Clinical trial results:
A PROSPECTIVE, MULTICENTER, PHASE-II TRIAL EVALUATING EFFICACY AND SAFETY OF BENDAMUSTINE + GA101 (BG) IN PATIENTS WITH RELAPSED CLL FOLLOWED BY MAINTENANCE THERAPY WITH GA101 FOR RESPONDING PATIENTS.

Summary

EudraCT number	2013-001088-22
Trial protocol	DE
Global end of trial date	09 May 2022

Results information

Result version number	v1 (current)
This version publication date	26 May 2023
First version publication date	26 May 2023

Trial information

Trial identification

Sponsor protocol code	CLLR3

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02445131
WHO universal trial number (UTN)	-
Other trial identifiers	PEI: 2121

Notes:

Sponsors

Sponsor organisation name	Städtisches Klinikum München GmbH
Sponsor organisation address	Thalkirchner Str. 48, München, Germany, 80337
Public contact	Emily Holmes, Deutsche CLL Studiengruppe, 0049 22147896118, emily.holmes@uk-koeln.de
Scientific contact	Nadine Kutsch, Deutsche CLL Studiengruppe, 0049 22147888220, nadine.kutsch@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	01 September 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 May 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

A combination therapy with FC + GA101 (FCG) or B + GA101 (BG) followed by a maintenance therapy with GA101 for responding patients might further improve the therapeutic outcome in relapsed CLL. Therefore, the CLLR3 trial was designed to investigate and to evaluate the efficacy and safety of both immunochemotherapies FCG and BG followed additionally by a maintenance therapy with GA101 for patients responding to therapy. Recruitment of the FCG group was prematurely closed in the course of the study. Thus, the CLLR3 trial follows the objective to evaluate the efficacy and safety of induction therapy with BG followed additionally by a maintenance therapy with GA101 for responding patients.

Protection of trial subjects:

The most frequent expected treatment emerged events include hematological toxicities and infectious complications. Both of these toxicities are well known side effects in patients with chronic lymphocytic leukemia during chemoimmunotherapy. Hence, the protocol includes a section detailing the prevention and the treatment options in patients with cytopenia or infections. Also, guidance for infusion related reactions and tumour lysis syndrome were included in the protocol, because these events were frequently associated with chemoimmunotherapy. Worsening of pre-existing cardiac conditions might occur in this patient population, hence a section describing measurements are included in the protocol as well.

Background therapy:

Most patients with CLL will eventually relapse as neither immunochemotherapy nor myeloablative therapy followed by autologous stem cell transplantation have been shown to be curative in CLL. Furthermore, allogeneic stem cell transplantation as curative option is only considered for physically fit patients with a high-risk profile because of a high treatment related mortality. At time point of the planning for this study, there was no standard combination therapy for patients with relapsed or refractory CLL and according to the DGHO guideline, patients with relapsed CLL should be treated within clinical trials, if possible . Cramer et al. showed that therapy regimens chosen for second line treatment after FC or FCR were heterogeneous, which highlights the need to define treatment recommendations for patients with relapsed chronic lymphocytic leukemia in further trials.

Evidence for comparator:

At time point of the planning of this study, there was evidence that the immunochemotherapy with fludarabine, cyclophosphamide and rituximab (FCR) is active in patients with refractory and relapsed CLL. Badoux et al. showed that FCR in relapsed patients leads to an overall response rate of 74 %, an estimated median PFS of 20.9 months (95 % confidence interval (CI), 18.8-27.6 months), as well as an estimated median survival time of 46.7 months (95 % CI, 41.2-53.4 months), and conclude that FCR is active and well tolerated in patients with relapsed CLL.
Besides FCR, the combination of rituximab with bendamustine (BR), a hybrid alkylating agent with properties of a purine-analogue, has been shown to be active in both relapsed and previously untreated CLL patients.

Actual start date of recruitment	02 June 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 27
Worldwide total number of subjects	27
EEA total number of subjects	27

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)	15
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was recruited in November 2014. Due to the low recruitment the FCG-arm was closed in September 2016 (amendment 3). 20 patients have been randomized into the study and 10 patients have been included into the BG-arm until amendment 3. The study recruitment was terminated in April 2018. A total of 27 patients were included.

Pre-assignment

Screening details:

After obtaining informed consent, eligible patients started screening. To verify the eligibility of patients, an internal medical review of the screening documents was performed. Results of the baseline assessments including the completed screening CRF pages were reviewed and approved, if applicable.

Period 1

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

Blinding implementation details:

not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Fludarabine, Cyclophosphamide and Obinutuzumab

Arm description:

Obinutuzumab is administered before the FC infusion. In the first cycle obinutuzumab was administered on day one (100 mg), day two (900 mg), day eight (1000 mg) and day 15 (1000 mg). Obinutuzumab in cycle 1 could be administered either full dose (1000 mg) on day one if the first infusion of 100 mg was well tolerated by the patient or over two consecutive days (100 mg on first day, remaining 900 mg the following day). For all subsequent cycles patients received 1000 mg obinutuzumab on day one.
25 mg/m2 fludarabine were administered as iv infusion over 15 - 30 minutes on day three to five of cycle one or day two to four when obinutuzumab was completely dosed on day one; and day two to four of cycle two to six.
Patients received 250 mg/m2 cyclophosphamide as iv infusion over 15 - 30 minutes on day three to five of cycle one or day two to four when obinutuzumab was completely dosed on day one; and day two to four of cycle two to six.

Arm type	Experimental
Investigational medicinal product name	Fludarabine
Investigational medicinal product code	30590.00.00
Other name	L01AA01
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Fludarabine iv infusion 25 mg/m2 day 3-5 in cycle 1, respectively day 2-4 q4wks, cycle 2 to 6

Cycle 1	Day 3	25 mg/m2
	Day 4	25 mg/m2
	Day 5	25 mg/m2
Cycle 2 - 6	Day 2	25 mg/m2
	Day 3	25 mg/m2
	Day 4	25 mg/m2

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	1001995601
Other name	L01AA01
Pharmaceutical forms	Concentrate for solution for infusion

Routes of administration	Intravenous use

Dosage and administration details:

Cyclophosphamide iv infusion 250 mg/m2 day 3-5 in cycle 1, respectively day 2-4 q4wks, cycle 2 to 6
Cycle 1 Day 3 250 mg/m2
Day 4 250 mg/m2
Day 5 250 mg/m2
Cycle 2 – 6 Day 2 250 mg/m2
Day 3 250 mg/m2
Day 4 250 mg/m2

Investigational medicinal product name	Obinutuzumab
Investigational medicinal product code	R05072759
Other name	Gazyvaro
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

GA101 iv infusion:
Cycle 1 Day 1 100 mg
Day 2 900 mg
Day 8 1000 mg
Day 15 1000 mg
Cycle 2 - 6 Day 1 1000 mg
In case of a response to the induction therapy, a maintenance therapy consisting of 1000 mg Obinutuzumab i.v. every three months for up to two years is applied.

Arm title	Bendamustine and Obinutuzumab

Arm description:

Patients in the BG arm receive Obinutuzumab i.v. over six cycles. On day one of cycle one, the starting dosage is 100mg which is increased to 900 mg on day two of cycle one. On day 8 and 15 of the first cycle, patients receive 1000 mg. In cycles two to six, patients receive 1000 mg Obinutuzumab at day one
of each cycle. Bendamustine is given i.v. at a concentration of 70 mg/m² on day three and four of cycle one and on day two and three of cycles two to six.
In case of a response to the induction therapy, a maintenance therapy consisting of 1000 mg Obinutuzumab i.v. every three months for up to two years is applied.

Arm type	Experimental
Investigational medicinal product name	Obinutuzumab
Investigational medicinal product code	R05072759
Other name	Gazyvaro
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

GA101 iv infusion:
Cycle 1 Day 1 100 mg
Day 2 900 mg
Day 8 1000 mg
Day 15 1000 mg
Cycle 2 - 6 Day 1 1000 mg
In case of a response to the induction therapy, a maintenance therapy consisting of 1000 mg Obinutuzumab i.v. every three months for up to two years is applied.

Investigational medicinal product name	Bendamustine hydrochloride
Investigational medicinal product code	70972.00.00
Other name	Levact
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bendamustine Treatment
Cycle 1 Day 3 70 mg/m²

Day 4 70 mg/m²
Cycle 2 – 6 Day 2 70 mg/m²
Day 3 70 mg/m²

Number of subjects in period 1	Fludarabine, Cyclophosphamide and Obinutuzumab	Bendamustine and Obinutuzumab
Started	10	17
Completed	1	9
Not completed	9	8
Consent withdrawn by subject	2	-
Adverse event, non-fatal	5	4
Progressive disease	2	4

Baseline characteristics

Reporting groups

Reporting group title	Fludarabine, Cyclophosphamide and Obinutuzumab

Reporting group description:

Obinutuzumab is administered before the FC infusion. In the first cycle obinutuzumab was administered on day one (100 mg), day two (900 mg), day eight (1000 mg) and day 15 (1000 mg). Obinutuzumab in cycle 1 could be administered either full dose (1000 mg) on day one if the first infusion of 100 mg was well tolerated by the patient or over two consecutive days (100 mg on first day, remaining 900 mg the following day). For all subsequent cycles patients received 1000 mg obinutuzumab on day one.
25 mg/m2 fludarabine were administered as iv infusion over 15 - 30 minutes on day three to five of cycle one or day two to four when obinutuzumab was completely dosed on day one; and day two to four of cycle two to six.
Patients received 250 mg/m2 cyclophosphamide as iv infusion over 15 - 30 minutes on day three to five of cycle one or day two to four when obinutuzumab was completely dosed on day one; and day two to four of cycle two to six.

Reporting group title	Bendamustine and Obinutuzumab

Reporting group description:

Patients in the BG arm receive Obinutuzumab i.v. over six cycles. On day one of cycle one, the starting dosage is 100mg which is increased to 900 mg on day two of cycle one. On day 8 and 15 of the first cycle, patients receive 1000 mg. In cycles two to six, patients receive 1000 mg Obinutuzumab at day one
of each cycle. Bendamustine is given i.v. at a concentration of 70 mg/m² on day three and four of cycle one and on day two and three of cycles two to six.
In case of a response to the induction therapy, a maintenance therapy consisting of 1000 mg Obinutuzumab i.v. every three months for up to two years is applied.

Reporting group values	Fludarabine, Cyclophosphamide and Obinutuzumab	Bendamustine and Obinutuzumab	Total
Number of subjects	10	17	27
Age categorical			
Age according to categories as below.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	6	9	15
From 65-84 years	4	8	12
85 years and over	0	0	0
Age continuous			
Median age, IQR (interquartile range: 25% - 75% percentiles)			
Units: years			
median	61.5	63.0	
inter-quartile range (Q1-Q3)	57.3 to 68.8	55.0 to 71.5	-
Gender categorical			
Sex: male; female			
Units: Subjects			
Female	2	6	8

Male	8	11	19

CLL-IPI Score			
The International Prognostic Index for Chronic Lymphocytic Leukemia (CLL-IPI) stratifies patients with chronic lymphocytic leukemia into four risk categories.			
Units: Subjects			
Low	1	1	2
Intermediate	4	5	9
High	4	8	12
Very High	1	2	3
missing	0	1	1
Median CIRS Score			
The Cumulative Illness Rating Scale (CIRS) rates 13 body systems on a five-point pathophysiology severity scale to assess comorbidities in different organ systems.			
Units: Score			
median	3	1	
inter-quartile range (Q1-Q3)	0.8 to 4.3	0.5 to 4.0	-
Previous treatments for CLL			
Number of previous treatment lines for CLL were counted.			
Units: numbers			
median	1.5	1	
inter-quartile range (Q1-Q3)	1 to 2	1 to 2	-

End points

End points reporting groups

Reporting group title	Fludarabine, Cyclophosphamide and Obinutuzumab

Reporting group description:

Obinutuzumab is administered before the FC infusion. In the first cycle obinutuzumab was administered on day one (100 mg), day two (900 mg), day eight (1000 mg) and day 15 (1000 mg). Obinutuzumab in cycle 1 could be administered either full dose (1000 mg) on day one if the first infusion of 100 mg was well tolerated by the patient or over two consecutive days (100 mg on first day, remaining 900 mg the following day). For all subsequent cycles patients received 1000 mg obinutuzumab on day one.
25 mg/m2 fludarabine were administered as iv infusion over 15 - 30 minutes on day three to five of cycle one or day two to four when obinutuzumab was completely dosed on day one; and day two to four of cycle two to six.
Patients received 250 mg/m2 cyclophosphamide as iv infusion over 15 - 30 minutes on day three to five of cycle one or day two to four when obinutuzumab was completely dosed on day one; and day two to four of cycle two to six.

Reporting group title	Bendamustine and Obinutuzumab

Reporting group description:

Patients in the BG arm receive Obinutuzumab i.v. over six cycles. On day one of cycle one, the starting dosage is 100mg which is increased to 900 mg on day two of cycle one. On day 8 and 15 of the first cycle, patients receive 1000 mg. In cycles two to six, patients receive 1000 mg Obinutuzumab at day one
of each cycle. Bendamustine is given i.v. at a concentration of 70 mg/m² on day three and four of cycle one and on day two and three of cycles two to six.
In case of a response to the induction therapy, a maintenance therapy consisting of 1000 mg Obinutuzumab i.v. every three months for up to two years is applied.

Primary: Best overall response rate

End point title	Best overall response rate[1]

End point description:

Best overall response rate (ORR) defined as best response assessed until and including response assessment at follow up 2 (6 months after final restaging/ induction), defined by the proportion of patients that responded to therapy. Response is defined as having achieved a CR/ CRi, clinical CR/ CRi or nPR/ PR as best response based on the ITT (intention to treat) population (= number of patients with best response CR/ CRi, clinical CR/ CRi or nPR/ PR divided by the number of the ITT-population). Non-Response is defined by a reported stable disease or progressive disease as the outcome of therapy at follow up 2.

End point type	Primary

End point timeframe:

This primary endpoint is measured for each patient 6 months after the study treatment has been terminated and the final restaging has been performed.

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: The primary efficacy analysis was based on the estimation of the ORR and its corresponding exact confidence interval based on the ITT. According to the study protocol, no confirmatory statistical testing was performed.

End point values	Fludarabine, Cyclophosphamide and Obinutuzumab	Bendamustine and Obinutuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	17		
Units: Percentage				
number (not applicable)				

Overall response rate	40.0	94.1		
95% Confidence interval: lower bound	12.2	71.3		
95% Confidence interval: upper bound	73.8	99.9		

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	BG treatment

Reporting group description: -

Reporting group title	FCG treatment

Reporting group description: -

Serious adverse events	BG treatment	FCG treatment	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 17 (70.59%)	7 / 9 (77.78%)	
number of deaths (all causes)	1	3	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma	Additional description: Basal cell carcinoma		
subjects affected / exposed	2 / 17 (11.76%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's disease	Additional description: Bowen's disease		
subjects affected / exposed	1 / 17 (5.88%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome	Additional description: Myelodysplastic syndrome		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of the tongue	Additional description: Squamous cell carcinoma of the tongue		

subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Infusion related reaction	Additional description: Infusion related reaction		
subjects affected / exposed	1 / 17 (5.88%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture	Additional description: Rib fracture		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation	Additional description: Atrial fibrillation		
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease	Additional description: Coronary artery disease		
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral ischaemia	Additional description: Cerebral ischaemia		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage	Additional description: Subarachnoid haemorrhage		
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack	Additional description: Transient ischaemic attack		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood and lymphatic system disorders			
Febrile neutropenia	Additional description: Febrile neutropenia		
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia	Additional description: Pancytopenia		
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia	Additional description: Neutropenia		
subjects affected / exposed	3 / 17 (17.65%)	3 / 9 (33.33%)	
occurrences causally related to treatment / all	3 / 4	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Anal ulcer	Additional description: Anal ulcer		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus	Additional description: Ileus		
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia	Additional description: Dysphagia		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation	Additional description: Constipation		
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Tongue ulceration	Additional description: Tongue ulceration		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma	Additional description: Asthma		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chylothorax	Additional description: Chylothorax		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion	Additional description: Pleural effusion		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis	Additional description: Pulmonary fibrosis		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis cholestatic	Additional description: Hepatitis cholestatic		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Pemphigoid	Additional description: Pemphigoid		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panniculitis	Additional description: Panniculitis		

subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain	Additional description: Back pain		
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint effusion	Additional description: Joint effusion		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteolysis	Additional description: Osteolysis		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bursitis infective	Additional description: Bursitis infective		
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis	Additional description: Bronchitis		
subjects affected / exposed	1 / 17 (5.88%)	2 / 9 (22.22%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia	Additional description: Atypical pneumonia		
subjects affected / exposed	2 / 17 (11.76%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection	Additional description: Infection		
subjects affected / exposed	1 / 17 (5.88%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Erysipelas	Additional description: Erysipelas		
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis	Additional description: Diverticulitis		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia escherichia	Additional description: Pneumonia escherichia		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia chlamydial	Additional description: Pneumonia chlamydial		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (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	2 / 17 (11.76%)	3 / 9 (33.33%)	
occurrences causally related to treatment / all	1 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Listeriosis	Additional description: Listeriosis		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal sepsis	Additional description: Pseudomonal sepsis		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia fungal	Additional description: Pneumonia fungal		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			

Tumour lysis syndrome	Additional description: Tumour lysis syndrome		
subjects affected / exposed	0 / 17 (0.00%)	2 / 9 (22.22%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	BG treatment	FCG treatment	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 17 (100.00%)	9 / 9 (100.00%)	
Vascular disorders			
Circulatory collapse	Additional description: Circulatory collapse		
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Haematoma	Additional description: Haematoma		
subjects affected / exposed	2 / 17 (11.76%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Flushing	Additional description: Flushing		
subjects affected / exposed	2 / 17 (11.76%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Hypertension	Additional description: Hypertension		
subjects affected / exposed	4 / 17 (23.53%)	0 / 9 (0.00%)	
occurrences (all)	4	0	
Hypertensive crisis	Additional description: Hypertensive crisis		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Hypotension	Additional description: Hypotension		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia	Additional description: Asthenia		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Chills	Additional description: Chills		
subjects affected / exposed	4 / 17 (23.53%)	0 / 9 (0.00%)	
occurrences (all)	4	0	

Fatigue	Additional description: Fatigue		
subjects affected / exposed	6 / 17 (35.29%)	0 / 9 (0.00%)	
occurrences (all)	9	0	
Feeling cold	Additional description: Feeling cold		
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Malaise	Additional description: Malaise		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Oedema	Additional description: Oedema		
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Oedema peripheral	Additional description: Oedema peripheral		
subjects affected / exposed	4 / 17 (23.53%)	0 / 9 (0.00%)	
occurrences (all)	4	0	
Pain	Additional description: Pain		
subjects affected / exposed	1 / 17 (5.88%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	4 / 17 (23.53%)	1 / 9 (11.11%)	
occurrences (all)	11	1	
Swelling face	Additional description: Swelling face		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Swelling	Additional description: Swelling		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Hypersensitivity	Additional description: Hypersensitivity		
subjects affected / exposed	1 / 17 (5.88%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Immunodeficiency	Additional description: Immunodeficiency		
subjects affected / exposed	2 / 17 (11.76%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			

Chronic obstructive pulmonary disease	Additional description: Chronic obstructive pulmonary disease		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Cough	Additional description: Cough		
subjects affected / exposed	2 / 17 (11.76%)	2 / 9 (22.22%)	
occurrences (all)	2	2	
Bronchial obstruction	Additional description: Bronchial obstruction		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Dyspnoea exertional	Additional description: Dyspnoea exertional		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Dysphonia	Additional description: Dysphonia		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	5 / 17 (29.41%)	2 / 9 (22.22%)	
occurrences (all)	5	2	
Epistaxis	Additional description: Epistaxis		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Haemoptysis	Additional description: Haemoptysis		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Pleural effusion	Additional description: Pleural effusion		
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety	Additional description: Anxiety		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Confusional state	Additional description: Confusional state		
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Insomnia	Additional description: Insomnia		

subjects affected / exposed	3 / 17 (17.65%)	1 / 9 (11.11%)	
occurrences (all)	4	1	
Restlessness	Additional description: Restlessness		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Investigations			
Blood urea increased	Additional description: Blood urea increased		
subjects affected / exposed	2 / 17 (11.76%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Blood creatinine increased	Additional description: Blood creatinine increased		
subjects affected / exposed	2 / 17 (11.76%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Blood lactate dehydrogenase increased	Additional description: Blood lactate dehydrogenase increased		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Blood potassium decreased	Additional description: Blood potassium decreased		
subjects affected / exposed	0 / 17 (0.00%)	2 / 9 (22.22%)	
occurrences (all)	0	2	
C-reactive protein increased	Additional description: C-reactive protein increased		
subjects affected / exposed	3 / 17 (17.65%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
CD4 lymphocytes abnormal	Additional description: CD4 lymphocytes abnormal		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Immunoglobulins decreased	Additional description: Immunoglobulins decreased		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Lymphocyte count decreased	Additional description: Lymphocyte count decreased		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Transaminases increased	Additional description: Transaminases increased		
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Urine uric acid increased	Additional description: Urine uric acid increased		

subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Weight decreased	Additional description: Weight decreased		
subjects affected / exposed	2 / 17 (11.76%)	1 / 9 (11.11%)	
occurrences (all)	3	1	
Injury, poisoning and procedural complications			
Infusion related reaction	Additional description: Infusion related reaction		
subjects affected / exposed	2 / 17 (11.76%)	1 / 9 (11.11%)	
occurrences (all)	2	2	
Spinal fracture	Additional description: Spinal fracture		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Tongue injury	Additional description: Tongue injury		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Wound	Additional description: Wound		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Traumatic haematoma	Additional description: Traumatic haematoma		
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Cardiac disorders			
Angina pectoris	Additional description: Angina pectoris		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Cardiovascular disorder	Additional description: Cardiovascular disorder		
subjects affected / exposed	1 / 17 (5.88%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Extrasystoles	Additional description: Extrasystoles		
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Pericardial effusion	Additional description: Pericardial effusion		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Ventricular extrasystoles	Additional description: Ventricular extrasystoles		

subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Nervous system disorders			
Coordination abnormal	Additional description: Coordination abnormal		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Dizziness	Additional description: Dizziness		
subjects affected / exposed	2 / 17 (11.76%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Dysgeusia	Additional description: Dysgeusia		
subjects affected / exposed	1 / 17 (5.88%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Headache	Additional description: Headache		
subjects affected / exposed	4 / 17 (23.53%)	2 / 9 (22.22%)	
occurrences (all)	8	2	
Memory impairment	Additional description: Memory impairment		
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Orthostatic intolerance	Additional description: Orthostatic intolerance		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Polyneuropathy	Additional description: Polyneuropathy		
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Restless legs syndrome	Additional description: Restless legs syndrome		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Tremor	Additional description: Tremor		
subjects affected / exposed	2 / 17 (11.76%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
subjects affected / exposed	5 / 17 (29.41%)	3 / 9 (33.33%)	
occurrences (all)	6	5	
Febrile neutropenia	Additional description: Febrile neutropenia		

subjects affected / exposed	2 / 17 (11.76%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Leukopenia	Additional description: Leukopenia		
subjects affected / exposed	6 / 17 (35.29%)	4 / 9 (44.44%)	
occurrences (all)	8	10	
Lymphopenia	Additional description: Lymphopenia		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Pancytopenia	Additional description: Pancytopenia		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Neutropenia	Additional description: Neutropenia		
subjects affected / exposed	7 / 17 (41.18%)	5 / 9 (55.56%)	
occurrences (all)	8	9	
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed	10 / 17 (58.82%)	4 / 9 (44.44%)	
occurrences (all)	15	5	
Ear and labyrinth disorders			
Ear pain	Additional description: Ear pain		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Hypoacusis	Additional description: Hypoacusis		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Tinnitus	Additional description: Tinnitus		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Vertigo	Additional description: Vertigo		
subjects affected / exposed	2 / 17 (11.76%)	1 / 9 (11.11%)	
occurrences (all)	2	1	
Eye disorders			
Metamorphopsia	Additional description: Metamorphopsia		
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Visual impairment	Additional description: Visual impairment		

subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal distension	Additional description: Abdominal distension		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Abdominal discomfort	Additional description: Abdominal discomfort		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper	Additional description: Abdominal pain upper		
subjects affected / exposed	2 / 17 (11.76%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Angular cheilitis	Additional description: Angular cheilitis		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Constipation	Additional description: Constipation		
subjects affected / exposed	2 / 17 (11.76%)	1 / 9 (11.11%)	
occurrences (all)	2	1	
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	2 / 17 (11.76%)	1 / 9 (11.11%)	
occurrences (all)	4	1	
Dyspepsia	Additional description: Dyspepsia		
subjects affected / exposed	2 / 17 (11.76%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Dysphagia	Additional description: Dysphagia		
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Dry mouth	Additional description: Dry mouth		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Inguinal hernia	Additional description: Inguinal hernia		
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Oedema mouth	Additional description: Oedema mouth		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	

Nausea	Additional description: Nausea		
subjects affected / exposed	8 / 17 (47.06%)	2 / 9 (22.22%)	
occurrences (all)	13	4	
Stomatitis	Additional description: Stomatitis		
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Vomiting	Additional description: Vomiting		
subjects affected / exposed	2 / 17 (11.76%)	4 / 9 (44.44%)	
occurrences (all)	2	4	
Tongue ulceration	Additional description: Tongue ulceration		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Alopecia	Additional description: Alopecia		
subjects affected / exposed	2 / 17 (11.76%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Actinic keratosis	Additional description: Actinic keratosis		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Dermal cyst	Additional description: Dermal cyst		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Dermatitis	Additional description: Dermatitis		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Dry skin	Additional description: Dry skin		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Eczema	Additional description: Eczema		
subjects affected / exposed	2 / 17 (11.76%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Hyperhidrosis	Additional description: Hyperhidrosis		
subjects affected / exposed	2 / 17 (11.76%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Onychoclasis	Additional description: Onychoclasis		

subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Papule	Additional description: Papule		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Night sweats	Additional description: Night sweats		
subjects affected / exposed	1 / 17 (5.88%)	2 / 9 (22.22%)	
occurrences (all)	1	2	
Purpura	Additional description: Purpura		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Rash	Additional description: Rash		
subjects affected / exposed	5 / 17 (29.41%)	0 / 9 (0.00%)	
occurrences (all)	5	0	
Pruritus	Additional description: Pruritus		
subjects affected / exposed	2 / 17 (11.76%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Solar dermatitis	Additional description: Solar dermatitis		
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Nocturia	Additional description: Nocturia		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Renal pain	Additional description: Renal pain		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Renal failure	Additional description: Renal failure		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia	Additional description: Arthralgia		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Back pain	Additional description: Back pain		

subjects affected / exposed	4 / 17 (23.53%)	0 / 9 (0.00%)	
occurrences (all)	6	0	
Bone pain	Additional description: Bone pain		
subjects affected / exposed	2 / 17 (11.76%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Myalgia	Additional description: Myalgia		
subjects affected / exposed	2 / 17 (11.76%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Joint swelling	Additional description: Joint swelling		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Muscle cramp	Additional description: Muscle cramp		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal chest pain	Additional description: Musculoskeletal chest pain		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain	Additional description: Musculoskeletal pain		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Pain in extremity	Additional description: Pain in extremity		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Acute sinusitis	Additional description: Acute sinusitis		
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Bronchitis	Additional description: Bronchitis		
subjects affected / exposed	2 / 17 (11.76%)	1 / 9 (11.11%)	
occurrences (all)	2	1	
Candida infection	Additional description: Candida infection		
subjects affected / exposed	2 / 17 (11.76%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Gingivitis	Additional description: Gingivitis		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	

Febrile infection	Additional description: Febrile infection		
subjects affected / exposed	2 / 17 (11.76%)	1 / 9 (11.11%)	
occurrences (all)	3	1	
Influenza	Additional description: Influenza		
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Infection	Additional description: Infection		
subjects affected / exposed	2 / 17 (11.76%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Herpes zoster	Additional description: Herpes zoster		
subjects affected / exposed	2 / 17 (11.76%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Lyme disease	Additional description: Lyme disease		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Oral candidiasis	Additional description: Oral candidiasis		
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Oral herpes	Additional description: Oral herpes		
subjects affected / exposed	1 / 17 (5.88%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Nasopharyngitis	Additional description: Nasopharyngitis		
subjects affected / exposed	5 / 17 (29.41%)	0 / 9 (0.00%)	
occurrences (all)	6	0	
Pneumonia	Additional description: Pneumonia		
subjects affected / exposed	1 / 17 (5.88%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Sinusitis	Additional description: Sinusitis		
subjects affected / exposed	1 / 17 (5.88%)	2 / 9 (22.22%)	
occurrences (all)	1	2	
Sinobronchitis	Additional description: Sinobronchitis		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Sialoadenitis	Additional description: Sialoadenitis		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	

Rhinitis	Additional description: Rhinitis		
subjects affected / exposed	1 / 17 (5.88%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Respiratory tract infection	Additional description: Respiratory tract infection		
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	2	
Tinea pedis	Additional description: Tinea pedis		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection	Additional description: Upper respiratory tract infection		
subjects affected / exposed	2 / 17 (11.76%)	1 / 9 (11.11%)	
occurrences (all)	2	2	
Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased appetite	Additional description: Decreased appetite		
subjects affected / exposed	4 / 17 (23.53%)	3 / 9 (33.33%)	
occurrences (all)	5	3	
Dehydration	Additional description: Dehydration		
subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Diabetes mellitus	Additional description: Diabetes mellitus		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Gout	Additional description: Gout		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Hyperkalaemia	Additional description: Hyperkalaemia		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Hypocalcaemia	Additional description: Hypocalcaemia		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Hypokalaemia	Additional description: Hypokalaemia		

subjects affected / exposed	0 / 17 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Type 2 diabetes mellitus	Additional description: Type 2 diabetes mellitus		
subjects affected / exposed	1 / 17 (5.88%)	0 / 9 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 August 2015	Introduction of infection prophylaxis for the patients. Approval by competent authority on 28-Aug-2015.
08 February 2016	New safety data on Obinutuzumab, changes to ICF. Approval by Competent authority on 08-Feb-2016.
21 September 2016	New safety data on Obinutuzumab, changes to ICF. Due to the low recruitment the FCG-arm was closed in September 2016 (following the approval of amendment 3)
01 June 2017	New safety data on Obinutuzumab, changes to ICF.
23 July 2020	New safety data on Obinutuzumab.

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.

A total of 27 pts were enrolled in the study, and the recruitment was not completed due to low interest.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/36423347