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 ofatumumab and ibrutinib followed by ibrutinib and ofatumumab maintenance in CLL patients (CLL2-BIO-trial of the GCLLSG)

Summary

EudraCT number	2014-000590-39
Trial protocol	DE
Global end of trial date	06 February 2020
Results information	
Result version number	v1 (current)
This version publication date	24 February 2021
First version publication date	24 February 2021

Trial information

Trial identification	
Sponsor protocol code	CLL2-BIO
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02689141
WHO universal trial number (UTN)	-
Other trial identifiers	Uni-Sponsor No: UNI-KOELN-1773

Notes:

Sponsors	
Sponsor organisation name	University of Cologne
Sponsor organisation address	Albertus-Magnus-Platz, Cologne, Germany, 50923
Public contact	Information Desk, German CLL Study Group, 0049 0221478 88220, cllstudie@uk-koeln.de
Scientific contact	Information Desk, German CLL Study Group, 0049 0221478 88220, cllstudie@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	04 April 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 April 2018
Global end of trial reached?	Yes
Global end of trial date	06 February 2020
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 ofatumumab and ibrutinib for induction and maintenance treatment in CLL patients. The primary efficacy parameter (primary endpoint) is the overall response rate (ORR) by investigator assessement. 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.

Protection of trial subjects:

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

Evidence for comparator:

not available, single-arm phase II trial.

Actual start date of recruitment	23 November 2015
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)	37
From 65 to 84 years	29
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between 4th February and 4th October 2016, 66 patients were enrolled; one first-line patient with less than two induction cycles (treatment discontinuation due to a generalized seizure on day 4 of induction cycle 2) was excluded from the efficacy analysis as predefined by the protocol but remained in the safety population

Pre-assignment

Screening details:

68 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. 2 patients were not eligible for participitation.

Pre-assignment period milestones

Number of subjects started	68[1]
Number of subjects completed	66

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Physician decision: 2

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: 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. 68 pats were screened and 66 enrolled

Period 1

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

Arms

Arm title	Bendamustine/Ofatumumab/Ibrutinib

Arm description:

Chemotherapy with Bendamustine (2 optional cycles), Anti-Cd20 monoclobnal antibody Ofatumumab and BTK-inhibitor Ibrutinib

Arm type	Experimental
Investigational medicinal product name	Bendamustine
Investigational medicinal product code	MA number: 70972.00.00
Other name	Levact
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	Ofatumumab
Investigational medicinal product code	EU/1/10/625/001
Other name	Arzerra
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Induction, cycle 1, day 1: 300 mg; 0.3 mg/ml; Induction cycle 1, days 8 and 15, cycles 2 - 6, day 1,: 1000 mg; 1 mg/ml; Maintenance: cycles 1 – 8, day 1: 1000 mg; 1 mg/ml

Investigational medicinal product name	Ibrutinib
Investigational medicinal product code	EU/1/14/945/001
Other name	Imbruvica
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Induction, Cycle 1: - -, Cycles 2-6: Days 1-28: Ibrutinib 420 mg (3 tabl.) p.o.; Maintenance, cycles 1-8, days 1-84: Ibrutinib 420 mg (3 tabl.) p.o.

Number of subjects in period 1	Bendamustine/Ofatumumab/Ibrutinib
Started	66
Completed	45
Not completed	21
Adverse event, serious fatal	1
Consent withdrawn by subject	2
Adverse event, non-fatal	10
Lack of efficacy	8

Baseline characteristics

Reporting groups

Reporting group title	Overall trial period

Reporting group description: -

Reporting group values	Overall trial period	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)	37	37	
From 65-84 years	29	29	
85 years and over	0	0	
Age continuous Units: years			
median	61.0		
inter-quartile range (Q1-Q3)	51.5 to 72.0	-	
Gender categorical Units: Subjects			
Female	24	24	
Male	42	42	

End points

End points reporting groups

Reporting group title	Bendamustine/Ofatumumab/Ibrutinib

Reporting group description:

Chemotherapy with Bendamustine (2 optional cycles), Anti-Cd20 monoclobnal antibody Ofatumumab and BTK-inhibitor Ibrutinib

Primary: Primary endpoint

End point title	Primary endpoint[1]

End point description:

The primary efficacy parameter is the overall response rate (ORR) by investigator assessment at the final restaging (RE) 12 weeks after the start of the last cycle of induction therapy (end of induction treatment response = EOIT) including all patients achieving

- a (clinical) complete response (CR),
- a (clinical) CR with incomplete recovery of the bone marrow (CRi) or
- a partial response (PR) or
- PR with lymphocytosis

End point type	Primary

End point timeframe:

The primary efficacy parameter is the overall response rate (ORR) by investigator assessment at the final restaging (RE) 12 weeks after the start of the last cycle of induction therapy (end of induction treatment response = EOIT).

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 BIO regimen is assessed uninteresting if the ORR rate is less than 75% and 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/ Ofatumumab/I brutinib			
Subject group type	Reporting group			
Number of subjects analysed	65			
Units: percent				
number (confidence interval 95%)	92.3 (83.0 to 97.5)			

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	25 / 40 (62.50%)	19 / 26 (73.08%)	
number of deaths (all causes)	2	4	
number of deaths resulting from adverse events	2	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma	Additional description: Basal cell carcinoma		
subjects affected / exposed	1 / 40 (2.50%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial carcinoma	Additional description: Bronchial carcinoma		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma	Additional description: Lung adenocarcinoma		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Rectal adenocarcinoma	Additional description: Rectal adenocarcinoma		

subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (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	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin	Additional description: Squamous cell carcinoma of skin		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Radiotherapy	Additional description: Radiotherapy		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
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			
General physical health deterioration	Additional description: General physical health deterioration		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing	Additional description: Impaired healing		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (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	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction	Additional description: Anaphylactic reaction		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Drug hypersensitivity	Additional description: Drug hypersensitivity		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity	Additional description: Hypersensitivity		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (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			
Bronchitis chronic	Additional description: Bronchitis chronic		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough	Additional description: Cough		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis	Additional description: Pneumonitis		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory gas exchange disorder	Additional description: Respiratory gas exchange disorder		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 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 / 40 (2.50%)	0 / 26 (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			
Fibula fracture	Additional description: Fibula fracture		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (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	6 / 40 (15.00%)	7 / 26 (26.92%)	
occurrences causally related to treatment / all	10 / 10	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis chemical	Additional description: Pneumonitis chemical		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture	Additional description: Rib fracture		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture	Additional description: Spinal fracture		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome	Additional description: Acute coronary syndrome		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation	Additional description: Atrial fibrillation		
subjects affected / exposed	4 / 40 (10.00%)	3 / 26 (11.54%)	
occurrences causally related to treatment / all	5 / 5	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure	Additional description: Cardiac failure		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Extrasystoles	Additional description: Extrasystoles		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction	Additional description: Myocardial infarction		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral microangiopathy	Additional description: Cerebral microangiopathy		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache	Additional description: Headache		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cerebral infarction	Additional description: Ischaemic cerebral infarction		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Seizure	Additional description: Seizure		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope	Additional description: Syncope		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack	Additional description: Transient ischaemic attack		
subjects affected / exposed	0 / 40 (0.00%)	2 / 26 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Anaemia	Additional description: Anaemia		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolysis	Additional description: Haemolysis		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy	Additional description: Lymphadenopathy		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
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 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract	Additional description: Cataract		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dacryostenosis acquired	Additional description: Dacryostenosis acquired		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glaucoma	Additional description: Glaucoma		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ascites	Additional description: Ascites		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	1 / 40 (2.50%)	2 / 26 (7.69%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Eosinophilic cellulitis	Additional description: Eosinophilic cellulitis		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash	Additional description: Rash		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Solar dermatitis	Additional description: Solar dermatitis		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic epidermal necrolysis	Additional description: Toxic epidermal necrolysis		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 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 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain	Additional description: Musculoskeletal chest pain		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess limb	Additional description: Abscess limb		

subjects affected / exposed	0 / 40 (0.00%)	2 / 26 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia	Additional description: Atypical pneumonia		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis	Additional description: Bronchitis		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis	Additional description: Bronchopulmonary aspergillosis		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis infective	Additional description: Bursitis infective		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis	Additional description: Clostridium difficile colitis		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis	Additional description: Diverticulitis		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas	Additional description: Erysipelas		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile Infection	Additional description: Febrile Infection		

subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis	Additional description: Gastroenteritis		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis clostridial	Additional description: Gastroenteritis clostridial		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus	Additional description: Gastroenteritis norovirus		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection	Additional description: Infection		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion	Additional description: Infectious pleural effusion		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis meningococcal	Additional description: Meningitis meningococcal		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection	Additional description: Neutropenic infection		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis	Additional description: Oesophageal candidiasis		

subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis infective	Additional description: Pericarditis infective		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia	Additional description: Pneumonia		
subjects affected / exposed	0 / 40 (0.00%)	6 / 26 (23.08%)	
occurrences causally related to treatment / all	0 / 0	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal	Additional description: Pneumonia influenzal		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia legionella	Additional description: Pneumonia legionella		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis	Additional description: Pulmonary sepsis		
subjects affected / exposed	2 / 40 (5.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis	Additional description: Sepsis		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock	Additional description: Septic shock		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Urinary tract infection	Additional description: Urinary tract infection		

subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypercalcaemia	Additional description: Hypercalcaemia		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome	Additional description: Tumour lysis syndrome		
subjects affected / exposed	2 / 40 (5.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	2 / 2	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	40 / 40 (100.00%)	26 / 26 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma of liver	Additional description: Haemangioma of liver		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Seborrhoeic keratosis	Additional description: Seborrhoeic keratosis		
subjects affected / exposed	0 / 40 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Vascular disorders			
Circulatory collapse	Additional description: Circulatory collapse		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Flushing	Additional description: Flushing		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Haematoma	Additional description: Haematoma		
subjects affected / exposed	3 / 40 (7.50%)	6 / 26 (23.08%)	
occurrences (all)	4	7	

Hypertension	Additional description: Hypertension		
subjects affected / exposed	9 / 40 (22.50%)	1 / 26 (3.85%)	
occurrences (all)	9	1	
Hypertensive crisis	Additional description: Hypertensive crisis		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Hypotension	Additional description: Hypotension		
subjects affected / exposed	1 / 40 (2.50%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Raynaud's phenomenon	Additional description: Raynaud's phenomenon		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Thrombophlebitis	Additional description: Thrombophlebitis		
subjects affected / exposed	2 / 40 (5.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Vascular calcification	Additional description: Vascular calcification		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Vasculitis	Additional description: Vasculitis		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Cataract operation	Additional description: Cataract operation		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	2	
Dental implantation	Additional description: Dental implantation		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Phlebectomy	Additional description: Phlebectomy		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Tooth extraction	Additional description: Tooth extraction		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	2	
General disorders and administration site conditions			

Chest discomfort	Additional description: Chest discomfort		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Chest pain	Additional description: Chest pain		
subjects affected / exposed	2 / 40 (5.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Chills	Additional description: Chills		
subjects affected / exposed	2 / 40 (5.00%)	2 / 26 (7.69%)	
occurrences (all)	2	2	
Extravasation	Additional description: Extravasation		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Fatigue	Additional description: Fatigue		
subjects affected / exposed	16 / 40 (40.00%)	10 / 26 (38.46%)	
occurrences (all)	18	12	
Gait disturbance	Additional description: Gait disturbance		
subjects affected / exposed	2 / 40 (5.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
General physical health deterioration	Additional description: General physical health deterioration		
subjects affected / exposed	3 / 40 (7.50%)	0 / 26 (0.00%)	
occurrences (all)	3	0	
Impaired healing	Additional description: Impaired healing		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Injection site phlebitis	Additional description: Injection site phlebitis		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Mucosal inflammation	Additional description: Mucosal inflammation		
subjects affected / exposed	4 / 40 (10.00%)	1 / 26 (3.85%)	
occurrences (all)	7	1	
Oedema	Additional description: Oedema		
subjects affected / exposed	2 / 40 (5.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Oedema peripheral	Additional description: Oedema peripheral		
subjects affected / exposed	5 / 40 (12.50%)	7 / 26 (26.92%)	
occurrences (all)	5	9	

Pain	Additional description: Pain		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Peripheral swelling	Additional description: Peripheral swelling		
subjects affected / exposed	1 / 40 (2.50%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	3 / 40 (7.50%)	1 / 26 (3.85%)	
occurrences (all)	5	1	
Soft tissue inflammation	Additional description: Soft tissue inflammation		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Immune system disorders			
Drug hypersensitivity	Additional description: Drug hypersensitivity		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Hypersensitivity	Additional description: Hypersensitivity		
subjects affected / exposed	3 / 40 (7.50%)	1 / 26 (3.85%)	
occurrences (all)	3	1	
Hypogammaglobulinaemia	Additional description: Hypogammaglobulinaemia		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Immunodeficiency	Additional description: Immunodeficiency		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Immunodeficiency common variable	Additional description: Immunodeficiency common variable		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Social circumstances			
Menopause	Additional description: Menopause		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Benign prostatic hyperplasia	Additional description: Benign prostatic hyperplasia		
subjects affected / exposed	1 / 40 (2.50%)	1 / 26 (3.85%)	
occurrences (all)	1	1	

Menorrhagia	Additional description: Menorrhagia		
subjects affected / exposed	2 / 40 (5.00%)	0 / 26 (0.00%)	
occurrences (all)	4	0	
Prostatitis	Additional description: Prostatitis		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Uterine prolapse	Additional description: Uterine prolapse		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Bronchial wall thickening	Additional description: Bronchial wall thickening		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Cough	Additional description: Cough		
subjects affected / exposed	4 / 40 (10.00%)	4 / 26 (15.38%)	
occurrences (all)	6	4	
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	3 / 40 (7.50%)	1 / 26 (3.85%)	
occurrences (all)	3	1	
Dyspnoea exertional	Additional description: Dyspnoea exertional		
subjects affected / exposed	1 / 40 (2.50%)	2 / 26 (7.69%)	
occurrences (all)	1	2	
Emphysema	Additional description: Emphysema		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Epistaxis	Additional description: Epistaxis		
subjects affected / exposed	6 / 40 (15.00%)	4 / 26 (15.38%)	
occurrences (all)	8	4	
Nasal dryness	Additional description: Nasal dryness		
subjects affected / exposed	1 / 40 (2.50%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Nasal mucosal disorder	Additional description: Nasal mucosal disorder		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain	Additional description: Oropharyngeal pain		

subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Pleural effusion	Additional description: Pleural effusion		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Pneumonitis	Additional description: Pneumonitis		
subjects affected / exposed	2 / 40 (5.00%)	1 / 26 (3.85%)	
occurrences (all)	2	1	
Rhinorrhoea	Additional description: Rhinorrhoea		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Psychiatric disorders			
Agitation	Additional description: Agitation		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Burnout syndrome	Additional description: Burnout syndrome		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Depression	Additional description: Depression		
subjects affected / exposed	2 / 40 (5.00%)	1 / 26 (3.85%)	
occurrences (all)	2	1	
Insomnia	Additional description: Insomnia		
subjects affected / exposed	2 / 40 (5.00%)	2 / 26 (7.69%)	
occurrences (all)	3	2	
Sleep disorder	Additional description: Sleep disorder		
subjects affected / exposed	1 / 40 (2.50%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Hepatobiliary disorders			
Cholecystitis chronic	Additional description: Cholecystitis chronic		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Hepatic steatosis	Additional description: Hepatic steatosis		
subjects affected / exposed	2 / 40 (5.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Hepatotoxicity	Additional description: Hepatotoxicity		

subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Steatohepatitis	Additional description: Steatohepatitis		
subjects affected / exposed	2 / 40 (5.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Investigations			
blood bilirubin increased	Additional description: blood bilirubin increased		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Blood creatinine increased	Additional description: Blood creatinine increased		
subjects affected / exposed	1 / 40 (2.50%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Borrelia test negative	Additional description: Borrelia test negative		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Endoscopy upper gastrointestinal tract	Additional description: Endoscopy upper gastrointestinal tract		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Eosinophil count increased	Additional description: Eosinophil count increased		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Gamma-glutamyltransferase increased	Additional description: Gamma-glutamyltransferase increased		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Haematocrit increased	Additional description: Haematocrit increased		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Hepatic enzyme increased	Additional description: Hepatic enzyme increased		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Laboratory test interference	Additional description: Laboratory test interference		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Prostatic specific antigen increased	Additional description: Prostatic specific antigen increased		

subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Weight decreased	Additional description: Weight decreased		
subjects affected / exposed	2 / 40 (5.00%)	2 / 26 (7.69%)	
occurrences (all)	2	2	
Weight increased	Additional description: Weight increased		
subjects affected / exposed	2 / 40 (5.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Injury, poisoning and procedural complications			
Arthropod bite	Additional description: Arthropod bite		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Contusion	Additional description: Contusion		
subjects affected / exposed	2 / 40 (5.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Fracture	Additional description: Fracture		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Head injury	Additional description: Head injury		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Infusion related reaction	Additional description: Infusion related reaction		
subjects affected / exposed	14 / 40 (35.00%)	9 / 26 (34.62%)	
occurrences (all)	30	14	
Joint dislocation	Additional description: Joint dislocation		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Lumbar vertebral fracture	Additional description: Lumbar vertebral fracture		
subjects affected / exposed	1 / 40 (2.50%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Pneumonitis chemical	Additional description: Pneumonitis chemical		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Post procedural haematoma	Additional description: Post procedural haematoma		

subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Scratch	Additional description: Scratch		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Thermal burn	Additional description: Thermal burn		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Thoracic vertebral fracture	Additional description: Thoracic vertebral fracture		
subjects affected / exposed	0 / 40 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Tooth fracture	Additional description: Tooth fracture		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Congenital, familial and genetic disorders			
Gilbert's syndrome	Additional description: Gilbert's syndrome		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Cardiac disorders			
Atrial fibrillation	Additional description: Atrial fibrillation		
subjects affected / exposed	1 / 40 (2.50%)	2 / 26 (7.69%)	
occurrences (all)	1	2	
Cardiovascular disorder	Additional description: Cardiovascular disorder		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Coronary artery disease	Additional description: Coronary artery disease		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Diastolic dysfunction	Additional description: Diastolic dysfunction		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Extrasystoles	Additional description: Extrasystoles		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Mitral valve incompetence	Additional description: Mitral valve incompetence		

subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Palpitations	Additional description: Palpitations		
subjects affected / exposed	2 / 40 (5.00%)	1 / 26 (3.85%)	
occurrences (all)	3	1	
Tricuspid valve incompetence	Additional description: Tricuspid valve incompetence		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Nervous system disorders			
Burning sensation	Additional description: Burning sensation		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Carpal tunnel syndrome	Additional description: Carpal tunnel syndrome		
subjects affected / exposed	2 / 40 (5.00%)	1 / 26 (3.85%)	
occurrences (all)	2	1	
Cerebral amyloid angiopathy	Additional description: Cerebral amyloid angiopathy		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Cerebral atrophy	Additional description: Cerebral atrophy		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Cluster headache	Additional description: Cluster headache		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Dizziness	Additional description: Dizziness		
subjects affected / exposed	4 / 40 (10.00%)	2 / 26 (7.69%)	
occurrences (all)	4	2	
Encephalopathy	Additional description: Encephalopathy		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Headache	Additional description: Headache		
subjects affected / exposed	7 / 40 (17.50%)	2 / 26 (7.69%)	
occurrences (all)	10	2	
Hyperaesthesia	Additional description: Hyperaesthesia		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	

Hypoaesthesia	Additional description: Hypoaesthesia		
subjects affected / exposed	1 / 40 (2.50%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Hypotonia	Additional description: Hypotonia		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Memory impairment	Additional description: Memory impairment		
subjects affected / exposed	3 / 40 (7.50%)	0 / 26 (0.00%)	
occurrences (all)	3	0	
Mental impairment	Additional description: Mental impairment		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Muscle spasticity	Additional description: Muscle spasticity		
subjects affected / exposed	2 / 40 (5.00%)	0 / 26 (0.00%)	
occurrences (all)	3	0	
Nerve compression	Additional description: Nerve compression		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Nervous system disorder	Additional description: Nervous system disorder		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Paraesthesia	Additional description: Paraesthesia		
subjects affected / exposed	4 / 40 (10.00%)	1 / 26 (3.85%)	
occurrences (all)	4	1	
Peripheral sensory neuropathy	Additional description: Peripheral sensory neuropathy		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Polyneuropathy	Additional description: Polyneuropathy		
subjects affected / exposed	1 / 40 (2.50%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Sciatica	Additional description: Sciatica		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Syncope	Additional description: Syncope		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	

Tremor	Additional description: Tremor		
subjects affected / exposed	1 / 40 (2.50%)	3 / 26 (11.54%)	
occurrences (all)	1	3	
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
subjects affected / exposed	3 / 40 (7.50%)	4 / 26 (15.38%)	
occurrences (all)	5	4	
Leukopenia	Additional description: Leukopenia		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Lymph node pain	Additional description: Lymph node pain		
subjects affected / exposed	0 / 40 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Neutropenia	Additional description: Neutropenia		
subjects affected / exposed	16 / 40 (40.00%)	9 / 26 (34.62%)	
occurrences (all)	21	17	
Perisplenitis	Additional description: Perisplenitis		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed	4 / 40 (10.00%)	4 / 26 (15.38%)	
occurrences (all)	4	4	
Ear and labyrinth disorders			
Ear pain	Additional description: Ear pain		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Inner ear disorder	Additional description: Inner ear disorder		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	2	
Tinnitus	Additional description: Tinnitus		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Vertigo	Additional description: Vertigo		
subjects affected / exposed	5 / 40 (12.50%)	4 / 26 (15.38%)	
occurrences (all)	6	5	
Eye disorders			

Blepharitis	Additional description: Blepharitis		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Cataract	Additional description: Cataract		
subjects affected / exposed	2 / 40 (5.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Conjunctival haemorrhage	Additional description: Conjunctival haemorrhage		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Dry eye	Additional description: Dry eye		
subjects affected / exposed	1 / 40 (2.50%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Exophthalmos	Additional description: Exophthalmos		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Eye haematoma	Additional description: Eye haematoma		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Eye haemorrhage	Additional description: Eye haemorrhage		
subjects affected / exposed	3 / 40 (7.50%)	0 / 26 (0.00%)	
occurrences (all)	3	0	
Eyelid oedema	Additional description: Eyelid oedema		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Glaucoma	Additional description: Glaucoma		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Lacrimation increased	Additional description: Lacrimation increased		
subjects affected / exposed	0 / 40 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Periorbital oedema	Additional description: Periorbital oedema		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Vision blurred	Additional description: Vision blurred		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	

Visual impairment	Additional description: Visual impairment		
subjects affected / exposed	1 / 40 (2.50%)	1 / 26 (3.85%)	
occurrences (all)	1	2	
Gastrointestinal disorders			
Abdominal discomfort	Additional description: Abdominal discomfort		
subjects affected / exposed	2 / 40 (5.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Abdominal distension	Additional description: Abdominal distension		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed	1 / 40 (2.50%)	2 / 26 (7.69%)	
occurrences (all)	2	3	
Abdominal pain upper	Additional description: Abdominal pain upper		
subjects affected / exposed	5 / 40 (12.50%)	4 / 26 (15.38%)	
occurrences (all)	6	5	
Anal haemorrhage	Additional description: Anal haemorrhage		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Aphthous ulcer	Additional description: Aphthous ulcer		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Constipation	Additional description: Constipation		
subjects affected / exposed	4 / 40 (10.00%)	2 / 26 (7.69%)	
occurrences (all)	5	2	
Dental caries	Additional description: Dental caries		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	21 / 40 (52.50%)	9 / 26 (34.62%)	
occurrences (all)	38	15	
Diverticulum	Additional description: Diverticulum		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Dry mouth	Additional description: Dry mouth		

subjects affected / exposed	1 / 40 (2.50%)	2 / 26 (7.69%)	
occurrences (all)	1	2	
Dyspepsia	Additional description: Dyspepsia		
subjects affected / exposed	3 / 40 (7.50%)	2 / 26 (7.69%)	
occurrences (all)	5	2	
Endocrine disorders	Additional description: Endocrine disorders		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Faecaloma	Additional description: Faecaloma		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Faeces discoloured	Additional description: Faeces discoloured		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Flatulence	Additional description: Flatulence		
subjects affected / exposed	2 / 40 (5.00%)	2 / 26 (7.69%)	
occurrences (all)	2	3	
Gastric ulcer	Additional description: Gastric ulcer		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Gastritis	Additional description: Gastritis		
subjects affected / exposed	2 / 40 (5.00%)	1 / 26 (3.85%)	
occurrences (all)	2	1	
Gastritis erosive	Additional description: Gastritis erosive		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Gastrointestinal disorder	Additional description: Gastrointestinal disorder		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Gastrointestinal pain	Additional description: Gastrointestinal pain		
subjects affected / exposed	2 / 40 (5.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Gastrooesophageal reflux disease	Additional description: Gastrooesophageal reflux disease		
subjects affected / exposed	3 / 40 (7.50%)	5 / 26 (19.23%)	
occurrences (all)	3	6	
Gingival bleeding	Additional description: Gingival bleeding		

subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Haemorrhoidal haemorrhage	Additional description: Haemorrhoidal haemorrhage		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Haemorrhoids	Additional description: Haemorrhoids		
subjects affected / exposed	2 / 40 (5.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Hiatus hernia	Additional description: Hiatus hernia		
subjects affected / exposed	1 / 40 (2.50%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Inguinal hernia	Additional description: Inguinal hernia		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Large intestine polyp	Additional description: Large intestine polyp		
subjects affected / exposed	0 / 40 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Leukoplakia oral	Additional description: Leukoplakia oral		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Nausea	Additional description: Nausea		
subjects affected / exposed	12 / 40 (30.00%)	7 / 26 (26.92%)	
occurrences (all)	18	10	
Oral dysaesthesia	Additional description: Oral dysaesthesia		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Paraesthesia oral	Additional description: Paraesthesia oral		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Periodontal disease	Additional description: Periodontal disease		
subjects affected / exposed	2 / 40 (5.00%)	0 / 26 (0.00%)	
occurrences (all)	3	0	
Stomatitis	Additional description: Stomatitis		
subjects affected / exposed	2 / 40 (5.00%)	0 / 26 (0.00%)	
occurrences (all)	3	0	
Tooth loss	Additional description: Tooth loss		

subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	2	
Toothache	Additional description: Toothache		
subjects affected / exposed	2 / 40 (5.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Acne	Additional description: Acne		
subjects affected / exposed	2 / 40 (5.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Actinic keratosis	Additional description: Actinic keratosis		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Alopecia	Additional description: Alopecia		
subjects affected / exposed	2 / 40 (5.00%)	1 / 26 (3.85%)	
occurrences (all)	2	1	
Blood blister	Additional description: Blood blister		
subjects affected / exposed	2 / 40 (5.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Decubitus ulcer	Additional description: Decubitus ulcer		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Dermatitis	Additional description: Dermatitis		
subjects affected / exposed	2 / 40 (5.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Dermatitis allergic	Additional description: Dermatitis allergic		
subjects affected / exposed	2 / 40 (5.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Dry skin	Additional description: Dry skin		
subjects affected / exposed	3 / 40 (7.50%)	2 / 26 (7.69%)	
occurrences (all)	3	2	
Ecchymosis	Additional description: Ecchymosis		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Eczema	Additional description: Eczema		
subjects affected / exposed	3 / 40 (7.50%)	1 / 26 (3.85%)	
occurrences (all)	3	1	

Erythema	Additional description: Erythema		
subjects affected / exposed	3 / 40 (7.50%)	1 / 26 (3.85%)	
occurrences (all)	3	2	
Hyperhidrosis	Additional description: Hyperhidrosis		
subjects affected / exposed	2 / 40 (5.00%)	3 / 26 (11.54%)	
occurrences (all)	2	3	
Hypotrichosis	Additional description: Hypotrichosis		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Nail ridging	Additional description: Nail ridging		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Night sweats	Additional description: Night sweats		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Onychoclasis	Additional description: Onychoclasis		
subjects affected / exposed	7 / 40 (17.50%)	1 / 26 (3.85%)	
occurrences (all)	8	1	
Petechiae	Additional description: Petechiae		
subjects affected / exposed	2 / 40 (5.00%)	3 / 26 (11.54%)	
occurrences (all)	2	3	
Pruritus	Additional description: Pruritus		
subjects affected / exposed	7 / 40 (17.50%)	2 / 26 (7.69%)	
occurrences (all)	7	2	
Pruritus generalised	Additional description: Pruritus generalised		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Psoriasis	Additional description: Psoriasis		
subjects affected / exposed	2 / 40 (5.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Rash	Additional description: Rash		
subjects affected / exposed	15 / 40 (37.50%)	8 / 26 (30.77%)	
occurrences (all)	19	8	
Rash maculo-papular	Additional description: Rash maculo-papular		
subjects affected / exposed	4 / 40 (10.00%)	0 / 26 (0.00%)	
occurrences (all)	6	0	

Rash papular	Additional description: Rash papular		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Skin burning sensation	Additional description: Skin burning sensation		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Skin fissures	Additional description: Skin fissures		
subjects affected / exposed	2 / 40 (5.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Skin lesion	Additional description: Skin lesion		
subjects affected / exposed	2 / 40 (5.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Skin ulcer	Additional description: Skin ulcer		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	5	
Renal and urinary disorders			
Acute kidney injury	Additional description: Acute kidney injury		
subjects affected / exposed	3 / 40 (7.50%)	0 / 26 (0.00%)	
occurrences (all)	4	0	
Chronic kidney disease	Additional description: Chronic kidney disease		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Cystitis noninfective	Additional description: Cystitis noninfective		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	2	
Dysuria	Additional description: Dysuria		
subjects affected / exposed	1 / 40 (2.50%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Haematuria	Additional description: Haematuria		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Nocturia	Additional description: Nocturia		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Pollakiuria	Additional description: Pollakiuria		

subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Strangury	Additional description: Strangury		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Urge incontinence	Additional description: Urge incontinence		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Urinary tract disorder	Additional description: Urinary tract disorder		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Urinary tract obstruction	Additional description: Urinary tract obstruction		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Endocrine disorders			
Hyperthyroidism	Additional description: Hyperthyroidism		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Hypothyroidism	Additional description: Hypothyroidism		
subjects affected / exposed	1 / 40 (2.50%)	2 / 26 (7.69%)	
occurrences (all)	1	2	
Thyroid cyst	Additional description: Thyroid cyst		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Thyroid mass	Additional description: Thyroid mass		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia	Additional description: Arthralgia		
subjects affected / exposed	8 / 40 (20.00%)	5 / 26 (19.23%)	
occurrences (all)	11	7	
Arthritis	Additional description: Arthritis		
subjects affected / exposed	1 / 40 (2.50%)	2 / 26 (7.69%)	
occurrences (all)	1	2	
Back pain	Additional description: Back pain		

subjects affected / exposed	7 / 40 (17.50%)	2 / 26 (7.69%)	
occurrences (all)	8	2	
Bone pain	Additional description: Bone pain		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Bursitis	Additional description: Bursitis		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Gouty arthritis	Additional description: Gouty arthritis		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Intervertebral disc protrusion	Additional description: Intervertebral disc protrusion		
subjects affected / exposed	1 / 40 (2.50%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Joint swelling	Additional description: Joint swelling		
subjects affected / exposed	1 / 40 (2.50%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Muscle spasms	Additional description: Muscle spasms		
subjects affected / exposed	5 / 40 (12.50%)	8 / 26 (30.77%)	
occurrences (all)	10	10	
Muscle tightness	Additional description: Muscle tightness		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal chest pain	Additional description: Musculoskeletal chest pain		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain	Additional description: Musculoskeletal pain		
subjects affected / exposed	3 / 40 (7.50%)	2 / 26 (7.69%)	
occurrences (all)	4	2	
Myalgia	Additional description: Myalgia		
subjects affected / exposed	10 / 40 (25.00%)	2 / 26 (7.69%)	
occurrences (all)	12	2	
Myosclerosis	Additional description: Myosclerosis		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Neck pain	Additional description: Neck pain		

subjects affected / exposed	2 / 40 (5.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Osteoarthritis	Additional description: Osteoarthritis		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Osteoporosis	Additional description: Osteoporosis		
subjects affected / exposed	2 / 40 (5.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Pain in extremity	Additional description: Pain in extremity		
subjects affected / exposed	2 / 40 (5.00%)	2 / 26 (7.69%)	
occurrences (all)	2	3	
Plantar fasciitis	Additional description: Plantar fasciitis		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Polyarthritis	Additional description: Polyarthritis		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Synovial cyst	Additional description: Synovial cyst		
subjects affected / exposed	2 / 40 (5.00%)	1 / 26 (3.85%)	
occurrences (all)	2	1	
Tendon disorder	Additional description: Tendon disorder		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Tendonitis	Additional description: Tendonitis		
subjects affected / exposed	2 / 40 (5.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Trigger finger	Additional description: Trigger finger		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Infections and infestations			
Abscess	Additional description: Abscess		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Abscess limb	Additional description: Abscess limb		
subjects affected / exposed	1 / 40 (2.50%)	1 / 26 (3.85%)	
occurrences (all)	1	1	

Anal abscess	Additional description: Anal abscess		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Angular cheilitis	Additional description: Angular cheilitis		
subjects affected / exposed	2 / 40 (5.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Bacterial infection	Additional description: Bacterial infection		
subjects affected / exposed	2 / 40 (5.00%)	1 / 26 (3.85%)	
occurrences (all)	2	1	
Balanitis candida	Additional description: Balanitis candida		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Borrelia infection	Additional description: Borrelia infection		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Bronchitis	Additional description: Bronchitis		
subjects affected / exposed	14 / 40 (35.00%)	5 / 26 (19.23%)	
occurrences (all)	16	8	
Bursitis infective	Additional description: Bursitis infective		
subjects affected / exposed	1 / 40 (2.50%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Chronic sinusitis	Additional description: Chronic sinusitis		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Conjunctivitis	Additional description: Conjunctivitis		
subjects affected / exposed	3 / 40 (7.50%)	4 / 26 (15.38%)	
occurrences (all)	3	4	
Cystitis	Additional description: Cystitis		
subjects affected / exposed	4 / 40 (10.00%)	3 / 26 (11.54%)	
occurrences (all)	5	10	
Diarrhoea infectious	Additional description: Diarrhoea infectious		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Enterocolitis infectious	Additional description: Enterocolitis infectious		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	

Erythema migrans	Additional description: Erythema migrans		
subjects affected / exposed	2 / 40 (5.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Eyelid infection	Additional description: Eyelid infection		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Febrile Infection	Additional description: Febrile Infection		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Gastric infection	Additional description: Gastric infection		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis	Additional description: Gastroenteritis		
subjects affected / exposed	3 / 40 (7.50%)	0 / 26 (0.00%)	
occurrences (all)	5	0	
Gastroenteritis viral	Additional description: Gastroenteritis viral		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal infection	Additional description: Gastrointestinal infection		
subjects affected / exposed	3 / 40 (7.50%)	1 / 26 (3.85%)	
occurrences (all)	3	1	
Genital infection fungal	Additional description: Genital infection fungal		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Gingivitis	Additional description: Gingivitis		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Herpes virus infection	Additional description: Herpes virus infection		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Herpes zoster	Additional description: Herpes zoster		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Infected bite	Additional description: Infected bite		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	

Infection	Additional description: Infection		
subjects affected / exposed	1 / 40 (2.50%)	2 / 26 (7.69%)	
occurrences (all)	2	3	
Infection susceptibility increased	Additional description: Infection susceptibility increased		
subjects affected / exposed	2 / 40 (5.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Influenza	Additional description: Influenza		
subjects affected / exposed	1 / 40 (2.50%)	2 / 26 (7.69%)	
occurrences (all)	1	2	
Lip infection	Additional description: Lip infection		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Localised infection	Additional description: Localised infection		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis	Additional description: Nasopharyngitis		
subjects affected / exposed	21 / 40 (52.50%)	8 / 26 (30.77%)	
occurrences (all)	32	13	
Neutropenic infection	Additional description: Neutropenic infection		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	2	
Onychomycosis	Additional description: Onychomycosis		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Oral candidiasis	Additional description: Oral candidiasis		
subjects affected / exposed	3 / 40 (7.50%)	1 / 26 (3.85%)	
occurrences (all)	3	1	
Oral herpes	Additional description: Oral herpes		
subjects affected / exposed	5 / 40 (12.50%)	2 / 26 (7.69%)	
occurrences (all)	7	2	
Osteomyelitis	Additional description: Osteomyelitis		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Otitis media	Additional description: Otitis media		
subjects affected / exposed	3 / 40 (7.50%)	0 / 26 (0.00%)	
occurrences (all)	3	0	

Paronychia	Additional description: Paronychia		
subjects affected / exposed	2 / 40 (5.00%)	0 / 26 (0.00%)	
occurrences (all)	5	0	
Parotitis	Additional description: Parotitis		
subjects affected / exposed	1 / 40 (2.50%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Periodontitis	Additional description: Periodontitis		
subjects affected / exposed	2 / 40 (5.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Pertussis	Additional description: Pertussis		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Pharyngitis	Additional description: Pharyngitis		
subjects affected / exposed	5 / 40 (12.50%)	2 / 26 (7.69%)	
occurrences (all)	7	2	
Pneumonia	Additional description: Pneumonia		
subjects affected / exposed	4 / 40 (10.00%)	3 / 26 (11.54%)	
occurrences (all)	4	3	
Pseudomonas infection	Additional description: Pseudomonas infection		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Respiratory tract infection	Additional description: Respiratory tract infection		
subjects affected / exposed	3 / 40 (7.50%)	4 / 26 (15.38%)	
occurrences (all)	3	5	
Rhinitis	Additional description: Rhinitis		
subjects affected / exposed	4 / 40 (10.00%)	2 / 26 (7.69%)	
occurrences (all)	6	2	
Root canal infection	Additional description: Root canal infection		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Sinusitis	Additional description: Sinusitis		
subjects affected / exposed	2 / 40 (5.00%)	3 / 26 (11.54%)	
occurrences (all)	3	6	
Skin infection	Additional description: Skin infection		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	

Soft tissue infection	Additional description: Soft tissue infection		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Systemic infection	Additional description: Systemic infection		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Tonsillitis	Additional description: Tonsillitis		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Upper respiratory tract infection	Additional description: Upper respiratory tract infection		
subjects affected / exposed	9 / 40 (22.50%)	2 / 26 (7.69%)	
occurrences (all)	11	3	
Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed	7 / 40 (17.50%)	1 / 26 (3.85%)	
occurrences (all)	11	4	
Viral oesophagitis	Additional description: Viral oesophagitis		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Viral pharyngitis	Additional description: Viral pharyngitis		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Wound infection	Additional description: Wound infection		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Abnormal loss of weight	Additional description: Abnormal loss of weight		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Decreased appetite	Additional description: Decreased appetite		
subjects affected / exposed	2 / 40 (5.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Gout	Additional description: Gout		
subjects affected / exposed	1 / 40 (2.50%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Hypercalcaemia	Additional description: Hypercalcaemia		

subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Hypercholesterolaemia	Additional description: Hypercholesterolaemia		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Hyperglycaemia	Additional description: Hyperglycaemia		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Hyperkalaemia	Additional description: Hyperkalaemia		
subjects affected / exposed	1 / 40 (2.50%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Hyperuricaemia	Additional description: Hyperuricaemia		
subjects affected / exposed	4 / 40 (10.00%)	1 / 26 (3.85%)	
occurrences (all)	5	1	
Hypokalaemia	Additional description: Hypokalaemia		
subjects affected / exposed	1 / 40 (2.50%)	2 / 26 (7.69%)	
occurrences (all)	1	3	
Iron overload	Additional description: Iron overload		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Vitamin D deficiency	Additional description: Vitamin D deficiency		
subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Weight fluctuation	Additional description: Weight fluctuation		
subjects affected / exposed	0 / 40 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 July 2016	Due to one case of interstitial lung disease, which is described in an addendum to the IB of ibrutinib, this risk and recommendations for the potential management were included into the protocol. The recommendation for the interval between administration of allopurinol and bendamustine was aligned with the recommendation of other GCLLSG protocols, e.g. the CLL2-BAG protocol. It is now stated that the interval between allopurinol and bendamustine administration should be ≥ 24-48 hrs. Due to the expiry of the patent protection for bendamustine in Germany and because commercially available bendamustine is used for the debulking treatment in this trial, an addendum for the protocol was used to allow the pharmacists to use generic medicinal products which they have in stock. With this amendment, this is now also implemented in the trial protocol and the specification of the tradename was deleted throughout the protocol. Due to HBV reactivation in another trial in a patient who did not receive a prophylactic treatment for HBV despite a positive anti-HBc, this is now recommended Due to queries by the treating physicians/investigators if heparine can be used concomitantly with ibrutinib, this information was also included in the protocol. Also, the information regarding the use of vitamin k antagonists and novel anticoagulants was updated
09 May 2017	Ofatumumab is now also licensed in combination with fludarabine and cyclophosphamide (FC) for the use in patients with relapsed CLL, this was included in the second chapter " General aspects of the drugs used in the trial" Additional information on the potential risk of liver failure with ibrutinib was included into the paragraph "diarrhea and gastrointestinal AEs" Frequent updates of the IB for ibrutinib and publication of addenda to the IB have necessitated amendments of trial protocol and patient´s informed consent without adding clinically relevant information. Therefore and because ibrutinib is approved since 2014, it was decided together with the leading EC to change the safety reference document from IB to SMPC.
12 March 2018	Additional information regarding safety of vaccinations with live, attenuated vaccines and safety and efficacy of other vaccinations were included into chapter "8.5.2 Prohibited medications and medications to be used with caution" Additional information regarding a potential fetal B-cell depletion was included into the Paragraph "Ofatumumab" in chapter "8.8.1.4 Teratogenicity and mutagenicity". Additional information on the potential risk of Hepatitis B reactivation with ibrutinib was included into the paragraph "Cytopenias and infections with ibrutinib" and as a new paragraph into the chapter "Potential risks with Ibrutinib". As ibrutinib may also cause other types of cardiac arrhythmias, this information was included and the title of the respective chapter was re-named from "Atrial fibrillation and worsening of pre-exsisting cardiac conditions" to "Cardiac arrythmias and worsening of …". Based on the experiences from the primary endpoint analyses of the CLL2-BIG and CLL2-BAG trials, the statistical sections of the protocol were updated. The per protocol analysis was removed. The CLL2-BIO protocol still contains two populations, the safety population and the full analysis set. The latter comprises of all enrolled patients who received at least two complete cycles of induction therapy. This already represents a relatively strict definition due to the target number of treatment cycles. According to our experiences from the final analyses of the CLL2-BIG and CLL2-BAG trials, most of the critical protocol violations were prevented by our central screening process. Thus, the per protocol population and the full analysis set were somewhat identical.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

On 28 February 2019, the European Commission withdrew the marketing authorisation for Arzerra (ofatumumab) in the European Union (EU). The withdrawal was at the request of the marketing authorisation holder, Novartis Europharm Limited.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32107341