

**Clinical trial results:****A Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib (PCI-32765) versus Ofatumumab in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma**
Summary

EudraCT number	2012-000694-23
Trial protocol	GB IE PL ES IT AT BE
Global end of trial date	25 October 2018

Results information

Result version number	v2 (current)
This version publication date	08 November 2019
First version publication date	14 October 2016
Version creation reason	<ul style="list-style-type: none">• New data added to full data set Results updated with data from the final analysis.

Trial information**Trial identification**

Sponsor protocol code	PCYC-1112-CA
-----------------------	--------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01578707
WHO universal trial number (UTN)	-
Other trial identifiers	provider NLM_DES study id: S0003GEU

Notes:

Sponsors

Sponsor organisation name	Pharmacyclics LLC
Sponsor organisation address	999 E Arques Ave, Sunnyvale, United States, 94085
Public contact	Medinfo, Pharmacyclics LLC, +1 408-774-0330, info@pcyc.com
Scientific contact	Medinfo, Pharmacyclics LLC, +1 408-774-0330, info@pcyc.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	26 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 October 2018
Global end of trial reached?	Yes
Global end of trial date	25 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study was to evaluate whether treatment with ibrutinib as a monotherapy results in a clinically significant improvement in progression free survival (PFS) as compared to treatment with ofatumumab in patients with relapsed or refractory Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL)

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki and ICH GCP.

Background therapy: -

Evidence for comparator:

NCCN and ESMO Guidelines Support the use of ofatumumab in the target patient population.

Actual start date of recruitment	22 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	Australia: 29
Country: Number of subjects enrolled	United States: 192
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	France: 27
Country: Number of subjects enrolled	United Kingdom: 73
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	Ireland: 9
Country: Number of subjects enrolled	Austria: 16
Worldwide total number of subjects	391
EEA total number of subjects	170

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)	152
From 65 to 84 years	235
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

A total of 391 subjects were enrolled in the study from sites located in the US, Europe, and Australia. The first subject consented 22 June 2012. After the primary analysis patients were followed-up for 5 years until 25 October 2018 (LPLV).

Pre-assignment

Screening details:

Patients with previously treated CLL were screened for potential participation by the investigators based on the eligibility criteria. Patients who met the criteria were asked whether they were willing to participate in the study. A total of 391 subjects were randomized.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ofatumumab (Arm A)

Arm description:

The ofatumumab (IV) dosage and schedule was 12 doses administered over 24 weeks or until disease progression or unacceptable toxicity.

Arm type	Active comparator
Investigational medicinal product name	ofatumumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

The ofatumumab (IV) dosage and schedule was 12 doses administered over 24 weeks or until disease progression, unacceptable toxicity.

Week 1: 300 mg initial dose

Week 2 through 8: 2,000 mg (once weekly)

Week 12, 16, 20 and 24: 2,000 mg (every 4 weeks)

Arm title	ibrutinib (Arm B)
------------------	-------------------

Arm description:

Ibrutinib 420 mg daily administered until disease progression or unacceptable toxicity.

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

Dosage and administration details:

ibrutinib 420 mg (3 x 140-mg capsules) was administered orally once daily until disease progression or unacceptable toxicity

Number of subjects in period 1	Ofatumumab (Arm A)	ibrutinib (Arm B)
Started	196	195
Completed	185	180
Not completed	11	15
Consent withdrawn by subject	6	15
Did not receive study drug	5	-

Baseline characteristics

Reporting groups

Reporting group title	Ofatumumab (Arm A)
-----------------------	--------------------

Reporting group description:

The ofatumumab (IV) dosage and schedule was 12 doses administered over 24 weeks or until disease progression or unacceptable toxicity.

Reporting group title	ibrutinib (Arm B)
-----------------------	-------------------

Reporting group description:

Ibrutinib 420 mg daily administered until disease progression or unacceptable toxicity.

Reporting group values	Ofatumumab (Arm A)	ibrutinib (Arm B)	Total
Number of subjects	196	195	391
Age Categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	75	77	152
>=65 years	121	118	239
Age Continuous Units: years			
arithmetic mean	66.8	66.1	
standard deviation	± 8.88	± 10.15	-
Gender, Male/Female Units: Subjects			
Female	59	66	125
Male	137	129	266

End points

End points reporting groups

Reporting group title	Ofatumumab (Arm A)
Reporting group description: The ofatumumab (IV) dosage and schedule was 12 doses administered over 24 weeks or until disease progression or unacceptable toxicity.	
Reporting group title	ibrutinib (Arm B)
Reporting group description: Ibrutinib 420 mg daily administered until disease progression or unacceptable toxicity.	

Primary: mPFS (median Progression Free Survival)

End point title	mPFS (median Progression Free Survival)
End point description: The primary objective of this study was to evaluate the efficacy of ibrutinib compared to ofatumumab based on progression-free survival (PFS) assessed by the Independent Review Committee (IRC) per International Workshop on Chronic Lymphocytic Leukemia Criteria (IWCLL; Hallek et al, 2008) in subjects with relapsed or refractory CLL/SLL. IRC assessment was discontinued after the primary analysis. Therefore, the present data are based on investigator assessment.	
End point type	Primary
End point timeframe: Analysis was conducted after observing 298 PFS events. Median follow-up time in the study was 65.4 month.	

End point values	Ofatumumab (Arm A)	ibrutinib (Arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	195		
Units: months				
number (confidence interval 95%)	8.1 (7.79 to 8.25)	44.1 (38.47 to 56.18)		

Statistical analyses

Statistical analysis title	PFS (Progression free survival)
Comparison groups	Ofatumumab (Arm A) v ibrutinib (Arm B)
Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Kaplan-Meier estimates
Parameter estimate	Hazard ratio (HR)
Point estimate	0.148

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.113
upper limit	0.196

Secondary: mOS (median Overall Survival)

End point title	mOS (median Overall Survival)
-----------------	-------------------------------

End point description:

Crossover from ofatumumab to ibrutinib treatment upon IRC-confirmed disease progression was instituted starting in August 2013 and 133 of 196 subjects (67.9%) randomized to ofatumumab had crossed over to ibrutinib treatment as subsequent therapy impacting on the outcome of this endpoint.

End point type	Secondary
----------------	-----------

End point timeframe:

Analysis was conducted after observing 176 death events. Median follow-up time in the study was 65.4 months.

End point values	Ofatumumab (Arm A)	ibrutinib (Arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	195		
Units: months				
number (not applicable)	65.1	67.7		

Statistical analyses

Statistical analysis title	mOS (median Overall Survival)
----------------------------	-------------------------------

Statistical analysis description:

Analysis confounded by crossover of two thirds of ofatumumab subjects to ibrutinib.

Comparison groups	ibrutinib (Arm B) v Ofatumumab (Arm A)
Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1653
Method	Kaplan-Meier Estimates
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.602
upper limit	1.091

Secondary: ORR (Overall Response Rate)

End point title	ORR (Overall Response Rate)
-----------------	-----------------------------

End point description:

ORR was defined as the Proportion of subjects who achieved Complete Response (CR), Complete Response with incomplete marrow recovery (CRi), nodule Partial Response (nPR), or Partial Response (PR) per investigator assessment.

End point type	Secondary
----------------	-----------

End point timeframe:

Median follow-up time in the study was 65.4 months.

End point values	Ofatumumab (Arm A)	ibrutinib (Arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	195		
Units: percentage				
number (not applicable)	22.4	87.7		

Statistical analyses

Statistical analysis title	ORR (Overall response rate)
Comparison groups	Ofatumumab (Arm A) v ibrutinib (Arm B)
Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact

Secondary: PFS2

End point title	PFS2
-----------------	------

End point description:

PFS2 was defined as the time from date of randomization to the date of the earliest of the following 3 types of events:

- Progressive disease per investigator response assessment after administration of the first subsequent anti-neoplastic therapy
- Death at any time on study due to any cause
- Initiation of a second subsequent antineoplastic therapy

End point type	Secondary
----------------	-----------

End point timeframe:

Assessment after a median time on study of 65.4 months.

End point values	Ofatumumab (Arm A)	ibrutinib (Arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	191		
Units: months				
number (not applicable)	38.5	65.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Sustained hemoglobin improvement

End point title	Sustained hemoglobin improvement
-----------------	----------------------------------

End point description:

Sustained hemoglobin improvement was defined as hemoglobin increase ≥ 20 g/L over baseline continuously for ≥ 56 days without blood transfusion or growth factors.

End point type	Secondary
----------------	-----------

End point timeframe:

Analysis was conducted after observing 298 PFS events. Median follow-up time in the study was 65.4 month.

End point values	Ofatumumab (Arm A)	ibrutinib (Arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	195		
Units: patients	37	91		

Statistical analyses

No statistical analyses for this end point

Secondary: Sustained platelet improvement

End point title	Sustained platelet improvement
-----------------	--------------------------------

End point description:

Sustained platelet improvement is defined as platelet increase $\geq 50\%$ over baseline continuously for ≥ 56 days without blood transfusion or growth factors.

End point type	Secondary
----------------	-----------

End point timeframe:

Analysis was conducted after observing 298 PFS events. Median follow-up time in the study was 65.4 month.

End point values	Ofatumumab (Arm A)	ibrutinib (Arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	195		
Units: patients	10	74		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From June 2012 through October 2018

Adverse event reporting additional description:

Note: Exposure to ibrutinib at the final analysis has been about 8 times longer (median 41.0 months) as compared to ofatumumab (median 5.3 months). Adverse event reporting has not been adjusted for exposure.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	21.0
--------------------	------

Reporting groups

Reporting group title	Ofatumumab (Arm A)
-----------------------	--------------------

Reporting group description:

An anti-CD20 monoclonal antibody

Ofatumumab: The ofatumumab (IV) dosage and schedule was 12 doses administered over 24 weeks or until disease progression, unacceptable toxicity.

Reporting group title	ibrutinib (Arm B)
-----------------------	-------------------

Reporting group description:

A Bruton Tyrosine Kinase Inhibitor

ibrutinib: ibrutinib 420 mg (3 x 140-mg capsules) was administered orally once daily until disease progression or unacceptable toxicity

Serious adverse events	Ofatumumab (Arm A)	ibrutinib (Arm B)	
Total subjects affected by serious adverse events			
subjects affected / exposed	59 / 191 (30.89%)	141 / 195 (72.31%)	
number of deaths (all causes)	91	85	
number of deaths resulting from adverse events	16	24	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leukaemia			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chronic lymphocytic leukaemia			
subjects affected / exposed	3 / 191 (1.57%)	5 / 195 (2.56%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 2	0 / 3	
Gastrointestinal carcinoma			

subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung adenocarcinoma			
subjects affected / exposed	0 / 191 (0.00%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 191 (0.52%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastatic squamous cell carcinoma			
subjects affected / exposed	1 / 191 (0.52%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Richter's syndrome			
subjects affected / exposed	0 / 191 (0.00%)	3 / 195 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Tumour flare			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	1 / 191 (0.52%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			

subjects affected / exposed	0 / 191 (0.00%)	3 / 195 (1.54%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hodgkin's disease			
subjects affected / exposed	0 / 191 (0.00%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 191 (0.00%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone cancer metastatic			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain neoplasm malignant			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon adenoma			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Desmoid tumour			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Histiocytic sarcoma			

subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraductal papillary mucinous neoplasm			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 191 (0.52%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aneurysm			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 191 (0.00%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
Cyst			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 191 (0.00%)	3 / 195 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 191 (2.09%)	15 / 195 (7.69%)	
occurrences causally related to treatment / all	2 / 4	7 / 22	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malaise			
subjects affected / exposed	0 / 191 (0.00%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			

subjects affected / exposed	0 / 191 (0.00%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Asthenia			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site pain			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site extravasation			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Effusion			
subjects affected / exposed	1 / 191 (0.52%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	1 / 191 (0.52%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 191 (0.52%)	3 / 195 (1.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bronchopneumopathy			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 191 (0.52%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 191 (0.52%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 191 (0.52%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 191 (0.52%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			
subjects affected / exposed	1 / 191 (0.52%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract inflammation			
subjects affected / exposed	1 / 191 (0.52%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			

subjects affected / exposed	0 / 191 (0.00%)	4 / 195 (2.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 191 (0.00%)	3 / 195 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 191 (0.00%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 191 (0.00%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 191 (0.52%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			

subjects affected / exposed	1 / 191 (0.52%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mania			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 191 (0.00%)	3 / 195 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination, visual			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Immunoglobulins decreased			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Muscle strain			
subjects affected / exposed	1 / 191 (0.52%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Post procedural haemorrhage subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction subjects affected / exposed	2 / 191 (1.05%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture subjects affected / exposed	1 / 191 (0.52%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures subjects affected / exposed	1 / 191 (0.52%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma subjects affected / exposed	0 / 191 (0.00%)	6 / 195 (3.08%)	
occurrences causally related to treatment / all	0 / 0	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Femur fracture subjects affected / exposed	0 / 191 (0.00%)	4 / 195 (2.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall subjects affected / exposed	0 / 191 (0.00%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture subjects affected / exposed	0 / 191 (0.00%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthropod bite			

subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain contusion			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Burns third degree			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haematoma			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			

subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haematoma			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 191 (0.52%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 191 (0.52%)	11 / 195 (5.64%)	
occurrences causally related to treatment / all	0 / 1	2 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	0 / 191 (0.00%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			

subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 191 (0.52%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	0 / 1	1 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 191 (0.00%)	3 / 195 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 191 (0.52%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 191 (0.52%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 191 (0.52%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve disease			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Myocardial ischaemia			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Seizure			
subjects affected / exposed	0 / 191 (0.00%)	3 / 195 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 191 (0.00%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 191 (0.00%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			

subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	4 / 191 (2.09%)	7 / 195 (3.59%)	
occurrences causally related to treatment / all	3 / 8	4 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	4 / 191 (2.09%)	5 / 195 (2.56%)	
occurrences causally related to treatment / all	1 / 4	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune haemolytic anaemia			
subjects affected / exposed	1 / 191 (0.52%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 191 (1.05%)	4 / 195 (2.05%)	
occurrences causally related to treatment / all	1 / 2	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Methaemoglobinaemia			
subjects affected / exposed	1 / 191 (0.52%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			

subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia			
subjects affected / exposed	1 / 191 (0.52%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spontaneous haematoma			
subjects affected / exposed	0 / 191 (0.00%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Vitreous haemorrhage			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 191 (0.52%)	0 / 195 (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	1 / 191 (0.52%)	6 / 195 (3.08%)	
occurrences causally related to treatment / all	0 / 2	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abdominal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 191 (0.52%)	4 / 195 (2.05%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malabsorption			
subjects affected / exposed	1 / 191 (0.52%)	0 / 195 (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	0 / 191 (0.00%)	3 / 195 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal spasm			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Poor dental condition			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vomiting			
subjects affected / exposed	0 / 191 (0.00%)	5 / 195 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	0 / 191 (0.00%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 191 (0.00%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorectal discomfort			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal perforation			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucous stools			

subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal obstruction			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal spasm			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyoderma gangrenosum			

subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	1 / 191 (0.52%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 191 (0.52%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	2 / 191 (1.05%)	4 / 195 (2.05%)	
occurrences causally related to treatment / all	0 / 2	1 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Haematuria			
subjects affected / exposed	0 / 191 (0.00%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 191 (0.00%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus bladder			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			

subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 191 (0.00%)	4 / 195 (2.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	0 / 191 (0.00%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 191 (0.52%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pain in extremity			
subjects affected / exposed	0 / 191 (0.00%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			

subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 191 (0.52%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal infection			
subjects affected / exposed	1 / 191 (0.52%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspergillus infection			
subjects affected / exposed	0 / 191 (0.00%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	2 / 191 (1.05%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	0 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteroides bacteraemia			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 191 (1.05%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	

Breast cellulitis			
subjects affected / exposed	1 / 191 (0.52%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 191 (0.00%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis bacterial			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter gastroenteritis			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 191 (0.52%)	8 / 195 (4.10%)	
occurrences causally related to treatment / all	0 / 1	3 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal infection			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 191 (0.00%)	4 / 195 (2.05%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			

subjects affected / exposed	0 / 191 (0.00%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Folliculitis			
subjects affected / exposed	1 / 191 (0.52%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	1 / 191 (0.52%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex			
subjects affected / exposed	1 / 191 (0.52%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophilus sepsis			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophilus bacteraemia			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes virus infection			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			

subjects affected / exposed	1 / 191 (0.52%)	3 / 195 (1.54%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 191 (0.52%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impetigo			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	1 / 191 (0.52%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	2 / 191 (1.05%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung infection			
subjects affected / exposed	0 / 191 (0.00%)	7 / 195 (3.59%)	
occurrences causally related to treatment / all	0 / 0	5 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	2 / 191 (1.05%)	4 / 195 (2.05%)	
occurrences causally related to treatment / all	1 / 2	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymph gland infection			

subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal sepsis			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nocardiosis			
subjects affected / exposed	1 / 191 (0.52%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	2 / 191 (1.05%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	2 / 2	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 1	
Pneumocystis jirovecii infection			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 191 (0.52%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	12 / 191 (6.28%)	42 / 195 (21.54%)	
occurrences causally related to treatment / all	8 / 14	23 / 60	
deaths causally related to treatment / all	1 / 3	1 / 5	
Pneumonia bacterial			

subjects affected / exposed	1 / 191 (0.52%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia mycoplasmal			
subjects affected / exposed	1 / 191 (0.52%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 191 (0.52%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 191 (1.05%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis syndrome			
subjects affected / exposed	1 / 191 (0.52%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Rhinovirus infection			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 191 (1.05%)	8 / 195 (4.10%)	
occurrences causally related to treatment / all	0 / 2	2 / 8	
deaths causally related to treatment / all	0 / 0	0 / 2	
Tonsillitis fungal			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			

subjects affected / exposed	0 / 191 (0.00%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	4 / 191 (2.09%)	4 / 195 (2.05%)	
occurrences causally related to treatment / all	1 / 4	1 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Stenotrophomonas infection			
subjects affected / exposed	2 / 191 (1.05%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal skin infection			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral pharyngitis			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 191 (0.00%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 191 (0.00%)	9 / 195 (4.62%)	
occurrences causally related to treatment / all	0 / 0	3 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethritis			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	0 / 191 (0.00%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonal			
subjects affected / exposed	1 / 191 (0.52%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia staphylococcal			
subjects affected / exposed	0 / 191 (0.00%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal sepsis			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
H1N1 influenza			

subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophilus infection			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of bronchiectasis			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection bacterial			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis pneumococcal			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mycobacterium avium complex infection			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis externa			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			

subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal sepsis			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas infection			
subjects affected / exposed	2 / 191 (1.05%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection pseudomonal			

subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection pseudomonal			
subjects affected / exposed	1 / 191 (0.52%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ophthalmic herpes zoster			
subjects affected / exposed	1 / 191 (0.52%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	1 / 191 (0.52%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 191 (0.00%)	3 / 195 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 191 (0.00%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency			

subjects affected / exposed	0 / 191 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ofatumumab (Arm A)	ibrutinib (Arm B)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	185 / 191 (96.86%)	194 / 195 (99.49%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	2 / 191 (1.05%)	18 / 195 (9.23%)	
occurrences (all)	2	31	
Squamous cell carcinoma			
subjects affected / exposed	2 / 191 (1.05%)	13 / 195 (6.67%)	
occurrences (all)	3	19	
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 191 (2.09%)	40 / 195 (20.51%)	
occurrences (all)	5	53	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	8 / 191 (4.19%)	22 / 195 (11.28%)	
occurrences (all)	8	40	
Fatigue			
subjects affected / exposed	57 / 191 (29.84%)	82 / 195 (42.05%)	
occurrences (all)	78	145	
Oedema peripheral			
subjects affected / exposed	16 / 191 (8.38%)	46 / 195 (23.59%)	
occurrences (all)	19	68	
Pyrexia			
subjects affected / exposed	27 / 191 (14.14%)	66 / 195 (33.85%)	
occurrences (all)	39	123	
Chills			

subjects affected / exposed	6 / 191 (3.14%)	16 / 195 (8.21%)	
occurrences (all)	8	27	
Influenza like illness			
subjects affected / exposed	5 / 191 (2.62%)	16 / 195 (8.21%)	
occurrences (all)	5	27	
Malaise			
subjects affected / exposed	1 / 191 (0.52%)	10 / 195 (5.13%)	
occurrences (all)	1	10	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	43 / 191 (22.51%)	78 / 195 (40.00%)	
occurrences (all)	55	135	
Dyspnoea			
subjects affected / exposed	18 / 191 (9.42%)	32 / 195 (16.41%)	
occurrences (all)	20	46	
Epistaxis			
subjects affected / exposed	5 / 191 (2.62%)	30 / 195 (15.38%)	
occurrences (all)	6	41	
Oropharyngeal pain			
subjects affected / exposed	9 / 191 (4.71%)	33 / 195 (16.92%)	
occurrences (all)	10	43	
Rhinorrhoea			
subjects affected / exposed	6 / 191 (3.14%)	19 / 195 (9.74%)	
occurrences (all)	6	22	
Nasal congestion			
subjects affected / exposed	6 / 191 (3.14%)	17 / 195 (8.72%)	
occurrences (all)	7	19	
Dyspnoea exertional			
subjects affected / exposed	4 / 191 (2.09%)	14 / 195 (7.18%)	
occurrences (all)	4	18	
Productive cough			
subjects affected / exposed	5 / 191 (2.62%)	14 / 195 (7.18%)	
occurrences (all)	7	19	
Dysphonia			

subjects affected / exposed occurrences (all)	0 / 191 (0.00%) 0	10 / 195 (5.13%) 13	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	16 / 191 (8.38%)	17 / 195 (8.72%)	
occurrences (all)	16	20	
Anxiety			
subjects affected / exposed	9 / 191 (4.71%)	18 / 195 (9.23%)	
occurrences (all)	9	20	
Depression			
subjects affected / exposed	3 / 191 (1.57%)	17 / 195 (8.72%)	
occurrences (all)	3	19	
Confusional state			
subjects affected / exposed	4 / 191 (2.09%)	11 / 195 (5.64%)	
occurrences (all)	4	16	
Investigations			
Weight decreased			
subjects affected / exposed	11 / 191 (5.76%)	25 / 195 (12.82%)	
occurrences (all)	11	33	
Blood creatinine increased			
subjects affected / exposed	0 / 191 (0.00%)	12 / 195 (6.15%)	
occurrences (all)	0	18	
Platelet count decreased			
subjects affected / exposed	0 / 191 (0.00%)	11 / 195 (5.64%)	
occurrences (all)	0	13	
Weight increased			
subjects affected / exposed	0 / 191 (0.00%)	11 / 195 (5.64%)	
occurrences (all)	0	17	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	64 / 191 (33.51%)	0 / 195 (0.00%)	
occurrences (all)	94	0	
Contusion			
subjects affected / exposed	6 / 191 (3.14%)	38 / 195 (19.49%)	
occurrences (all)	6	52	
Fall			

subjects affected / exposed occurrences (all)	1 / 191 (0.52%) 1	18 / 195 (9.23%) 40	
Traumatic haematoma subjects affected / exposed occurrences (all)	0 / 191 (0.00%) 0	12 / 195 (6.15%) 19	
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	0 / 191 (0.00%) 0	19 / 195 (9.74%) 26	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	12 / 191 (6.28%) 12	41 / 195 (21.03%) 62	
Dizziness subjects affected / exposed occurrences (all)	10 / 191 (5.24%) 11	33 / 195 (16.92%) 50	
Paraesthesia subjects affected / exposed occurrences (all)	10 / 191 (5.24%) 12	14 / 195 (7.18%) 16	
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	26 / 191 (13.61%) 33	22 / 195 (11.28%) 27	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	32 / 191 (16.75%) 58	62 / 195 (31.79%) 115	
Increased tendency to bruise subjects affected / exposed occurrences (all)	4 / 191 (2.09%) 4	45 / 195 (23.08%) 60	
Neutropenia subjects affected / exposed occurrences (all)	25 / 191 (13.09%) 61	60 / 195 (30.77%) 184	
Thrombocytopenia subjects affected / exposed occurrences (all)	22 / 191 (11.52%) 30	45 / 195 (23.08%) 86	
lymphocytosis			

subjects affected / exposed occurrences (all)	5 / 191 (2.62%) 6	10 / 195 (5.13%) 15	
Eye disorders			
Lacrimation increased subjects affected / exposed occurrences (all)	5 / 191 (2.62%) 5	27 / 195 (13.85%) 35	
Dry eye subjects affected / exposed occurrences (all)	10 / 191 (5.24%) 10	33 / 195 (16.92%) 39	
Vision blurred subjects affected / exposed occurrences (all)	6 / 191 (3.14%) 6	30 / 195 (15.38%) 36	
Cataract subjects affected / exposed occurrences (all)	2 / 191 (1.05%) 2	26 / 195 (13.33%) 31	
Visual acuity reduced subjects affected / exposed occurrences (all)	1 / 191 (0.52%) 1	19 / 195 (9.74%) 25	
Eye irritation subjects affected / exposed occurrences (all)	3 / 191 (1.57%) 3	17 / 195 (8.72%) 19	
eye pain subjects affected / exposed occurrences (all)	5 / 191 (2.62%) 6	15 / 195 (7.69%) 20	
Photophobia subjects affected / exposed occurrences (all)	4 / 191 (2.09%) 4	14 / 195 (7.18%) 21	
Vitreous floaters subjects affected / exposed occurrences (all)	3 / 191 (1.57%) 3	14 / 195 (7.18%) 15	
Gastrointestinal disorders			
Dry mouth subjects affected / exposed occurrences (all)	1 / 191 (0.52%) 1	19 / 195 (9.74%) 23	
Dyspepsia			

subjects affected / exposed	6 / 191 (3.14%)	22 / 195 (11.28%)	
occurrences (all)	6	32	
Diarrhoea			
subjects affected / exposed	33 / 191 (17.28%)	120 / 195 (61.54%)	
occurrences (all)	39	247	
Constipation			
subjects affected / exposed	19 / 191 (9.95%)	45 / 195 (23.08%)	
occurrences (all)	20	72	
Abdominal pain			
subjects affected / exposed	19 / 191 (9.95%)	30 / 195 (15.38%)	
occurrences (all)	21	39	
Vomiting			
subjects affected / exposed	11 / 191 (5.76%)	39 / 195 (20.00%)	
occurrences (all)	14	81	
Nausea			
subjects affected / exposed	38 / 191 (19.90%)	69 / 195 (35.38%)	
occurrences (all)	53	122	
Stomatitis			
subjects affected / exposed	5 / 191 (2.62%)	30 / 195 (15.38%)	
occurrences (all)	5	41	
Flatulence			
subjects affected / exposed	2 / 191 (1.05%)	10 / 195 (5.13%)	
occurrences (all)	2	11	
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 191 (1.57%)	21 / 195 (10.77%)	
occurrences (all)	3	23	
Abdominal pain upper			
subjects affected / exposed	3 / 191 (1.57%)	16 / 195 (8.21%)	
occurrences (all)	3	30	
Haemorrhoids			
subjects affected / exposed	3 / 191 (1.57%)	10 / 195 (5.13%)	
occurrences (all)	3	10	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	7 / 191 (3.66%)	26 / 195 (13.33%)	
occurrences (all)	9	39	

Pruritus		
subjects affected / exposed	18 / 191 (9.42%)	19 / 195 (9.74%)
occurrences (all)	20	26
Rash		
subjects affected / exposed	7 / 191 (3.66%)	19 / 195 (9.74%)
occurrences (all)	9	32
Rash erythematous		
subjects affected / exposed	9 / 191 (4.71%)	20 / 195 (10.26%)
occurrences (all)	13	26
Petechiae		
subjects affected / exposed	2 / 191 (1.05%)	28 / 195 (14.36%)
occurrences (all)	2	38
Night sweats		
subjects affected / exposed	23 / 191 (12.04%)	24 / 195 (12.31%)
occurrences (all)	26	29
Skin lesion		
subjects affected / exposed	5 / 191 (2.62%)	24 / 195 (12.31%)
occurrences (all)	5	40
Dry skin		
subjects affected / exposed	3 / 191 (1.57%)	18 / 195 (9.23%)
occurrences (all)	3	22
Actinic keratosis		
subjects affected / exposed	5 / 191 (2.62%)	16 / 195 (8.21%)
occurrences (all)	5	21
Ecchymosis		
subjects affected / exposed	0 / 191 (0.00%)	12 / 195 (6.15%)
occurrences (all)	0	22
Onychoclasia		
subjects affected / exposed	0 / 191 (0.00%)	12 / 195 (6.15%)
occurrences (all)	0	12
Blood blister		
subjects affected / exposed	1 / 191 (0.52%)	10 / 195 (5.13%)
occurrences (all)	1	14
Skin ulcer		
subjects affected / exposed	0 / 191 (0.00%)	10 / 195 (5.13%)
occurrences (all)	0	13

Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	3 / 191 (1.57%)	19 / 195 (9.74%)	
occurrences (all)	3	21	
Dysuria			
subjects affected / exposed	1 / 191 (0.52%)	12 / 195 (6.15%)	
occurrences (all)	1	14	
Haematuria			
subjects affected / exposed	2 / 191 (1.05%)	12 / 195 (6.15%)	
occurrences (all)	2	16	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	14 / 191 (7.33%)	39 / 195 (20.00%)	
occurrences (all)	17	49	
Arthralgia			
subjects affected / exposed	14 / 191 (7.33%)	53 / 195 (27.18%)	
occurrences (all)	17	103	
Pain in extremity			
subjects affected / exposed	9 / 191 (4.71%)	29 / 195 (14.87%)	
occurrences (all)	10	39	
Myalgia			
subjects affected / exposed	7 / 191 (3.66%)	24 / 195 (12.31%)	
occurrences (all)	9	34	
Muscle spasms			
subjects affected / exposed	16 / 191 (8.38%)	46 / 195 (23.59%)	
occurrences (all)	18	71	
Musculoskeletal pain			
subjects affected / exposed	9 / 191 (4.71%)	20 / 195 (10.26%)	
occurrences (all)	10	23	
Bone pain			
subjects affected / exposed	3 / 191 (1.57%)	10 / 195 (5.13%)	
occurrences (all)	4	11	
Muscular weakness			
subjects affected / exposed	3 / 191 (1.57%)	10 / 195 (5.13%)	
occurrences (all)	4	11	
Neck pain			

subjects affected / exposed occurrences (all)	0 / 191 (0.00%) 0	10 / 195 (5.13%) 13	
Infections and infestations			
Sinusitis			
subjects affected / exposed	12 / 191 (6.28%)	50 / 195 (25.64%)	
occurrences (all)	15	77	
Upper respiratory tract infection			
subjects affected / exposed	17 / 191 (8.90%)	77 / 195 (39.49%)	
occurrences (all)	19	124	
Urinary tract infection			
subjects affected / exposed	10 / 191 (5.24%)	46 / 195 (23.59%)	
occurrences (all)	11	76	
Bronchitis			
subjects affected / exposed	2 / 191 (1.05%)	28 / 195 (14.36%)	
occurrences (all)	2	45	
Nasopharyngitis			
subjects affected / exposed	7 / 191 (3.66%)	22 / 195 (11.28%)	
occurrences (all)	8	30	
Conjunctivitis			
subjects affected / exposed	2 / 191 (1.05%)	21 / 195 (10.77%)	
occurrences (all)	2	23	
Pneumonia			
subjects affected / exposed	3 / 191 (1.57%)	21 / 195 (10.77%)	
occurrences (all)	4	29	
Cellulitis			
subjects affected / exposed	3 / 191 (1.57%)	15 / 195 (7.69%)	
occurrences (all)	4	29	
Lower respiratory tract infection			
subjects affected / exposed	0 / 191 (0.00%)	15 / 195 (7.69%)	
occurrences (all)	0	20	
Herpes zoster			
subjects affected / exposed	3 / 191 (1.57%)	14 / 195 (7.18%)	
occurrences (all)	5	15	
Ear infection			
subjects affected / exposed	2 / 191 (1.05%)	13 / 195 (6.67%)	
occurrences (all)	2	16	

Folliculitis subjects affected / exposed occurrences (all)	0 / 191 (0.00%) 0	10 / 195 (5.13%) 11	
Metabolism and nutrition disorders			
Hyperglycaemia subjects affected / exposed occurrences (all)	6 / 191 (3.14%) 10	16 / 195 (8.21%) 31	
Hyperuricaemia subjects affected / exposed occurrences (all)	4 / 191 (2.09%) 4	22 / 195 (11.28%) 26	
Decreased appetite subjects affected / exposed occurrences (all)	16 / 191 (8.38%) 16	32 / 195 (16.41%) 40	
Hypokalaemia subjects affected / exposed occurrences (all)	5 / 191 (2.62%) 5	22 / 195 (11.28%) 39	
Hyponatraemia subjects affected / exposed occurrences (all)	3 / 191 (1.57%) 3	12 / 195 (6.15%) 18	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 September 2012	Updated the following information: <ul style="list-style-type: none">• Secondary and exploratory objectives/endpoints including corresponding changes to statistical analysis section• Updated response criteria inclusive of the June 2012 clarification to IWCLL 2008 criteria for assessing response with BCR-inhibiting agents, including guidance to assess the clinical improvement in other disease parameters upon observation of lymphocytosis• Guidelines for concomitant use of CYP inhibiting/inducing drugs, QT prolonging medications, and antiplatelet agents and anticoagulants• Revised Inclusion criteria #5 to include subjects age ≥ 70 years who have received ≥ 2 prior lines of systemic therapy• Clarified that 2 separate randomization schemes were to be generated (one for each geographic region [US versus non-US])
13 December 2012	<ul style="list-style-type: none">• Provided instructions on administration of ibrutinib in case of planned or unplanned surgery• Allowed allogeneic stem cell transplant within 6 months prior to randomization with no active graft vs. host disease.• Clarified that pre-treatment FISH should be performed on marrow sample for subjects without lymphocytosis (eg, SLL)• Included provisional language for supplying ibrutinib to control arm subjects• Allowed screening computed tomography (CT) scan from up to 6 weeks prior to randomization
08 August 2013	<ul style="list-style-type: none">• Allowed subjects treated with ofatumumab and with documented IRC-confirmed progression to receive therapy with ibrutinib at investigator's discretion• Updated guideline for concomitant use local site or hormonal therapy for non-B cell malignancies and growth factors• Added collection for other malignancies that develop at anytime during study follow-up
24 September 2013	<ul style="list-style-type: none">• Changed the overall two-sided significance level for PFS from 0.01 to 0.05 following review with global regulatory authorities.
16 January 2014	Pharmacyclics amended this protocol to <ul style="list-style-type: none">• allow patients randomized to ofatumumab arm to receive next-line therapy with ibrutinib at investigator's discretion and to remove the requirement of disease progression confirmation by Independent Review Committee (IRC)• reduce the frequency of CT scans to every 24 weeks after 12 months• update Summary of Clinical Safety of Ibrutinib (Section 1.3.2.2.) per Investigator's Brochure version 7
27 October 2014	Pharmacyclics amended this protocol to <ul style="list-style-type: none">• extend the study duration from 3 to 5 years• update Summary of Clinical Safety of Ibrutinib (Section 1.3.2.2.) per Investigator's Brochure version 8• reduce the frequency of CT scans to annually for patients who have been receiving ibrutinib for 36 months, as well as for patients who were randomized to ofatumumab arm and currently receiving next-line ibrutinib
28 September 2016	Pharmacyclics is amended this protocol to: <ul style="list-style-type: none">• extend the study duration beyond 5 years• implement updates per revised ibrutinib Investigator's Brochure and label

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/24881631>