

**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
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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 assessment. 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 participation.

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
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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
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Arm description:

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

Primary: Primary endpoint

End point title	Primary endpoint ^[1]
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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
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	FL patient
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Reporting group description: -

Reporting group title	RR patient
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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	Additional description: Cerebral microangiopathy		
	Cerebral microangiopathy		
	subjects affected / exposed	1 / 40 (2.50%)	0 / 26 (0.00%)
	occurrences causally related to treatment / all	0 / 1	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			

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

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

Menorrhagia subjects affected / exposed occurrences (all)	Additional description: Menorrhagia	
	2 / 40 (5.00%) 4	0 / 26 (0.00%) 0
Prostatitis subjects affected / exposed occurrences (all)	Additional description: Prostatitis	
	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0
Uterine prolapse subjects affected / exposed occurrences (all)	Additional description: Uterine prolapse	
	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0
Respiratory, thoracic and mediastinal disorders		
Bronchial wall thickening subjects affected / exposed occurrences (all)	Additional description: Bronchial wall thickening	
	0 / 40 (0.00%) 0	1 / 26 (3.85%) 1
Cough subjects affected / exposed occurrences (all)	Additional description: Cough	
	4 / 40 (10.00%) 6	4 / 26 (15.38%) 4
Dyspnoea subjects affected / exposed occurrences (all)	Additional description: Dyspnoea	
	3 / 40 (7.50%) 3	1 / 26 (3.85%) 1
Dyspnoea exertional subjects affected / exposed occurrences (all)	Additional description: Dyspnoea exertional	
	1 / 40 (2.50%) 1	2 / 26 (7.69%) 2
Emphysema subjects affected / exposed occurrences (all)	Additional description: Emphysema	
	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0
Epistaxis subjects affected / exposed occurrences (all)	Additional description: Epistaxis	
	6 / 40 (15.00%) 8	4 / 26 (15.38%) 4
Nasal dryness subjects affected / exposed occurrences (all)	Additional description: Nasal dryness	
	1 / 40 (2.50%) 1	1 / 26 (3.85%) 1
Nasal mucosal disorder subjects affected / exposed occurrences (all)	Additional description: Nasal mucosal disorder	
	1 / 40 (2.50%) 1	0 / 26 (0.00%) 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 occurrences (all)	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0	
Steatohepatitis	Additional description: Steatohepatitis		
subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2	0 / 26 (0.00%) 0	
Investigations			
blood bilirubin increased	Additional description: blood bilirubin increased		
subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0	
Blood creatinine increased	Additional description: Blood creatinine increased		
subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	1 / 26 (3.85%) 1	
Borrelia test negative	Additional description: Borrelia test negative		
subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0	
Endoscopy upper gastrointestinal tract	Additional description: Endoscopy upper gastrointestinal tract		
subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0	
Eosinophil count increased	Additional description: Eosinophil count increased		
subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0	
Gamma-glutamyltransferase increased	Additional description: Gamma-glutamyltransferase increased		
subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	1 / 26 (3.85%) 1	
Haematocrit increased	Additional description: Haematocrit increased		
subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0	
Hepatic enzyme increased	Additional description: Hepatic enzyme increased		
subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0	
Laboratory test interference	Additional description: Laboratory test interference		
subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	1 / 26 (3.85%) 1	
Prostatic specific antigen increased	Additional description: Prostatic specific antigen increased		

subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0	
Weight decreased	Additional description: Weight decreased		
subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2	2 / 26 (7.69%) 2	
Weight increased	Additional description: Weight increased		
subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2	0 / 26 (0.00%) 0	
Injury, poisoning and procedural complications			
Arthropod bite	Additional description: Arthropod bite		
subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0	
Contusion	Additional description: Contusion		
subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2	0 / 26 (0.00%) 0	
Fracture	Additional description: Fracture		
subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0	
Head injury	Additional description: Head injury		
subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0	
Infusion related reaction	Additional description: Infusion related reaction		
subjects affected / exposed occurrences (all)	14 / 40 (35.00%) 30	9 / 26 (34.62%) 14	
Joint dislocation	Additional description: Joint dislocation		
subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0	
Lumbar vertebral fracture	Additional description: Lumbar vertebral fracture		
subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	1 / 26 (3.85%) 1	
Pneumonitis chemical	Additional description: Pneumonitis chemical		
subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	1 / 26 (3.85%) 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 occurrences (all)	0 / 40 (0.00%) 0	1 / 26 (3.85%) 1	
Palpitations	Additional description: Palpitations		
subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 3	1 / 26 (3.85%) 1	
Tricuspid valve incompetence	Additional description: Tricuspid valve incompetence		
subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	1 / 26 (3.85%) 1	
Nervous system disorders			
Burning sensation	Additional description: Burning sensation		
subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	1 / 26 (3.85%) 1	
Carpal tunnel syndrome	Additional description: Carpal tunnel syndrome		
subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2	1 / 26 (3.85%) 1	
Cerebral amyloid angiopathy	Additional description: Cerebral amyloid angiopathy		
subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0	
Cerebral atrophy	Additional description: Cerebral atrophy		
subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0	
Cluster headache	Additional description: Cluster headache		
subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	1 / 26 (3.85%) 1	
Dizziness	Additional description: Dizziness		
subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 4	2 / 26 (7.69%) 2	
Encephalopathy	Additional description: Encephalopathy		
subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0	
Headache	Additional description: Headache		
subjects affected / exposed occurrences (all)	7 / 40 (17.50%) 10	2 / 26 (7.69%) 2	
Hyperaesthesia	Additional description: Hyperaesthesia		
subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	1 / 26 (3.85%) 1	

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

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

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

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

subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	2 / 26 (7.69%) 2	
Dyspepsia	Additional description: Dyspepsia		
subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 5	2 / 26 (7.69%) 2	
Endocrine disorders	Additional description: Endocrine disorders		
subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0	
Faecaloma	Additional description: Faecaloma		
subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0	
Faeces discoloured	Additional description: Faeces discoloured		
subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	1 / 26 (3.85%) 1	
Flatulence	Additional description: Flatulence		
subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2	2 / 26 (7.69%) 3	
Gastric ulcer	Additional description: Gastric ulcer		
subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0	
Gastritis	Additional description: Gastritis		
subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2	1 / 26 (3.85%) 1	
Gastritis erosive	Additional description: Gastritis erosive		
subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	1 / 26 (3.85%) 1	
Gastrointestinal disorder	Additional description: Gastrointestinal disorder		
subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	1 / 26 (3.85%) 1	
Gastrointestinal pain	Additional description: Gastrointestinal pain		
subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2	0 / 26 (0.00%) 0	
Gastrooesophageal reflux disease	Additional description: Gastrooesophageal reflux disease		
subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3	5 / 26 (19.23%) 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 occurrences (all)	0 / 40 (0.00%) 0	1 / 26 (3.85%) 2	
Toothache	Additional description: Toothache		
subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2	0 / 26 (0.00%) 0	
Skin and subcutaneous tissue disorders	Additional description: Acne		
Acne	Additional description: Acne		
subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2	0 / 26 (0.00%) 0	
Actinic keratosis	Additional description: Actinic keratosis		
subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	1 / 26 (3.85%) 1	
Alopecia	Additional description: Alopecia		
subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2	1 / 26 (3.85%) 1	
Blood blister	Additional description: Blood blister		
subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2	0 / 26 (0.00%) 0	
Decubitus ulcer	Additional description: Decubitus ulcer		
subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0	
Dermatitis	Additional description: Dermatitis		
subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2	0 / 26 (0.00%) 0	
Dermatitis allergic	Additional description: Dermatitis allergic		
subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2	0 / 26 (0.00%) 0	
Dry skin	Additional description: Dry skin		
subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3	2 / 26 (7.69%) 2	
Ecchymosis	Additional description: Ecchymosis		
subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0	
Eczema	Additional description: Eczema		
subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3	1 / 26 (3.85%) 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
Onychoclasia	Additional description: Onychoclasia	
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 subjects affected / exposed occurrences (all)	Additional description: Rash papular	
	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0
Skin burning sensation subjects affected / exposed occurrences (all)	Additional description: Skin burning sensation	
	0 / 40 (0.00%) 0	1 / 26 (3.85%) 1
Skin fissures subjects affected / exposed occurrences (all)	Additional description: Skin fissures	
	2 / 40 (5.00%) 2	0 / 26 (0.00%) 0
Skin lesion subjects affected / exposed occurrences (all)	Additional description: Skin lesion	
	2 / 40 (5.00%) 2	0 / 26 (0.00%) 0
Skin ulcer subjects affected / exposed occurrences (all)	Additional description: Skin ulcer	
	0 / 40 (0.00%) 0	1 / 26 (3.85%) 5
Renal and urinary disorders		
Acute kidney injury subjects affected / exposed occurrences (all)	Additional description: Acute kidney injury	
	3 / 40 (7.50%) 4	0 / 26 (0.00%) 0
Chronic kidney disease subjects affected / exposed occurrences (all)	Additional description: Chronic kidney disease	
	1 / 40 (2.50%) 2	0 / 26 (0.00%) 0
Cystitis noninfective subjects affected / exposed occurrences (all)	Additional description: Cystitis noninfective	
	0 / 40 (0.00%) 0	1 / 26 (3.85%) 2
Dysuria subjects affected / exposed occurrences (all)	Additional description: Dysuria	
	1 / 40 (2.50%) 1	1 / 26 (3.85%) 1
Haematuria subjects affected / exposed occurrences (all)	Additional description: Haematuria	
	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0
Nocturia subjects affected / exposed occurrences (all)	Additional description: Nocturia	
	0 / 40 (0.00%) 0	1 / 26 (3.85%) 1
Pollakiuria	Additional description: Pollakiuria	

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

subjects affected / exposed occurrences (all)	7 / 40 (17.50%) 8	2 / 26 (7.69%) 2	
Bone pain	Additional description: Bone pain		
subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0	
Bursitis	Additional description: Bursitis		
subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	1 / 26 (3.85%) 1	
Gouty arthritis	Additional description: Gouty arthritis		
subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0	
Intervertebral disc protrusion	Additional description: Intervertebral disc protrusion		
subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	1 / 26 (3.85%) 1	
Joint swelling	Additional description: Joint swelling		
subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	1 / 26 (3.85%) 1	
Muscle spasms	Additional description: Muscle spasms		
subjects affected / exposed occurrences (all)	5 / 40 (12.50%) 10	8 / 26 (30.77%) 10	
Muscle tightness	Additional description: Muscle tightness		
subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0	
Musculoskeletal chest pain	Additional description: Musculoskeletal chest pain		
subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0	
Musculoskeletal pain	Additional description: Musculoskeletal pain		
subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 4	2 / 26 (7.69%) 2	
Myalgia	Additional description: Myalgia		
subjects affected / exposed occurrences (all)	10 / 40 (25.00%) 12	2 / 26 (7.69%) 2	
Myosclerosis	Additional description: Myosclerosis		
subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	1 / 26 (3.85%) 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 subjects affected / exposed occurrences (all)	Additional description: Anal abscess	
	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0
Angular cheilitis subjects affected / exposed occurrences (all)	Additional description: Angular cheilitis	
	2 / 40 (5.00%) 2	0 / 26 (0.00%) 0
Bacterial infection subjects affected / exposed occurrences (all)	Additional description: Bacterial infection	
	2 / 40 (5.00%) 2	1 / 26 (3.85%) 1
Balanitis candida subjects affected / exposed occurrences (all)	Additional description: Balanitis candida	
	0 / 40 (0.00%) 0	1 / 26 (3.85%) 1
Borrelia infection subjects affected / exposed occurrences (all)	Additional description: Borrelia infection	
	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0
Bronchitis subjects affected / exposed occurrences (all)	Additional description: Bronchitis	
	14 / 40 (35.00%) 16	5 / 26 (19.23%) 8
Bursitis infective subjects affected / exposed occurrences (all)	Additional description: Bursitis infective	
	1 / 40 (2.50%) 1	1 / 26 (3.85%) 1
Chronic sinusitis subjects affected / exposed occurrences (all)	Additional description: Chronic sinusitis	
	0 / 40 (0.00%) 0	1 / 26 (3.85%) 1
Conjunctivitis subjects affected / exposed occurrences (all)	Additional description: Conjunctivitis	
	3 / 40 (7.50%) 3	4 / 26 (15.38%) 4
Cystitis subjects affected / exposed occurrences (all)	Additional description: Cystitis	
	4 / 40 (10.00%) 5	3 / 26 (11.54%) 10
Diarrhoea infectious subjects affected / exposed occurrences (all)	Additional description: Diarrhoea infectious	
	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0
Enterocolitis infectious subjects affected / exposed occurrences (all)	Additional description: Enterocolitis infectious	
	0 / 40 (0.00%) 0	1 / 26 (3.85%) 1

Erythema migrans subjects affected / exposed occurrences (all)	Additional description: Erythema migrans	
	2 / 40 (5.00%) 2	0 / 26 (0.00%) 0
Eyelid infection subjects affected / exposed occurrences (all)	Additional description: Eyelid infection	
	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0
Febrile Infection subjects affected / exposed occurrences (all)	Additional description: Febrile Infection	
	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0
Gastric infection subjects affected / exposed occurrences (all)	Additional description: Gastric infection	
	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0
Gastroenteritis subjects affected / exposed occurrences (all)	Additional description: Gastroenteritis	
	3 / 40 (7.50%) 5	0 / 26 (0.00%) 0
Gastroenteritis viral subjects affected / exposed occurrences (all)	Additional description: Gastroenteritis viral	
	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0
Gastrointestinal infection subjects affected / exposed occurrences (all)	Additional description: Gastrointestinal infection	
	3 / 40 (7.50%) 3	1 / 26 (3.85%) 1
Genital infection fungal subjects affected / exposed occurrences (all)	Additional description: Genital infection fungal	
	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0
Gingivitis subjects affected / exposed occurrences (all)	Additional description: Gingivitis	
	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0
Herpes virus infection subjects affected / exposed occurrences (all)	Additional description: Herpes virus infection	
	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0
Herpes zoster subjects affected / exposed occurrences (all)	Additional description: Herpes zoster	
	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0
Infected bite subjects affected / exposed occurrences (all)	Additional description: Infected bite	
	1 / 40 (2.50%) 1	0 / 26 (0.00%) 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 subjects affected / exposed occurrences (all)	Additional description: Soft tissue infection	
	0 / 40 (0.00%) 0	1 / 26 (3.85%) 1
Systemic infection subjects affected / exposed occurrences (all)	Additional description: Systemic infection	
	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0
Tonsillitis subjects affected / exposed occurrences (all)	Additional description: Tonsillitis	
	0 / 40 (0.00%) 0	1 / 26 (3.85%) 1
Upper respiratory tract infection subjects affected / exposed occurrences (all)	Additional description: Upper respiratory tract infection	
	9 / 40 (22.50%) 11	2 / 26 (7.69%) 3
Urinary tract infection subjects affected / exposed occurrences (all)	Additional description: Urinary tract infection	
	7 / 40 (17.50%) 11	1 / 26 (3.85%) 4
Viral oesophagitis subjects affected / exposed occurrences (all)	Additional description: Viral oesophagitis	
	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0
Viral pharyngitis subjects affected / exposed occurrences (all)	Additional description: Viral pharyngitis	
	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0
Wound infection subjects affected / exposed occurrences (all)	Additional description: Wound infection	
	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0
Metabolism and nutrition disorders Abnormal loss of weight subjects affected / exposed occurrences (all)	Additional description: Abnormal loss of weight	
	1 / 40 (2.50%) 1	0 / 26 (0.00%) 0
Decreased appetite subjects affected / exposed occurrences (all)	Additional description: Decreased appetite	
	2 / 40 (5.00%) 2	0 / 26 (0.00%) 0
Gout subjects affected / exposed occurrences (all)	Additional description: Gout	
	1 / 40 (2.50%) 1	1 / 26 (3.85%) 1
Hypercalcaemia	Additional description: Hypercalcaemia	

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 July 2016	<p>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.</p> <p>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 $\geq 24-48$ hrs.</p> <p>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.</p> <p>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</p> <p>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</p>
09 May 2017	<p>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"</p> <p>Additional information on the potential risk of liver failure with ibrutinib was included into the paragraph "diarrhea and gastrointestinal AEs"</p> <p>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.</p>
12 March 2018	<p>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"</p> <p>Additional information regarding a potential fetal B-cell depletion was included into the Paragraph "Ofatumumab" in chapter "8.8.1.4 Teratogenicity and mutagenicity".</p> <p>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".</p> <p>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-existing cardiac conditions" to "Cardiac arrhythmias and worsening of ...".</p> <p>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.</p>

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>