Clinical trial results:
A prospective, open-label, multicentre phase-II trial to evaluate the efficacy and safety of a sequential regimen of bendamustine followed by GA101 and ibrutinib (BIG) followed by ibrutinib and GA101 maintenance in CLL patients (CLL2-BIG protocol)

Summary

EudraCT number	2014-000569-35
Trial protocol	DE
Global end of trial date	29 March 2019

Results information

Result version number	v1 (current)
This version publication date	11 September 2020
First version publication date	11 September 2020

Trial information

Trial identification

Sponsor protocol code	CLL2-BIG

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02345863
WHO universal trial number (UTN)	-
Other trial identifiers	2243/01: PEI

Notes:

Sponsors

Sponsor organisation name	German CLL Study Group
Sponsor organisation address	University Hospital Cologne, Gleuelerstr. 176-178, Cologne, Germany, 50935
Public contact	Information Desk, German CLL Study Group, +49 221478 88198, cll-studie@uk-koeln.de
Scientific contact	Information Desk, German CLL Study Group, +49 221478 88198, cll-studie@uk-koeln.de

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	07 August 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 March 2019
Global end of trial reached?	Yes
Global end of trial date	29 March 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the efficacy of a regimen of two debulking cycles of bendamustine chemotherapy followed by a sequential combination therapy of GA101 (obinutuzumab) and ibrutinib for induction and maintenance therapy in CLL patients. For this, the overall response rate (ORR) at final restaging (RE) 12 weeks after start of the last cycle of induction therapy (end of induction treatment response = EOIT) will be used as primary parameter of efficacy. In the ORR all patients achieving a (clinical) complete response (CR) / complete response with incomplete recovery of the bone marrow (CRi), partial response (PR) and PR with lymphocytosis will be included. The response will be assessed according to the iwCLL criteria

Protection of trial subjects:

Debulking treatment with Bendamustine should be stopped after the 1st cycle only if severe adverse events occur.

Obinutuzumab must be administered in a clinical setting (inpatient or outpatient). Patients should be under close supervision of the investigator at all times; resuscitation equipment and medications (including epinephrine for subcutaneous injections, corticosteroids, antihistamines for i.v. injection) should be available for immediate use.

Background therapy:

In this prospective single-arm phase-II trial, the feasibility regarding efficacy and safety of a regimen consisting of two cycles of bendamustine for debulking, followed by a sequential application of GA101 (obinutuzumab) and ibrutinib as induction and as maintenance therapy until achievement of a MRD negative remission for up to 2 years of maintenance will be evaluated in both previously untreated or relapsed/refractory and physically fit or unfit CLL patients.
A treatment with one of kinase inhibitors, namely ibrutinib and an antibody, namely GA101 combines two targeted and very effective agents with a favourable toxicity profile. Thus, the combination of ibrutinib and GA101 is expected to have a high efficacy without overlapping or increased toxicities. In addition, this combinations appears to be a rational approach because of theoretical considerations: ibrutinib inhibits the migration and adhesion of CLL cells to the protecting microenvironment and thereby leads to a redistribution and mobilization of these cells to peripheral blood and cause a lymphocytosis. All antibodies, especially the highly effective GA101 lead to early infusion-related side effects, such as cytokine-release- and tumor lysis syndromes. Therefore, the combination of a drug that leads to a lymphocytosis through a redistribution of leukemic cells to the peripheral blood and a very effective antibody that acts predominantly in the peripheral blood and targets the redistributed cells, the efficacy of both drugs should be increased through synergistic mechanism of action and could potentially eradicate the residual CLL cells.
In order to avoid additional toxicities due to these distinctive features, these two drugs will be started sequentially. And in addition, a debulking treatment with two cycles of chemotherapy with bendamustine will be given ahead of the sequential administration of GA101 (obinutuzumab) and ibrutinib to mitigate the early side effects and to optimize the efficacy.

Evidence for comparator:

n/a

Actual start date of recruitment	01 October 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 66
Worldwide total number of subjects	66
EEA total number of subjects	66

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)	29
From 65 to 84 years	36
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

66 patients were enrolled between 01/2015 and 09/2015.

Pre-assignment

Screening details:

69 patients diagnosed with CLL were registered for central screening. The central screening was performed by the GCLLSG central study office in Cologne, Germany and included immunophenotyping, FISH, evaluation of the comorbidity and renal function. 3 patients were not eligible for participitation.

Pre-assignment period milestones

Number of subjects started	69[1]
Number of subjects completed	66

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Protocol deviation: 3

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: To verify the eligibility of patients, a central medical review of the screening data was performed and were reviewed by one of the GCLLSG study physicians together with the results of the baseline assessments in the central laboratories, including immunophenotyping and cytogenetics, for confirmation of the eligibility of the patient. 69 pats were screened and 66 enrolled.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Bendamustine/Obinutuzumab/Ibrutinib

Arm description:

Chemotherapy with Bendamustine, obinutuzumab and ibrutinib

Arm type	Experimental
Investigational medicinal product name	Bendamustine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Phase 1 Debulking: Cycle 1-2 on days 1 and 2: 70mg/m2 iv

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

Dosage and administration details:

Phase 2 Induction: Cycle 1 on day 1 100mg, day 1 (or 2) 900mg, day 8 1000mg, day 15 1000mg; Cycle 2-6 on day 1 1000mg
Phase 3 Maintenance: every 3 months 1000mg

Investigational medicinal product name	Ibrutinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Phase 2 Induction: Cycle 2-6 daily 420mg;
Phase 3 Maintenance: daily 420mg

Number of subjects in period 1	Bendamustine/Obinutuzumab/Ibrutinib
Started	66
treatment allocation	66
treatment	66
follow-up	37
Completed	13
Not completed	53
Adverse event, serious fatal	4
Consent withdrawn by subject	5
Physician decision	1
Adverse event, non-fatal	10
various reasons	33

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	66	66	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	29	29	
From 65-84 years	36	36	
85 years and over	1	1	
Age continuous Units: years			
median	66.5		
inter-quartile range (Q1-Q3)	61 to 74.75	-	
Gender categorical Units: Subjects			
Female	28	28	
Male	38	38	

End points

End points reporting groups

Reporting group title	Bendamustine/Obinutuzumab/Ibrutinib

Reporting group description:

Chemotherapy with Bendamustine, obinutuzumab and ibrutinib

Primary: Response at end of induction treatment

End point title	Response at end of induction treatment[1]

End point description:

The primary efficacy parameter (primary endpoint) is the best overall response rate (ORR) at final restaging after induction therapy (end of induction treatment response = EOIT). Best overall response rate is defined by the proportion of patients having achieved a CR/ CRi, clinical CR/CRi, PR or PR with lymphocytosis as best response based on the respective population (= number of patients with best response CR/CRi, clinical CR/CRi, PR or PR with lymphocytosis divided by the number of the respective population).

End point type	Primary

End point timeframe:

The primary endpoint was analyzed after all enrolled patients have achieved the final restaging.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the hypothesis states that the efficacy of the BIG regimen is confirmed if the ORR (at final restaging) is at least 90% and as there are no further comparisons between different treatment arms, a frequency tabulation with no further statistical analyses was sufficient. So there are no statistical values available to provide.

End point values	Bendamustine/ Obinutuzumab/ Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	61			
Units: number of patients	61			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	FL patient

Reporting group description: -

Reporting group title	RR patient

Reporting group description: -

Serious adverse events	FL patient	RR patient	
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 33 (63.64%)	22 / 33 (66.67%)	
number of deaths (all causes)	0	8	
number of deaths resulting from adverse events	0	7	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anal cancer	Additional description: Anal cancer		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma	Additional description: Basal cell carcinoma		
subjects affected / exposed	5 / 33 (15.15%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	5 / 10	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer	Additional description: Bladder cancer		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's disease	Additional description: Bowen's disease		

subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain neoplasm	Additional description: Brain neoplasm		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carcinoma in situ of skin	Additional description: Carcinoma in situ of skin		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma in situ	Additional description: Malignant melanoma in situ		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer	Additional description: Prostate cancer		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (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	Additional description: Squamous cell carcinoma		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aneurysm	Additional description: Aneurysm		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Internal fixation of spine	Additional description: Internal fixation of spine		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration			

site conditions			
General physical health deterioration	Additional description: General physical health deterioration		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyserositis	Additional description: Polyserositis		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome	Additional description: Systemic inflammatory response syndrome		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (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			
Obstructive airways disorder	Additional description: Obstructive airways disorder		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion	Additional description: Pleural effusion		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased	Additional description: Blood creatinine increased		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (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			
Arterial bypass stenosis	Additional description: Arterial bypass stenosis		

subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthropod bite	Additional description: Arthropod bite		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Forearm fracture	Additional description: Forearm fracture		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction	Additional description: Infusion related reaction		
subjects affected / exposed	2 / 33 (6.06%)	2 / 33 (6.06%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture	Additional description: Rib fracture		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seroma	Additional description: Seroma		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture	Additional description: Tendon rupture		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation	Additional description: Atrial fibrillation		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive	Additional description: Cardiac failure congestive		

subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction	Additional description: Myocardial infarction		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery stenosis	Additional description: Carotid artery stenosis		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction	Additional description: Cerebral infarction		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident	Additional description: Cerebrovascular accident		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Demyelinating polyneuropathy	Additional description: Demyelinating polyneuropathy		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache	Additional description: Headache		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thalamus haemorrhage	Additional description: Thalamus haemorrhage		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (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			

Autoimmune haemolytic anaemia	Additional description: Autoimmune haemolytic anaemia		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bicytopenia	Additional description: Bicytopenia		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia	Additional description: Febrile neutropenia		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Acute vestibular syndrome	Additional description: Acute vestibular syndrome		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract	Additional description: Cataract		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis	Additional description: Duodenitis		

subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Dysphagia	Additional description: Dysphagia		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal polyp haemorrhage	Additional description: Gastrointestinal polyp haemorrhage		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia	Additional description: Inguinal hernia		
subjects affected / exposed	2 / 33 (6.06%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis	Additional description: Cholangitis		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic	Additional description: Cholecystitis chronic		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis	Additional description: Cholestasis		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic artery aneurysm	Additional description: Hepatic artery aneurysm		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury	Additional description: Acute kidney injury		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure	Additional description: Renal failure		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (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			
Bursitis	Additional description: Bursitis		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion	Additional description: Intervertebral disc protrusion		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain	Additional description: Musculoskeletal pain		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seronegative arthritis	Additional description: Seronegative arthritis		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain	Additional description: Spinal pain		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Febrile infection	Additional description: Febrile infection		
subjects affected / exposed	2 / 33 (6.06%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lung infection	Additional description: Lung infection		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lymph node abscess	Additional description: Lymph node abscess		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pancreas infection	Additional description: Pancreas infection		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia	Additional description: Pneumonia		
subjects affected / exposed	4 / 33 (12.12%)	7 / 33 (21.21%)	
occurrences causally related to treatment / all	2 / 4	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	

Pneumonia bacterial	Additional description: Pneumonia bacterial		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia fungal	Additional description: Pneumonia fungal		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia influenzal	Additional description: Pneumonia influenzal		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia mycoplasmal	Additional description: Pneumonia mycoplasmal		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia parainfluenzae viral	Additional description: Pneumonia parainfluenzae viral

subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis	Additional description: Pulmonary sepsis		
subjects affected / exposed	0 / 33 (0.00%)	2 / 33 (6.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 2	
Respiratory tract infection	Additional description: Respiratory tract infection		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis	Additional description: Sepsis		
subjects affected / exposed	0 / 33 (0.00%)	2 / 33 (6.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 2	
Staphylococcal bacteraemia	Additional description: Staphylococcal bacteraemia		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis	Additional description: Tracheobronchitis		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Gout	Additional description: Gout		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Protein deficiency	Additional description: Protein deficiency		

subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome	Additional description: Tumour lysis syndrome		
subjects affected / exposed	3 / 33 (9.09%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	FL patient	RR patient	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 33 (93.94%)	33 / 33 (100.00%)	
Vascular disorders			
Aortic arteriosclerosis	Additional description: Aortic arteriosclerosis		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Arteriosclerosis	Additional description: Arteriosclerosis		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Flushing	Additional description: Flushing		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Haematoma	Additional description: Haematoma		
subjects affected / exposed	3 / 33 (9.09%)	3 / 33 (9.09%)	
occurrences (all)	3	5	
Haemorrhage	Additional description: Haemorrhage		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Hypertension	Additional description: Hypertension		
subjects affected / exposed	4 / 33 (12.12%)	2 / 33 (6.06%)	
occurrences (all)	4	2	
Thrombophlebitis	Additional description: Thrombophlebitis		
subjects affected / exposed	2 / 33 (6.06%)	2 / 33 (6.06%)	
occurrences (all)	2	2	

Thrombophlebitis superficial	Additional description: Thrombophlebitis superficial		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Tooth extraction	Additional description: Tooth extraction		
subjects affected / exposed	0 / 33 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Asthenia	Additional description: Asthenia		
subjects affected / exposed	0 / 33 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Chest discomfort	Additional description: Chest discomfort		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Chest pain	Additional description: Chest pain		
subjects affected / exposed	2 / 33 (6.06%)	2 / 33 (6.06%)	
occurrences (all)	2	2	
Chills	Additional description: Chills		
subjects affected / exposed	3 / 33 (9.09%)	3 / 33 (9.09%)	
occurrences (all)	3	3	
Drug intolerance	Additional description: Drug intolerance		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Face oedema	Additional description: Face oedema		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Fatigue	Additional description: Fatigue		
subjects affected / exposed	14 / 33 (42.42%)	10 / 33 (30.30%)	
occurrences (all)	17	12	
Gait disturbance	Additional description: Gait disturbance		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
General physical health deterioration	Additional description: General physical health deterioration		
subjects affected / exposed	1 / 33 (3.03%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Impaired healing	Additional description: Impaired healing		

subjects affected / exposed	1 / 33 (3.03%)	1 / 33 (3.03%)	
occurrences (all)	1	3	
Inflammation	Additional description: Inflammation		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Influenza like illness	Additional description: Influenza like illness		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Infusion site pain	Additional description: Infusion site pain		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Localised oedema	Additional description: Localised oedema		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Mucosal dryness	Additional description: Mucosal dryness		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Mucosal inflammation	Additional description: Mucosal inflammation		
subjects affected / exposed	2 / 33 (6.06%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Nodule	Additional description: Nodule		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Oedema	Additional description: Oedema		
subjects affected / exposed	2 / 33 (6.06%)	1 / 33 (3.03%)	
occurrences (all)	2	1	
Oedema peripheral	Additional description: Oedema peripheral		
subjects affected / exposed	4 / 33 (12.12%)	2 / 33 (6.06%)	
occurrences (all)	6	2	
Pain	Additional description: Pain		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Performance status decreased	Additional description: Performance status decreased		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Peripheral swelling	Additional description: Peripheral swelling		

subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	6 / 33 (18.18%)	4 / 33 (12.12%)	
occurrences (all)	8	5	
Immune system disorders			
Cytokine release syndrome	Additional description: Cytokine release syndrome		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Food allergy	Additional description: Food allergy		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Hypersensitivity	Additional description: Hypersensitivity		
subjects affected / exposed	3 / 33 (9.09%)	0 / 33 (0.00%)	
occurrences (all)	4	0	
Immunodeficiency	Additional description: Immunodeficiency		
subjects affected / exposed	1 / 33 (3.03%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Secondary immunodeficiency	Additional description: Secondary immunodeficiency		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Pelvic pain	Additional description: Pelvic pain		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Uterine prolapse	Additional description: Uterine prolapse		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease	Additional description: Chronic obstructive pulmonary disease		
subjects affected / exposed	1 / 33 (3.03%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Cough	Additional description: Cough		
subjects affected / exposed	6 / 33 (18.18%)	6 / 33 (18.18%)	
occurrences (all)	7	6	

Dysphonia	Additional description: Dysphonia		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	1 / 33 (3.03%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Dyspnoea exertional	Additional description: Dyspnoea exertional		
subjects affected / exposed	1 / 33 (3.03%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Epistaxis	Additional description: Epistaxis		
subjects affected / exposed	2 / 33 (6.06%)	1 / 33 (3.03%)	
occurrences (all)	2	2	
Nasal mucosal inflammation	Additional description: Nasal mucosal inflammation		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain	Additional description: Oropharyngeal pain		
subjects affected / exposed	2 / 33 (6.06%)	1 / 33 (3.03%)	
occurrences (all)	2	1	
Pleural effusion	Additional description: Pleural effusion		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Pulmonary fibrosis	Additional description: Pulmonary fibrosis		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Throat irritation	Additional description: Throat irritation		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Aggression	Additional description: Aggression		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Agitation	Additional description: Agitation		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Anxiety	Additional description: Anxiety		

subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Depression	Additional description: Depression		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Insomnia	Additional description: Insomnia		
subjects affected / exposed	0 / 33 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Irritability	Additional description: Irritability		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Sleep disorder	Additional description: Sleep disorder		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Investigations			
Aspartate aminotransferase increased	Additional description: Aspartate aminotransferase increased		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Bleeding time prolonged	Additional description: Bleeding time prolonged		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Blood creatinine increased	Additional description: Blood creatinine increased		
subjects affected / exposed	1 / 33 (3.03%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Blood lactate dehydrogenase increased	Additional description: Blood lactate dehydrogenase increased		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Gamma-glutamyltransferase increased	Additional description: Gamma-glutamyltransferase increased		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Prostatic specific antigen increased	Additional description: Prostatic specific antigen increased		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Weight decreased	Additional description: Weight decreased		

subjects affected / exposed	3 / 33 (9.09%)	3 / 33 (9.09%)	
occurrences (all)	3	3	
Injury, poisoning and procedural complications			
Arthropod bite	Additional description: Arthropod bite		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Fall	Additional description: Fall		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Infusion related reaction	Additional description: Infusion related reaction		
subjects affected / exposed	9 / 33 (27.27%)	14 / 33 (42.42%)	
occurrences (all)	9	15	
Laceration	Additional description: Laceration		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Muscle rupture	Additional description: Muscle rupture		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Muscle strain	Additional description: Muscle strain		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Skin injury	Additional description: Skin injury		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Tooth injury	Additional description: Tooth injury		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Traumatic haemorrhage	Additional description: Traumatic haemorrhage		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Wound	Additional description: Wound		
subjects affected / exposed	2 / 33 (6.06%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Cardiac disorders			

Arrhythmia supraventricular	Additional description: Arrhythmia supraventricular		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Atrial fibrillation	Additional description: Atrial fibrillation		
subjects affected / exposed	3 / 33 (9.09%)	3 / 33 (9.09%)	
occurrences (all)	3	3	
Atrial thrombosis	Additional description: Atrial thrombosis		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Cardiac failure	Additional description: Cardiac failure		
subjects affected / exposed	1 / 33 (3.03%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Cardiovascular disorder	Additional description: Cardiovascular disorder		
subjects affected / exposed	1 / 33 (3.03%)	1 / 33 (3.03%)	
occurrences (all)	2	1	
Cyanosis	Additional description: Cyanosis		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Palpitations	Additional description: Palpitations		
subjects affected / exposed	1 / 33 (3.03%)	3 / 33 (9.09%)	
occurrences (all)	1	3	
Supraventricular extrasystoles	Additional description: Supraventricular extrasystoles		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Tachycardia	Additional description: Tachycardia		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Tricuspid valve incompetence	Additional description: Tricuspid valve incompetence		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Ventricular arrhythmia	Additional description: Ventricular arrhythmia		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Ventricular extrasystoles	Additional description: Ventricular extrasystoles		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	

Nervous system disorders			
Arthropod bite	Additional description: Arthropod bite		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Cluster headache	Additional description: Cluster headache		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Dizziness	Additional description: Dizziness		
subjects affected / exposed	4 / 33 (12.12%)	2 / 33 (6.06%)	
occurrences (all)	4	2	
Dysgeusia	Additional description: Dysgeusia		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Headache	Additional description: Headache		
subjects affected / exposed	4 / 33 (12.12%)	4 / 33 (12.12%)	
occurrences (all)	4	5	
Hypertonia	Additional description: Hypertonia		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Hypoaesthesia	Additional description: Hypoaesthesia		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Memory impairment	Additional description: Memory impairment		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Migraine	Additional description: Migraine		
subjects affected / exposed	0 / 33 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Neuralgia	Additional description: Neuralgia		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Paraesthesia	Additional description: Paraesthesia		
subjects affected / exposed	1 / 33 (3.03%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Parosmia	Additional description: Parosmia		

subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Peripheral sensory neuropathy	Additional description: Peripheral sensory neuropathy		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	3	
Polyneuropathy	Additional description: Polyneuropathy		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Sciatica	Additional description: Sciatica		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
subjects affected / exposed	3 / 33 (9.09%)	4 / 33 (12.12%)	
occurrences (all)	4	6	
Autoimmune haemolytic anaemia	Additional description: Autoimmune haemolytic anaemia		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Granulocytopenia	Additional description: Granulocytopenia		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Immune thrombocytopenic purpura	Additional description: Immune thrombocytopenic purpura		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Increased tendency to bruise	Additional description: Increased tendency to bruise		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Iron deficiency anaemia	Additional description: Iron deficiency anaemia		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Leukopenia	Additional description: Leukopenia		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Lymph node pain	Additional description: Lymph node pain		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	

Lymphadenitis	Additional description: Lymphadenitis		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Lymphadenopathy	Additional description: Lymphadenopathy		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Neutropenia	Additional description: Neutropenia		
subjects affected / exposed	9 / 33 (27.27%)	8 / 33 (24.24%)	
occurrences (all)	11	13	
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed	6 / 33 (18.18%)	9 / 33 (27.27%)	
occurrences (all)	13	16	
Ear and labyrinth disorders			
Hyperacusis	Additional description: Hyperacusis		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Tinnitus	Additional description: Tinnitus		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	3	0	
Vertigo	Additional description: Vertigo		
subjects affected / exposed	3 / 33 (9.09%)	7 / 33 (21.21%)	
occurrences (all)	4	8	
Vertigo positional	Additional description: Vertigo positional		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	4	
Eye disorders			
Blepharitis	Additional description: Blepharitis		
subjects affected / exposed	1 / 33 (3.03%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Blindness	Additional description: Blindness		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Cataract	Additional description: Cataract		
subjects affected / exposed	1 / 33 (3.03%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Conjunctival haemorrhage	Additional description: Conjunctival haemorrhage		

subjects affected / exposed	1 / 33 (3.03%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Eye disorder	Additional description: Eye disorder		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Eye haemorrhage	Additional description: Eye haemorrhage		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Eyelid oedema	Additional description: Eyelid oedema		
subjects affected / exposed	1 / 33 (3.03%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Eyelid rash	Additional description: Eyelid rash		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Hypermetropia	Additional description: Hypermetropia		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Periorbital oedema	Additional description: Periorbital oedema		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Vision blurred	Additional description: Vision blurred		
subjects affected / exposed	1 / 33 (3.03%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Visual impairment	Additional description: Visual impairment		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain upper	Additional description: Abdominal pain upper		
subjects affected / exposed	2 / 33 (6.06%)	4 / 33 (12.12%)	
occurrences (all)	3	5	
Aphthous stomatitis	Additional description: Aphthous stomatitis		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Ascites	Additional description: Ascites		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	

Cheilitis	Additional description: Cheilitis		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Constipation	Additional description: Constipation		
subjects affected / exposed	2 / 33 (6.06%)	1 / 33 (3.03%)	
occurrences (all)	3	1	
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	14 / 33 (42.42%)	12 / 33 (36.36%)	
occurrences (all)	18	16	
Dry mouth	Additional description: Dry mouth		
subjects affected / exposed	2 / 33 (6.06%)	1 / 33 (3.03%)	
occurrences (all)	2	1	
Dyspepsia	Additional description: Dyspepsia		
subjects affected / exposed	4 / 33 (12.12%)	4 / 33 (12.12%)	
occurrences (all)	5	4	
Dysphagia	Additional description: Dysphagia		
subjects affected / exposed	1 / 33 (3.03%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Gastrointestinal disorder	Additional description: Gastrointestinal disorder		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	2	
Gastrooesophageal reflux disease	Additional description: Gastrooesophageal reflux disease		
subjects affected / exposed	2 / 33 (6.06%)	1 / 33 (3.03%)	
occurrences (all)	2	1	
Gingival discomfort	Additional description: Gingival discomfort		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Gingival pain	Additional description: Gingival pain		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Haemorrhoidal haemorrhage	Additional description: Haemorrhoidal haemorrhage		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Large intestine polyp	Additional description: Large intestine polyp		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	

Loose tooth	Additional description: Loose tooth		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Nausea	Additional description: Nausea		
subjects affected / exposed	9 / 33 (27.27%)	6 / 33 (18.18%)	
occurrences (all)	13	9	
Oesophagitis	Additional description: Oesophagitis		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Oral discomfort	Additional description: Oral discomfort		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Oral disorder	Additional description: Oral disorder		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Pancreatitis chronic	Additional description: Pancreatitis chronic		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Reflux gastritis	Additional description: Reflux gastritis		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Regurgitation	Additional description: Regurgitation		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Stomatitis	Additional description: Stomatitis		
subjects affected / exposed	1 / 33 (3.03%)	4 / 33 (12.12%)	
occurrences (all)	1	4	
Swollen tongue	Additional description: Swollen tongue		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Vomiting	Additional description: Vomiting		
subjects affected / exposed	5 / 33 (15.15%)	3 / 33 (9.09%)	
occurrences (all)	7	3	
Hepatobiliary disorders			
Cholangitis	Additional description: Cholangitis		

subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	3	
Cholestasis	Additional description: Cholestasis		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Hyperbilirubinaemia	Additional description: Hyperbilirubinaemia		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Alopecia	Additional description: Alopecia		
subjects affected / exposed	3 / 33 (9.09%)	1 / 33 (3.03%)	
occurrences (all)	3	1	
Alopecia areata	Additional description: Alopecia areata		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Dermatitis	Additional description: Dermatitis		
subjects affected / exposed	1 / 33 (3.03%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Dermatitis acneiform	Additional description: Dermatitis acneiform		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Dermatitis allergic	Additional description: Dermatitis allergic		
subjects affected / exposed	2 / 33 (6.06%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Dry skin	Additional description: Dry skin		
subjects affected / exposed	3 / 33 (9.09%)	2 / 33 (6.06%)	
occurrences (all)	4	2	
Ecchymosis	Additional description: Ecchymosis		
subjects affected / exposed	2 / 33 (6.06%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Eczema	Additional description: Eczema		
subjects affected / exposed	2 / 33 (6.06%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Erythema	Additional description: Erythema		
subjects affected / exposed	3 / 33 (9.09%)	0 / 33 (0.00%)	
occurrences (all)	3	0	

Erythema exsudativum multiforme	Additional description: Erythema exsudativum multiforme		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Hyperhidrosis	Additional description: Hyperhidrosis		
subjects affected / exposed	2 / 33 (6.06%)	2 / 33 (6.06%)	
occurrences (all)	2	2	
Nail bed inflammation	Additional description: Nail bed inflammation		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Nail fold inflammation	Additional description: Nail fold inflammation		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Night sweats	Additional description: Night sweats		
subjects affected / exposed	0 / 33 (0.00%)	3 / 33 (9.09%)	
occurrences (all)	0	3	
Petechiae	Additional description: Petechiae		
subjects affected / exposed	1 / 33 (3.03%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Photodermatosis	Additional description: Photodermatosis		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Pruritus	Additional description: Pruritus		
subjects affected / exposed	3 / 33 (9.09%)	1 / 33 (3.03%)	
occurrences (all)	3	2	
Psoriasis	Additional description: Psoriasis		
subjects affected / exposed	0 / 33 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Purpura	Additional description: Purpura		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Rash	Additional description: Rash		
subjects affected / exposed	12 / 33 (36.36%)	7 / 33 (21.21%)	
occurrences (all)	20	8	
Rash maculo-papular	Additional description: Rash maculo-papular		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	

Rash pruritic	Additional description: Rash pruritic		
subjects affected / exposed	2 / 33 (6.06%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Rosacea	Additional description: Rosacea		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Scab	Additional description: Scab		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Skin fissures	Additional description: Skin fissures		
subjects affected / exposed	0 / 33 (0.00%)	3 / 33 (9.09%)	
occurrences (all)	0	3	
Skin haemorrhage	Additional description: Skin haemorrhage		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Skin irritation	Additional description: Skin irritation		
subjects affected / exposed	1 / 33 (3.03%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Skin odour abnormal	Additional description: Skin odour abnormal		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Sweat gland disorder	Additional description: Sweat gland disorder		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Urticaria	Additional description: Urticaria		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Bladder dysfunction	Additional description: Bladder dysfunction		
subjects affected / exposed	1 / 33 (3.03%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Bladder pain	Additional description: Bladder pain		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Bladder trabeculation	Additional description: Bladder trabeculation		

subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Haematuria	Additional description: Haematuria		
subjects affected / exposed	2 / 33 (6.06%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Micturition disorder	Additional description: Micturition disorder		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Nocturia	Additional description: Nocturia		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Pollakiuria	Additional description: Pollakiuria		
subjects affected / exposed	0 / 33 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Polyuria	Additional description: Polyuria		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Renal colic	Additional description: Renal colic		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	3	0	
Urinary retention	Additional description: Urinary retention		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Endocrine disorders			
Hyperthyroidism	Additional description: Hyperthyroidism		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Hypothyroidism	Additional description: Hypothyroidism		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia	Additional description: Arthralgia		
subjects affected / exposed	6 / 33 (18.18%)	4 / 33 (12.12%)	
occurrences (all)	10	5	
Back pain	Additional description: Back pain		

subjects affected / exposed	7 / 33 (21.21%)	3 / 33 (9.09%)	
occurrences (all)	9	3	
Bone pain	Additional description: Bone pain		
subjects affected / exposed	1 / 33 (3.03%)	1 / 33 (3.03%)	
occurrences (all)	2	1	
Bursitis	Additional description: Bursitis		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Fibromyalgia	Additional description: Fibromyalgia		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Intervertebral disc protrusion	Additional description: Intervertebral disc protrusion		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Muscle haemorrhage	Additional description: Muscle haemorrhage		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Muscle spasms	Additional description: Muscle spasms		
subjects affected / exposed	3 / 33 (9.09%)	7 / 33 (21.21%)	
occurrences (all)	3	7	
Muscle tightness	Additional description: Muscle tightness		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Musculoskeletal discomfort	Additional description: Musculoskeletal discomfort		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal stiffness	Additional description: Musculoskeletal stiffness		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Myalgia	Additional description: Myalgia		
subjects affected / exposed	1 / 33 (3.03%)	2 / 33 (6.06%)	
occurrences (all)	1	2	
Neck pain	Additional description: Neck pain		
subjects affected / exposed	2 / 33 (6.06%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Pain in extremity	Additional description: Pain in extremity		

subjects affected / exposed	3 / 33 (9.09%)	2 / 33 (6.06%)	
occurrences (all)	4	2	
Infections and infestations			
Angular cheilitis	Additional description: Angular cheilitis		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Bronchiolitis	Additional description: Bronchiolitis		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Bronchitis	Additional description: Bronchitis		
subjects affected / exposed	3 / 33 (9.09%)	5 / 33 (15.15%)	
occurrences (all)	3	6	
Bronchitis bacterial	Additional description: Bronchitis bacterial		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Chlamydial infection	Additional description: Chlamydial infection		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Chronic sinusitis	Additional description: Chronic sinusitis		
subjects affected / exposed	1 / 33 (3.03%)	2 / 33 (6.06%)	
occurrences (all)	1	2	
Conjunctivitis	Additional description: Conjunctivitis		
subjects affected / exposed	2 / 33 (6.06%)	2 / 33 (6.06%)	
occurrences (all)	2	4	
Cystitis	Additional description: Cystitis		
subjects affected / exposed	2 / 33 (6.06%)	1 / 33 (3.03%)	
occurrences (all)	3	6	
Ear infection	Additional description: Ear infection		
subjects affected / exposed	3 / 33 (9.09%)	1 / 33 (3.03%)	
occurrences (all)	3	1	
Escherichia urinary tract infection	Additional description: Escherichia urinary tract infection		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Eye infection	Additional description: Eye infection		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	

Eye infection viral	Additional description: Eye infection viral		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Febrile infection	Additional description: Febrile infection		
subjects affected / exposed	2 / 33 (6.06%)	1 / 33 (3.03%)	
occurrences (all)	2	1	
Fungal skin infection	Additional description: Fungal skin infection		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Furuncle	Additional description: Furuncle		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	2	
Gastroenteritis escherichia coli	Additional description: Gastroenteritis escherichia coli		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis norovirus	Additional description: Gastroenteritis norovirus		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal infection	Additional description: Gastrointestinal infection		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Gingivitis	Additional description: Gingivitis		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Herpes ophthalmic	Additional description: Herpes ophthalmic		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Herpes simplex	Additional description: Herpes simplex		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	2	
Herpes virus infection	Additional description: Herpes virus infection		
subjects affected / exposed	2 / 33 (6.06%)	3 / 33 (9.09%)	
occurrences (all)	2	4	
Herpes zoster	Additional description: Herpes zoster		
subjects affected / exposed	2 / 33 (6.06%)	0 / 33 (0.00%)	
occurrences (all)	2	0	

Infected bites	Additional description: Infected bites		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Infection	Additional description: Infection		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Influenza	Additional description: Influenza		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Mucosal infection	Additional description: Mucosal infection		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Nail candida	Additional description: Nail candida		
subjects affected / exposed	2 / 33 (6.06%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Nasopharyngitis	Additional description: Nasopharyngitis		
subjects affected / exposed	6 / 33 (18.18%)	16 / 33 (48.48%)	
occurrences (all)	11	24	
Oral candidiasis	Additional description: Oral candidiasis		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Oral herpes	Additional description: Oral herpes		
subjects affected / exposed	0 / 33 (0.00%)	3 / 33 (9.09%)	
occurrences (all)	0	3	
Oropharyngeal candidiasis	Additional description: Oropharyngeal candidiasis		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Otitis media	Additional description: Otitis media		
subjects affected / exposed	3 / 33 (9.09%)	1 / 33 (3.03%)	
occurrences (all)	3	1	
Paronychia	Additional description: Paronychia		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Pharyngitis	Additional description: Pharyngitis		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	

Pneumonia	Additional description: Pneumonia		
subjects affected / exposed	3 / 33 (9.09%)	4 / 33 (12.12%)	
occurrences (all)	4	4	
Pulpitis dental	Additional description: Pulpitis dental		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Rash pustular	Additional description: Rash pustular		
subjects affected / exposed	0 / 33 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Respiratory tract infection	Additional description: Respiratory tract infection		
subjects affected / exposed	3 / 33 (9.09%)	1 / 33 (3.03%)	
occurrences (all)	3	1	
Respiratory tract infection bacterial	Additional description: Respiratory tract infection bacterial		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Rhinitis	Additional description: Rhinitis		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Sinusitis	Additional description: Sinusitis		
subjects affected / exposed	4 / 33 (12.12%)	5 / 33 (15.15%)	
occurrences (all)	7	7	
Skin infection	Additional description: Skin infection		
subjects affected / exposed	0 / 33 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Soft tissue infection	Additional description: Soft tissue infection		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Tonsillitis	Additional description: Tonsillitis		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Upper respiratory tract infection	Additional description: Upper respiratory tract infection		
subjects affected / exposed	3 / 33 (9.09%)	4 / 33 (12.12%)	
occurrences (all)	4	7	
Upper respiratory tract infection bacterial	Additional description: Upper respiratory tract infection bacterial		

subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed	6 / 33 (18.18%)	7 / 33 (21.21%)	
occurrences (all)	7	11	
Wound infection	Additional description: Wound infection		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite	Additional description: Decreased appetite		
subjects affected / exposed	4 / 33 (12.12%)	2 / 33 (6.06%)	
occurrences (all)	4	2	
Dehydration	Additional description: Dehydration		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Folate deficiency	Additional description: Folate deficiency		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Hyperkalaemia	Additional description: Hyperkalaemia		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Hyperuricaemia	Additional description: Hyperuricaemia		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Hypocalcaemia	Additional description: Hypocalcaemia		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Hypokalaemia	Additional description: Hypokalaemia		
subjects affected / exposed	0 / 33 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	3	
Tumour lysis syndrome	Additional description: Tumour lysis syndrome		
subjects affected / exposed	1 / 33 (3.03%)	0 / 33 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 December 2015	This amendment was made to provide the following information: - Additional testing timepoint - Additional information to tumour lysis syndrom - Additional information to the adverse drug reactions: infusion-related reactions (IRRs), neutropenia, thrombocytopenia - New information to adverse events - New information to the administration of obinutuzumab to patients with chronic infections and to premedication with obinutuzumab - New information to Hepatitis B reactivation - Additional information to progressive multifocal leukencephalopathy (PML) - New information to immunization
22 March 2017	This amendment was made to provide the following information: - New potential risk of gastrointestinal perforation with obinutuzumab - New information to the non-hematological adverse event interstitial lung disease

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported