



## 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
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##### 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
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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:

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**Results analysis stage**

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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:

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**General information about the trial**

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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 emergent 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:

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### 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:

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#### 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
<b>Arm title</b>	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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> day 3-5 in cycle 1, respectively day 2-4 q4wks, cycle 2 to 6

Cycle 1 Day 3 25 mg/m<sup>2</sup>  
Day 4 25 mg/m<sup>2</sup>  
Day 5 25 mg/m<sup>2</sup>  
Cycle 2 - 6 Day 2 25 mg/m<sup>2</sup>  
Day 3 25 mg/m<sup>2</sup>  
Day 4 25 mg/m<sup>2</sup>

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
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Dosage and administration details:

Cyclophosphamide iv infusion 250 mg/m<sup>2</sup> day 3-5 in cycle 1, respectively day 2-4 q4wks, cycle 2 to 6

Cycle 1	Day 3	250 mg/m <sup>2</sup>
	Day 4	250 mg/m <sup>2</sup>
	Day 5	250 mg/m <sup>2</sup>
Cycle 2 – 6	Day 2	250 mg/m <sup>2</sup>
	Day 3	250 mg/m <sup>2</sup>
	Day 4	250 mg/m <sup>2</sup>

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

<b>Arm title</b>	Bendamustine and Obinutuzumab
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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/m<sup>2</sup> 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
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Investigational medicinal product name	Obinutuzumab
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Investigational medicinal product code	R05072759
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Other name	Gazyvaro
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Pharmaceutical forms	Concentrate for solution for infusion
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Routes of administration	Intravenous use
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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
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Investigational medicinal product code	70972.00.00
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Other name	Levact
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Pharmaceutical forms	Concentrate and solvent for solution for infusion
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Routes of administration	Intravenous use
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Dosage and administration details:

Bendamustine Treatment

Cycle 1	Day 3	70 mg/m <sup>2</sup>
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Day 4 70 mg/m<sup>2</sup>  
Cycle 2 – 6 Day 2 70 mg/m<sup>2</sup>  
Day 3 70 mg/m<sup>2</sup>

<b>Number of subjects in period 1</b>	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
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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/m<sup>2</sup> 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/m<sup>2</sup> 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
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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/m<sup>2</sup> 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
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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
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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/m<sup>2</sup> 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.

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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/m<sup>2</sup> 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 <sup>[1]</sup>
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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
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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

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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	BG treatment
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Reporting group description: -

Reporting group title	FCG treatment
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Reporting group description: -

<b>Serious adverse events</b>	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	
<b>Injury, poisoning and procedural complications</b>			
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	
<b>Cardiac disorders</b>			
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	
<b>Nervous system disorders</b>			
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 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Tongue ulceration		
	1 / 17 (5.88%)	0 / 9 (0.00%)	
	0 / 1	0 / 0	
	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Asthma		
	1 / 17 (5.88%)	0 / 9 (0.00%)	
	0 / 1	0 / 0	
	0 / 0	0 / 0	
Chylothorax subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Chylothorax		
	1 / 17 (5.88%)	0 / 9 (0.00%)	
	0 / 1	0 / 0	
	0 / 0	0 / 0	
Pleural effusion subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Pleural effusion		
	1 / 17 (5.88%)	0 / 9 (0.00%)	
	0 / 1	0 / 0	
	0 / 0	0 / 0	
Pulmonary fibrosis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Pulmonary fibrosis		
	1 / 17 (5.88%)	0 / 9 (0.00%)	
	1 / 1	0 / 0	
	0 / 0	0 / 0	
Hepatobiliary disorders Hepatitis cholestatic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Hepatitis cholestatic		
	1 / 17 (5.88%)	0 / 9 (0.00%)	
	0 / 1	0 / 0	
	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders Pemphigoid subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Pemphigoid		
	1 / 17 (5.88%)	0 / 9 (0.00%)	
	0 / 1	0 / 0	
	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	
<b>Musculoskeletal and connective tissue disorders</b>			
<b>Back pain</b>	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	
<b>Joint effusion</b>	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	
<b>Osteolysis</b>	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	
<b>Infections and infestations</b>			
<b>Bursitis infective</b>	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	
<b>Bronchitis</b>	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	
<b>Atypical pneumonia</b>	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	
<b>Infection</b>	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 %

<b>Non-serious adverse events</b>	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 subjects affected / exposed occurrences (all)	Additional description: Fatigue	
	6 / 17 (35.29%) 9	0 / 9 (0.00%) 0
Feeling cold subjects affected / exposed occurrences (all)	Additional description: Feeling cold	
	0 / 17 (0.00%) 0	1 / 9 (11.11%) 1
Malaise subjects affected / exposed occurrences (all)	Additional description: Malaise	
	1 / 17 (5.88%) 1	0 / 9 (0.00%) 0
Oedema subjects affected / exposed occurrences (all)	Additional description: Oedema	
	0 / 17 (0.00%) 0	1 / 9 (11.11%) 1
Oedema peripheral subjects affected / exposed occurrences (all)	Additional description: Oedema peripheral	
	4 / 17 (23.53%) 4	0 / 9 (0.00%) 0
Pain subjects affected / exposed occurrences (all)	Additional description: Pain	
	1 / 17 (5.88%) 1	1 / 9 (11.11%) 1
Pyrexia subjects affected / exposed occurrences (all)	Additional description: Pyrexia	
	4 / 17 (23.53%) 11	1 / 9 (11.11%) 1
Swelling face subjects affected / exposed occurrences (all)	Additional description: Swelling face	
	1 / 17 (5.88%) 1	0 / 9 (0.00%) 0
Swelling subjects affected / exposed occurrences (all)	Additional description: Swelling	
	1 / 17 (5.88%) 1	0 / 9 (0.00%) 0
Immune system disorders		
Hypersensitivity subjects affected / exposed occurrences (all)	Additional description: Hypersensitivity	
	1 / 17 (5.88%) 1	1 / 9 (11.11%) 1
Immunodeficiency subjects affected / exposed occurrences (all)	Additional description: Immunodeficiency	
	2 / 17 (11.76%) 2	0 / 9 (0.00%) 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 occurrences (all)	3 / 17 (17.65%) 4	1 / 9 (11.11%) 1	
Restlessness	Additional description: Restlessness		
subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 9 (0.00%) 0	
Investigations			
Blood urea increased	Additional description: Blood urea increased		
subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2	0 / 9 (0.00%) 0	
Blood creatinine increased	Additional description: Blood creatinine increased		
subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2	0 / 9 (0.00%) 0	
Blood lactate dehydrogenase increased	Additional description: Blood lactate dehydrogenase increased		
subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 9 (0.00%) 0	
Blood potassium decreased	Additional description: Blood potassium decreased		
subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	2 / 9 (22.22%) 2	
C-reactive protein increased	Additional description: C-reactive protein increased		
subjects affected / exposed occurrences (all)	3 / 17 (17.65%) 3	0 / 9 (0.00%) 0	
CD4 lymphocytes abnormal	Additional description: CD4 lymphocytes abnormal		
subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 9 (0.00%) 0	
Immunoglobulins decreased	Additional description: Immunoglobulins decreased		
subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 9 (0.00%) 0	
Lymphocyte count decreased	Additional description: Lymphocyte count decreased		
subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 9 (0.00%) 0	
Transaminases increased	Additional description: Transaminases increased		
subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 9 (11.11%) 1	
Urine uric acid increased	Additional description: Urine uric acid increased		

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

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

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

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

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

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

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

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

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### 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:

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### Online references

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