comparison groups	Idelalisib + Bendamustine + Rituximab v Placebo + Bendamustine + Rituximab

Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.098
Method	Stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.03

Secondary: Complete Response Rate

End point title	Complete Response Rate
End point description:	
Complete response (CR) rate was defined as the percentage of participants who achieved a CR. Participants in the ITT Analysis Set were analysed.	
End point type	Secondary
End point timeframe:	
Up to 84 months	

End point values	Idelalisib + Bendamustine + Rituximab	Placebo + Bendamustine + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	209		
Units: percentage of participants				
number (confidence interval 95%)	4.3 (2.0 to 8.1)	0.5 (0 to 2.6)		

Statistical analyses

Statistical analysis title	Idela+Bend+Ritux vs Placebo+Bend+Ritux
Statistical analysis description:	
Idela= Idelalisib; Bend= Bendamustine; Ritux= Rituximab	
Comparison groups	Idelalisib + Bendamustine + Rituximab v Placebo + Bendamustine + Rituximab
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	9.55

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.19
upper limit	76.81

Notes:

[3] - Odds ratio, 95% CI and p-value are calculated from the CMH Chi-square test stratified by stratification factors in EDC (del17p/TP53, IgHV mutation and disease status).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose up to the last dose date plus 30 days (Up to approximately 67.7 months)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Idelalisib + Bendamustine + Rituximab

Reporting group description:

Idelalisib 150 mg tablet administered orally twice daily (until the earliest of subject withdrawal from study, definitive progression of CLL, intolerable toxicity, pregnancy, substantial noncompliance with study procedures, or study discontinuation) + rituximab 375 mg/m^2 on Day 1, then 500 mg/m^2 every 28 days administered intravenously for a total of 6 infusions + bendamustine 70 mg/mg^2/infusion on days 1 and 2 of each 28 day cycle, administered intravenously for a total of 6 cycles (12 infusions).

Reporting group title	Placebo + Bendamustine + Rituximab

Reporting group description:

Placebo to match idelalisib administered orally twice daily + rituximab 375 mg/m^2 on Day 1, then 500 mg/ m^2 every 28 days administered intravenously for a total of 6 infusions + bendamustine 70 mg/m^2/infusion on days 1 and 2 of each 28 day cycle administered intravenously for a total of 6 cycles (12 infusions).

Serious adverse events	Idelalisib + Bendamustine + Rituximab	Placebo + Bendamustine + Rituximab	
Total subjects affected by serious adverse events			
subjects affected / exposed	152 / 207 (73.43%)	94 / 209 (44.98%)	
number of deaths (all causes)	89	106	
number of deaths resulting from adverse events	28	19	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute leukaemia			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			
subjects affected / exposed	0 / 207 (0.00%)	2 / 209 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			

subjects affected / exposed	3 / 207 (1.45%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen’s disease			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic lymphocytic leukaemia			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leiomyosarcoma			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lip squamous cell carcinoma			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	1 / 207 (0.48%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung neoplasm malignant			

subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	2 / 207 (0.97%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	4 / 207 (1.93%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nasopharyngeal cancer			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oesophageal carcinoma			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	2 / 207 (0.97%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal adenocarcinoma			

subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary gland neoplasm			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 207 (0.48%)	5 / 209 (2.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	3 / 207 (1.45%)	2 / 209 (0.96%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
T-cell lymphoma			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			

subjects affected / exposed	2 / 207 (0.97%)	2 / 209 (0.96%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 207 (0.48%)	2 / 209 (0.96%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	2 / 207 (0.97%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	2 / 207 (0.97%)	2 / 209 (0.96%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 207 (0.48%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malaise			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 207 (0.48%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Pyrexia			

subjects affected / exposed	25 / 207 (12.08%)	11 / 209 (5.26%)	
occurrences causally related to treatment / all	9 / 32	8 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophagocytic lymphohistiocytosis			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	2 / 207 (0.97%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Cervical polyp			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perineal necrosis			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchial hyperreactivity			

subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	4 / 207 (1.93%)	2 / 209 (0.96%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	4 / 207 (1.93%)	3 / 209 (1.44%)	
occurrences causally related to treatment / all	3 / 5	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	2 / 207 (0.97%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	3 / 207 (1.45%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			

subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonitis			
subjects affected / exposed	4 / 207 (1.93%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 207 (0.97%)	5 / 209 (2.39%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pulmonary pain			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 207 (0.97%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			

subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delusion			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mood swings			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attack			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Personality change			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anticoagulation drug level above therapeutic			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			

subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bk polyomavirus test positive			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcus test positive			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			

subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye injury			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 207 (0.48%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	1 / 207 (0.48%)	3 / 209 (1.44%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periprosthetic fracture			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 207 (0.00%)	2 / 209 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Angina pectoris			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	1 / 207 (0.48%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 207 (0.48%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac failure			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular extrasystoles			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dizziness			

subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post herpetic neuralgia			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	0 / 207 (0.00%)	2 / 209 (0.96%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Anaemia			
subjects affected / exposed	8 / 207 (3.86%)	5 / 209 (2.39%)	
occurrences causally related to treatment / all	8 / 11	3 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Autoimmune haemolytic anaemia			

subjects affected / exposed	0 / 207 (0.00%)	2 / 209 (0.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Febrile neutropenia			
subjects affected / exposed	45 / 207 (21.74%)	10 / 209 (4.78%)	
occurrences causally related to treatment / all	47 / 60	9 / 13	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemolytic anaemia			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune thrombocytopenic purpura			
subjects affected / exposed	1 / 207 (0.48%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	9 / 207 (4.35%)	3 / 209 (1.44%)	
occurrences causally related to treatment / all	11 / 13	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	4 / 207 (1.93%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	2 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic thrombocytopenic purpura			

subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Rhegmatogenous retinal detachment			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vision blurred			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	4 / 207 (1.93%)	2 / 209 (0.96%)	
occurrences causally related to treatment / all	2 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 207 (0.00%)	2 / 209 (0.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	5 / 207 (2.42%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	5 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis microscopic			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			

subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	14 / 207 (6.76%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	12 / 15	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovesical fistula			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 207 (0.48%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 207 (0.48%)	2 / 209 (0.96%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			

subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	2 / 207 (0.97%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumatosis intestinalis			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoperitoneum			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 207 (0.00%)	2 / 209 (0.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary fistula			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			

subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatitis toxic			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			
subjects affected / exposed	2 / 207 (0.97%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis exfoliative			

subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis exfoliative generalised			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash macular			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stevens-Johnson syndrome			
subjects affected / exposed	2 / 207 (0.97%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 207 (0.48%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			

subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	2 / 207 (0.97%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondritis			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondrocalcinosis			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyarthritis			

subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reiter’s syndrome			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Aspergillus infection			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain abscess			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchitis			
subjects affected / exposed	1 / 207 (0.48%)	5 / 209 (2.39%)	
occurrences causally related to treatment / all	0 / 1	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter gastroenteritis			

subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	4 / 207 (1.93%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conjunctivitis bacterial			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus chorioretinitis			
subjects affected / exposed	1 / 207 (0.48%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus colitis			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus enteritis			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			

subjects affected / exposed	3 / 207 (1.45%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	3 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus viraemia			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	2 / 207 (0.97%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ecthyma			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	2 / 207 (0.97%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye infection toxoplasmal			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal infection			

subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 207 (0.97%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis cryptosporidial			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
H1n1 influenza			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemophilus infection			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	4 / 207 (1.93%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	3 / 4	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Human herpesvirus 6 infection			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impetigo			

subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	3 / 207 (1.45%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	7 / 207 (3.38%)	5 / 209 (2.39%)	
occurrences causally related to treatment / all	3 / 8	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection fungal			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 207 (0.00%)	3 / 209 (1.44%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis aseptic			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis bacterial			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis enteroviral			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			

subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	3 / 207 (1.45%)	6 / 209 (2.87%)	
occurrences causally related to treatment / all	2 / 3	6 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ophthalmic herpes zoster			
subjects affected / exposed	2 / 207 (0.97%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral herpes			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngitis fungal			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis externa			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	0 / 207 (0.00%)	2 / 209 (0.96%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perineal infection			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal abscess			

subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii infection			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	3 / 207 (1.45%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	38 / 207 (18.36%)	16 / 209 (7.66%)	
occurrences causally related to treatment / all	16 / 44	6 / 18	
deaths causally related to treatment / all	0 / 5	1 / 5	
Pneumonia bacterial			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumonia cytomegaloviral			
subjects affected / exposed	1 / 207 (0.48%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumonia pseudomonal			
subjects affected / exposed	2 / 207 (0.97%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mycosis			

subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pulmonary sepsis			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	5 / 207 (2.42%)	5 / 209 (2.39%)	
occurrences causally related to treatment / all	3 / 5	2 / 6	
deaths causally related to treatment / all	0 / 0	1 / 1	
Rhinovirus infection			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	11 / 207 (5.31%)	4 / 209 (1.91%)	
occurrences causally related to treatment / all	5 / 12	2 / 4	
deaths causally related to treatment / all	0 / 3	0 / 2	
Septic shock			
subjects affected / exposed	5 / 207 (2.42%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	4 / 5	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Sinusitis			
subjects affected / exposed	2 / 207 (0.97%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			

subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 207 (0.48%)	4 / 209 (1.91%)	
occurrences causally related to treatment / all	0 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection bacterial			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	7 / 207 (3.38%)	3 / 209 (1.44%)	
occurrences causally related to treatment / all	1 / 12	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			

subjects affected / exposed	2 / 207 (0.97%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Viral infection			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Decreased appetite			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 207 (0.48%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 207 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			

subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 207 (0.48%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 207 (0.97%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 207 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	3 / 207 (1.45%)	2 / 209 (0.96%)	
occurrences causally related to treatment / all	3 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Idelalisib + Bendamustine + Rituximab	Placebo + Bendamustine + Rituximab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	199 / 207 (96.14%)	196 / 209 (93.78%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	13 / 207 (6.28%)	5 / 209 (2.39%)	
occurrences (all)	13	6	

Hypotension			
subjects affected / exposed	14 / 207 (6.76%)	13 / 209 (6.22%)	
occurrences (all)	15	14	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	24 / 207 (11.59%)	20 / 209 (9.57%)	
occurrences (all)	32	27	
Chills			
subjects affected / exposed	22 / 207 (10.63%)	13 / 209 (6.22%)	
occurrences (all)	27	17	
Fatigue			
subjects affected / exposed	45 / 207 (21.74%)	52 / 209 (24.88%)	
occurrences (all)	56	59	
Oedema peripheral			
subjects affected / exposed	17 / 207 (8.21%)	18 / 209 (8.61%)	
occurrences (all)	20	18	
Pyrexia			
subjects affected / exposed	78 / 207 (37.68%)	55 / 209 (26.32%)	
occurrences (all)	156	89	
Immune system disorders			
Hypogammaglobulinaemia			
subjects affected / exposed	12 / 207 (5.80%)	10 / 209 (4.78%)	
occurrences (all)	12	13	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	52 / 207 (25.12%)	47 / 209 (22.49%)	
occurrences (all)	66	57	
Dyspnoea			
subjects affected / exposed	20 / 207 (9.66%)	26 / 209 (12.44%)	
occurrences (all)	23	28	
Oropharyngeal pain			
subjects affected / exposed	10 / 207 (4.83%)	14 / 209 (6.70%)	
occurrences (all)	17	15	
Productive cough			
subjects affected / exposed	17 / 207 (8.21%)	12 / 209 (5.74%)	
occurrences (all)	25	13	

Psychiatric disorders			
Anxiety			
subjects affected / exposed	6 / 207 (2.90%)	12 / 209 (5.74%)	
occurrences (all)	6	14	
Insomnia			
subjects affected / exposed	19 / 207 (9.18%)	13 / 209 (6.22%)	
occurrences (all)	19	13	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	32 / 207 (15.46%)	2 / 209 (0.96%)	
occurrences (all)	40	2	
Aspartate aminotransferase increased			
subjects affected / exposed	19 / 207 (9.18%)	2 / 209 (0.96%)	
occurrences (all)	22	2	
Weight decreased			
subjects affected / exposed	25 / 207 (12.08%)	12 / 209 (5.74%)	
occurrences (all)	26	12	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	29 / 207 (14.01%)	45 / 209 (21.53%)	
occurrences (all)	34	67	
Nervous system disorders			
Headache			
subjects affected / exposed	20 / 207 (9.66%)	21 / 209 (10.05%)	
occurrences (all)	24	27	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	54 / 207 (26.09%)	48 / 209 (22.97%)	
occurrences (all)	75	55	
Leukopenia			
subjects affected / exposed	17 / 207 (8.21%)	10 / 209 (4.78%)	
occurrences (all)	23	16	
Neutropenia			
subjects affected / exposed	129 / 207 (62.32%)	113 / 209 (54.07%)	
occurrences (all)	356	232	
Thrombocytopenia			

subjects affected / exposed	41 / 207 (19.81%)	46 / 209 (22.01%)	
occurrences (all)	57	60	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	21 / 207 (10.14%)	13 / 209 (6.22%)	
occurrences (all)	22	13	
Constipation			
subjects affected / exposed	32 / 207 (15.46%)	35 / 209 (16.75%)	
occurrences (all)	40	36	
Diarrhoea			
subjects affected / exposed	89 / 207 (43.00%)	47 / 209 (22.49%)	
occurrences (all)	182	79	
Dyspepsia			
subjects affected / exposed	15 / 207 (7.25%)	8 / 209 (3.83%)	
occurrences (all)	19	8	
Nausea			
subjects affected / exposed	60 / 207 (28.99%)	72 / 209 (34.45%)	
occurrences (all)	84	105	
Vomiting			
subjects affected / exposed	35 / 207 (16.91%)	31 / 209 (14.83%)	
occurrences (all)	42	50	
Skin and subcutaneous tissue disorders			
Night sweats			
subjects affected / exposed	18 / 207 (8.70%)	8 / 209 (3.83%)	
occurrences (all)	20	10	
Pruritus			
subjects affected / exposed	17 / 207 (8.21%)	12 / 209 (5.74%)	
occurrences (all)	18	13	
Rash			
subjects affected / exposed	36 / 207 (17.39%)	28 / 209 (13.40%)	
occurrences (all)	50	33	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	27 / 207 (13.04%)	16 / 209 (7.66%)	
occurrences (all)	30	16	
Back pain			

subjects affected / exposed	17 / 207 (8.21%)	15 / 209 (7.18%)	
occurrences (all)	21	18	
Infections and infestations			
Bronchitis			
subjects affected / exposed	20 / 207 (9.66%)	8 / 209 (3.83%)	
occurrences (all)	23	12	
Herpes zoster			
subjects affected / exposed	11 / 207 (5.31%)	6 / 209 (2.87%)	
occurrences (all)	11	6	
Lower respiratory tract infection			
subjects affected / exposed	13 / 207 (6.28%)	10 / 209 (4.78%)	
occurrences (all)	30	13	
Nasopharyngitis			
subjects affected / exposed	16 / 207 (7.73%)	11 / 209 (5.26%)	
occurrences (all)	20	13	
Pneumonia			
subjects affected / exposed	25 / 207 (12.08%)	13 / 209 (6.22%)	
occurrences (all)	30	13	
Respiratory tract infection			
subjects affected / exposed	7 / 207 (3.38%)	11 / 209 (5.26%)	
occurrences (all)	9	13	
Sinusitis			
subjects affected / exposed	19 / 207 (9.18%)	13 / 209 (6.22%)	
occurrences (all)	21	17	
Upper respiratory tract infection			
subjects affected / exposed	37 / 207 (17.87%)	21 / 209 (10.05%)	
occurrences (all)	48	23	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	24 / 207 (11.59%)	15 / 209 (7.18%)	
occurrences (all)	28	15	
Hypokalaemia			
subjects affected / exposed	21 / 207 (10.14%)	16 / 209 (7.66%)	
occurrences (all)	26	23	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 December 2012	1.Updated information regarding secondary and tertiary endpoints. 2.Clarified that the IRC findings would be considered primary for analyses of PFS and other tumor control endpoints. 3.Updated statistical plan to control Type I error rate for secondary endpoints. 4.Updated risk section to include phototoxicity risk. 5.Added guidelines for monitoring subjects for rituximab infusion toxicity. 6.Added urine pregnancy testing every 4 weeks and every visit after Visit 20. 7.Updated inclusion criteria relating to contraception. 8.Clarified that prior bendamustine use was allowed. 9.Updated platelet screening value to align with the bendamustine prescribing information. 10.Clarified that subjects who prematurely discontinued 1 drug could continue to receive the other drug therapies. 11.Increased the number of participating centers and study locations to be consistent with planned country list. 12.Updated safety and clinical information to align with the updated IB (Version 7). 13.Modified Timing of Assessments section to state that clinical and imaging-based tumor assessments could be performed within 6 (versus 4) weeks prior to the start of treatment and that on-study image-based assessments would be performed until 260 events were observed Added a new section to differentiate discontinuation from study versus discontinuation of study drug (IDL/placebo). 14.Added new references regarding modifications in the assessment of ALC in determining disease response and progression in subjects with CLL.15. Modified to allow enrollment of subjects with positive HBc antibody (due to intravenous immunoglobulin [Ig]) if hepatitis B virus (HBV) DNA was undetectable with quantitative polymerase chain reaction (PCR).16.Modified to allow for use of systemic corticosteroids as therapy for manifestations of CLL. 17.Changed Full Analysis Set to Intent-To-Treat (ITT) Analysis Set. 18. Added the Per-Protocol (PP) Analysis Set, consistent with other sections of the protocol.
19 December 2012	19. Modified efficacy assessments to provide clarity and consistency with current recommendations. 20. Modified the spleen upper limit of normal (ULN) measurement of the spleen from 10 cm to 12 cm based on expert radiology recommendations. 21. Clarified storage and handling of study drug (IDL/placebo). 22. Clarified required documentation for commercial versus noncommercial rituximab and bendamustine sources. 23. Clarified the prophylactic use of IV immunoglobulin for Pneumocystis (carinii) jirovecii and infectious events. 24. Clarified study drug (IDL/placebo), rituximab and bendamustine modifications. 25. Clarified information regarding known inhibitors or inducers of CYP3A4. 26. Provided screening guidelines for subjects who screen-failed this protocol but met eligibility for another IDL protocol. 27. Clarified definitions of 30-day follow-up, long-term follow-up, SAEs, and Special Situations.

01 May 2013	1. Increased the number of participating centers and study locations to be consistent with revised planned country list and number of sites. 2. Decreased the required creatinine clearance level in the inclusion criteria in order to align with the bendamustine prescribing information. 3. Corrected inconsistency between hematopoietic inclusion criteria lab values in the Required Screening Laboratory Values table to align with footnote (a) underneath the table. 4. Updated text for consistency regarding randomization or initiation of study drug (IDL/placebo) throughout the protocol. 5. Updated the nonclinical pharmacology and metabolism, nonclinical toxicology, clinical pharmacology, and PK sections to align with current analysis and to simplify and remove redundancy with the Investigator Brochure. 6. Modified language in Drugs that Alter CYP3A4-Dependent Metabolism section and Study Treatment Rationale regarding CYP3A4 inhibitors or inducers to reflect current research indicating IDL may be a relatively weak inhibitor of CYP3A4. 7. Updated final analysis of study data for the Phase 1 monotherapy study in subjects with hematological malignancies. 8. Updated to allow biological samples which were collected for a study procedure or as standard of care to be stored for future research on the safety, mechanism of action, and the effects on the disease of the study drug (IDL/placebo) (with subject's informed consent). 9. Corrected the clinical response section to align with the criteria for the IRC. 10. Added a local assessment of the hematology panel at Visit 2, in addition to the central lab assessment, in order to have results if the central lab results were unusable. 11. Clarified the assessment of clinical progression while subjects were receiving bendamustine (which may cause cytopenia). 12. Added significant subject noncompliance as a reason for study withdrawal.
06 November 2013	1. Updated drugs that alter CYP3A4-dependent metabolism and the study treatment rationale regarding CYP3A4 inhibitors or inducers to reflect current pharmacokinetic (PK) and pharmacodynamic research on IDL and its major metabolite, GS-563117. 2. Modified the criteria for splenic and hepatic progression or response for consistency with Hallek et al., 2008. 3. Updated text to reflect current understanding of the effect of IDL on hepatic events; added monitoring guidelines for subjects who are antihepatitis B core (HBc) antibody positive at screening. 4. Updated data for the recently completed Phase 1 monotherapy study in subjects with hematological malignancies. 5. Aligned the clinical response section with the criteria for the IRC. 6. Clarified the section on emergency unblinding. 7. Aligned disease response criteria with the revised IRC Charter. 8. Changed the testing hierarchy of the secondary endpoints to evaluate OS prior to complete response (CR) rate. 9. Clarified definitions, assessments, and reporting of AEs and serious adverse events (SAEs) in the section on safety. 10. Corrected the ANC grade range values to align with <Grade 3 where specified.
25 April 2014	Clarified that scans obtained as part of standard of care may be used for screening.
10 October 2014	1. Aligned the protocol with new information included in the updated IB (Edition 11): a. Guidance to investigators for evaluation, intervention, and drug interruption/discontinuation for specific adverse events (AEs). b. Information regarding the interaction of IDL with CYP3A inhibitors, inducers, and substrates.
15 December 2015	1. Crossover of subjects from placebo to idelalisib was added to the study design. 2. Modified the criteria for evaluation of absolute lymphocyte count (ALC), platelets, hemoglobin, and absolute neutrophil count (ANC) response rates to exclude values obtained within 4 weeks postbaseline and to include platelet, hemoglobin, and neutrophil values achieving their respective response thresholds only if thesubject was not receiving growth factor or transfusion support. 3. Modified additional therapies to exclude all systemic anticancer therapies and to allow the possible use of topical anticancer agents with the medical monitor's permission. 4. Modified end-of-study procedures such that an end-of-study scan was not required if progressive disease (PD) had already been confirmed prior to the visit.
25 March 2016	1. Crossover of subjects from placebo to idelalisib was removed from the study design following identification of the safety signal of increased risk of deaths and SAEs observed in first-line CLL and early-line indolent non-Hodgkin lymphoma studies. 2. Updated the safety information and guidelines for toxicity management to be consistent across idelalisib study protocols. These changes included mandated prophylaxis for PJP, CMV surveillance and increased monitoring.

03 August 2016	Aligned with Urgent Safety Measures to define the recommended versusrequired actions related to dose modifications for adverse events related to idelalisib.
24 October 2016	In order to provide clear guidance for idelalisib administration in the event of pneumonitis, the language around actions to be taken was revised.
21 September 2017	1. As the primary endpoint of the study has been met, the schedule of required CT/MRI scans is being modified in order to decrease radiation exposure to patients and burden to both patients and investigative sites. The protocol will now request one final CT/MRI scan at disease progression or discontinuation. 2. Organizing pneumonia (OP) emerged as a potential safety signal during Gilead routine signal detection monitoring. This risk is now included in the Investigator Brochure (IB). All idelalisib protocols with ongoing subjects are being amended to add OP as a potential risk. 3. The bendamustine Summary of Product Characteristics (SmPC) updated in May 2017 included safety information. The protocol was updated to align with the SmPC.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28139405

http://www.ncbi.nlm.nih.gov/pubmed/31729982