Clinical trial results:
An open-label, multi-center, three arm randomized, phase III study to compare the efficacy and safety of RO5072759 + chlorambucil (GClb), rituximab + chlorambucil (RClb) or chlorambucil (Clb) alone in previously untreated CLL patients with comorbidities.

Summary

EudraCT number	2009-012476-28
Trial protocol	DE FR GB AT ES CZ NL RO SK DK IT EE BG
Global end of trial date	23 August 2017

Results information

Result version number	v1 (current)
This version publication date	31 August 2018
First version publication date	24 August 2016

Trial information

Trial identification

Sponsor protocol code	BO21004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02053610
WHO universal trial number (UTN)	-
Other trial identifiers	ClinicalTrials.gov identifier: NCT01998880, ClinicalTrials.gov identifier: NCT01010061

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com

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	23 August 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial is to demonstrate clinically relevant statistical superiority in progression free survival (PFS) with RO5072759 plus chlorambucil (GClb) compared to rituximab plus chlorambucil (RClb) and chlorambucil (Clb) alone and RClb compared to Clb (GClb vs Clb [Stage 1a]; RClb vs Clb [Stage 1b]; GClb vs RClb [Stage 2]) in previously untreated chronic lymphocytic leukemia (CLL) subjects with comorbidities.

Protection of trial subjects:

All study subjects were required to read and sign an informed consent form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 December 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Romania: 20
Country: Number of subjects enrolled	Slovakia: 3
Country: Number of subjects enrolled	Spain: 109
Country: Number of subjects enrolled	United Kingdom: 33
Country: Number of subjects enrolled	Austria: 28
Country: Number of subjects enrolled	Bulgaria: 33
Country: Number of subjects enrolled	Czech Republic: 21
Country: Number of subjects enrolled	Denmark: 17
Country: Number of subjects enrolled	Estonia: 5
Country: Number of subjects enrolled	France: 74
Country: Number of subjects enrolled	Germany: 146
Country: Number of subjects enrolled	Italy: 57
Country: Number of subjects enrolled	Australia: 33
Country: Number of subjects enrolled	Croatia: 12
Country: Number of subjects enrolled	Canada: 30
Country: Number of subjects enrolled	Switzerland: 15

Country: Number of subjects enrolled	Argentina: 7
Country: Number of subjects enrolled	Thailand: 16
Country: Number of subjects enrolled	New Zealand: 3
Country: Number of subjects enrolled	Hong Kong: 1
Country: Number of subjects enrolled	Mexico: 11
Country: Number of subjects enrolled	Russian Federation: 93
Country: Number of subjects enrolled	Brazil: 2
Country: Number of subjects enrolled	United States: 3
Country: Number of subjects enrolled	Egypt: 8
Worldwide total number of subjects	781
EEA total number of subjects	559

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)	163
From 65 to 84 years	592
85 years and over	26

Subject disposition

Recruitment

Recruitment details:

A total of 787 subjects were enrolled in the study. Following a 6 subject safety run-in, prior to randomisation, 781 subjects were randomised.

Pre-assignment

Screening details:

589 subjects were randomised to 1 of 3 treatment groups in 2:2:1 ratio: Obinutuzumab + Chlorambucil (GClb) (n=238), Rituximab + Chlorambucil (RClb) (n=233) or Chlorambucil (Clb) (n=118) in Stage 1 and an additional 192 subjects were randomised in 1:1 ratio to GClb or RClb in Stage 2.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Stage 1: Rituximab + Chlorambucil (RClb)

Arm description:

Subjects received 375 mg/m^2 rituximab IV infusion on Day 1 of Cycle 1 then 500 mg/m^2 IV infusions on Day 1 of Cycles 2-6 (28-day cycles) plus chlorambucil 0.5 mg/kg orally on Day 1 and 15 of each 28-day cycle (6 cycles).

Arm type	Experimental
Investigational medicinal product name	Chlorambucil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Chlorambucil 0.5 mg/kg orally on Day 1 and 15 of each 28-day cycle.

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	Rituxan, Mabthera, RO0452294
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Rituximab 375 mg/m^2 by IV infusion on Days 1 of Cycle 1 then 500 mg/m^2 IV infusion on Day 1 of Cycles 2-6 (28-day cycles).

Arm title	Stage 1: Obinutuzumab + Chlorambucil (GClb)

Arm description:

Subjects received obinutuzumab 1000 milligram (mg) intravenous (IV) infusion, on Day 1 [First infusion split 100 mg on Day 1 and 900 mg on Day 2 as per protocol amendment], 8 and 15 in Cycle 1 and Day 1 of Cycles 2-6 (28-day cycles) plus chlorambucil 0.5 milligram per kilogram of body weight (mg/kg) orally on Day 1 and 15 of each 28-day cycle (6 Cycles).

Arm type	Experimental
Investigational medicinal product name	Obinutuzumab
Investigational medicinal product code	RO5072759
Other name	Gazyvaro, Gazyva
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Obinutuzumab 1000 mg by IV infusion on Days 1 [First infusion split 100 mg on Day 1 and 900 mg on Day 2 as per protocol amendment], 8 and 15 of the first treatment cycle (Cycle 1) and Day 1 of Cycles 2-6 (28-day cycles).

Investigational medicinal product name	Chlorambucil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Chlorambucil 0.5 mg/kg orally on Day 1 and 15 of each 28-day cycle.

Arm title	Stage 1: Chlorambucil (Clb)

Arm description:

Subjects received chlorambucil 0.5 mg/kg orally on Day 1 and 15 of each 28-day cycle (6 Cycles). Subjects with Progressive Disease or within 6 months of follow-up were allowed to cross over to receive obinutuzumab + chlorambucil.

Arm type	Experimental
Investigational medicinal product name	Chlorambucil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Chlorambucil 0.5 mg/kg orally on Day 1 and 15 of each 28-day cycle.

Arm title	Stage 2: Rituximab + Chlorambucil (RClb)

Arm description:

Subjects received rituximab 375 mg/m^2 IV infusion on Day 1 of Cycle 1 then 500 mg/m^2 IV infusions on Day 1 of Cycles 2-6 (28-day cycles) plus chlorambucil 0.5 mg/kg orally on Day 1 and 15 of each 28-day cycle (6 cycles).

Arm type	Experimental
Investigational medicinal product name	Chlorambucil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Chlorambucil 0.5 mg/kg orally on Day 1 and 15 of each 28-day cycle.

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	Rituxan, Mabthera, RO0452294
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Rituximab 375 mg/m^2 by IV infusion on Days 1 of Cycle 1 then 500 mg/m^2 IV infusion on Day 1 of Cycles 2-6 (28-day cycles).

Arm title	Stage 2: Obinutuzumab + Chlorambucil (GClb)

Arm description:

Subjects received obinutuzumab 1000 mg IV infusion, on Day 1 [First infusion split 100 mg on Day 1 and 900 mg on Day 2 as per protocol amendment], 8 and 15 in Cycle 1 and Day 1 of Cycles 2-6 (28-day cycles) plus chlorambucil 0.5 mg/kg orally on Day 1 and 15 of each 28-day cycle (6 Cycles).

Arm type	Experimental

Investigational medicinal product name	Obinutuzumab
Investigational medicinal product code	RO5072759
Other name	Gazyvaro, Gazyva
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Obinutuzumab 1000 mg by IV infusion on Days 1 [First infusion split 100 mg on Day 1 and 900 mg on Day 2 as per protocol amendment], 8 and 15 of the first treatment cycle (Cycle 1) and Day 1 of Cycles 2-6 (28-day cycles).

Investigational medicinal product name	Chlorambucil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Chlorambucil 0.5 mg/kg orally on Day 1 and 15 of each 28-day cycle.

Number of subjects in period 1	Stage 1: Rituximab + Chlorambucil (RClb)	Stage 1: Obinutuzumab + Chlorambucil (GClb)	Stage 1: Chlorambucil (Clb)
Started	233	238	118
Received study drug	230	236	116
Completed	205	190	78
Not completed	28	48	40
Withdrew Consent	2	5	1
Violation of Selection Criteria	-	-	1
Death	3	3	6
No Treatment Received	3	2	2
Adverse Event/Intercurrent Illness	16	33	16
Administrative/Other	1	-	1
Insufficient Therapeutic Response	1	1	5
Refused Treatment/Did Not Cooperate	1	2	-
Disease Progression	1	2	8

Number of subjects in period 1	Stage 2: Rituximab + Chlorambucil (RClb)	Stage 2: Obinutuzumab + Chlorambucil (GClb)
Started	330	333
Received study drug	326	331
Completed	288	266
Not completed	42	67
Withdrew Consent	2	9
Violation of Selection Criteria	1	-
Death	5	5
No Treatment Received	4	2

Adverse Event/Intercurrent Illness	25	43
Administrative/Other	1	1
Insufficient Therapeutic Response	1	1
Refused Treatment/Did Not Cooperate	1	3
Disease Progression	2	3

Baseline characteristics

Reporting groups[1]	
Reporting group title	Stage 1: Rituximab + Chlorambucil (RClb)
Reporting group description:	
Subjects received 375 mg/m^2 rituximab IV infusion on Day 1 of Cycle 1 then 500 mg/m^2 IV infusions on Day 1 of Cycles 2-6 (28-day cycles) plus chlorambucil 0.5 mg/kg orally on Day 1 and 15 of each 28-day cycle (6 cycles).	
Reporting group title	Stage 1: Obinutuzumab + Chlorambucil (GClb)
Reporting group description:	
Subjects received obinutuzumab 1000 milligram (mg) intravenous (IV) infusion, on Day 1 [First infusion split 100 mg on Day 1 and 900 mg on Day 2 as per protocol amendment], 8 and 15 in Cycle 1 and Day 1 of Cycles 2-6 (28-day cycles) plus chlorambucil 0.5 milligram per kilogram of body weight (mg/kg) orally on Day 1 and 15 of each 28-day cycle (6 Cycles).	
Reporting group title	Stage 1: Chlorambucil (Clb)
Reporting group description:	
Subjects received chlorambucil 0.5 mg/kg orally on Day 1 and 15 of each 28-day cycle (6 Cycles). Subjects with Progressive Disease or within 6 months of follow-up were allowed to cross over to receive obinutuzumab + chlorambucil.	
Reporting group title	Stage 2: Rituximab + Chlorambucil (RClb)
Reporting group description:	
Subjects received rituximab 375 mg/m^2 IV infusion on Day 1 of Cycle 1 then 500 mg/m^2 IV infusions on Day 1 of Cycles 2-6 (28-day cycles) plus chlorambucil 0.5 mg/kg orally on Day 1 and 15 of each 28-day cycle (6 cycles).	
Reporting group title	Stage 2: Obinutuzumab + Chlorambucil (GClb)
Reporting group description:	
Subjects received obinutuzumab 1000 mg IV infusion, on Day 1 [First infusion split 100 mg on Day 1 and 900 mg on Day 2 as per protocol amendment], 8 and 15 in Cycle 1 and Day 1 of Cycles 2-6 (28-day cycles) plus chlorambucil 0.5 mg/kg orally on Day 1 and 15 of each 28-day cycle (6 Cycles).	

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: A 3 arm, parallel group comparative study of GClb vs RClb vs Clb, study was split into two Stages for analysis: Stage 1 (Stage 1a - GClb vs Clb, and Stage 1b - RClb vs Clb) and Stage 2 (RClb vs GClb). In Stage 2, randomization continued in the GClb and RClb arms only. Stage 1 and Stage 2 are not temporally consecutive, but rather compare different treatment arms. All patients enrolled in GClb and RClb arms in Stage 1 were also part of Stage 2, irrespective of whether they had completed or not.

Reporting group values	Stage 1: Rituximab + Chlorambucil (RClb)	Stage 1: Obinutuzumab + Chlorambucil (GClb)	Stage 1: Chlorambucil (Clb)
Number of subjects	233	238	118
Age categorical Units: Subjects			
Less than (<) 65 years	47	42	26
Greater than or equal to (>=) 65 years	186	196	92
Gender categorical Units: Subjects			
Female	84	98	43
Male	149	140	75

Reporting group values	Stage 2: Rituximab + Chlorambucil (RClb)	Stage 2: Obinutuzumab + Chlorambucil (GClb)	Total
Number of subjects	330	333	781

Age categorical Units: Subjects			
Less than (<) 65 years	73	64	163
Greater than or equal to (>=) 65 years	257	269	618
Gender categorical Units: Subjects			
Female	126	130	299
Male	204	203	482

End points

End points reporting groups

Reporting group title	Stage 1: Rituximab + Chlorambucil (RClb)
Reporting group description:	
Subjects received 375 mg/m^2 rituximab IV infusion on Day 1 of Cycle 1 then 500 mg/m^2 IV infusions on Day 1 of Cycles 2-6 (28-day cycles) plus chlorambucil 0.5 mg/kg orally on Day 1 and 15 of each 28-day cycle (6 cycles).	
Reporting group title	Stage 1: Obinutuzumab + Chlorambucil (GClb)
Reporting group description:	
Subjects received obinutuzumab 1000 milligram (mg) intravenous (IV) infusion, on Day 1 [First infusion split 100 mg on Day 1 and 900 mg on Day 2 as per protocol amendment], 8 and 15 in Cycle 1 and Day 1 of Cycles 2-6 (28-day cycles) plus chlorambucil 0.5 milligram per kilogram of body weight (mg/kg) orally on Day 1 and 15 of each 28-day cycle (6 Cycles).	
Reporting group title	Stage 1: Chlorambucil (Clb)
Reporting group description:	
Subjects received chlorambucil 0.5 mg/kg orally on Day 1 and 15 of each 28-day cycle (6 Cycles). Subjects with Progressive Disease or within 6 months of follow-up were allowed to cross over to receive obinutuzumab + chlorambucil.	
Reporting group title	Stage 2: Rituximab + Chlorambucil (RClb)
Reporting group description:	
Subjects received rituximab 375 mg/m^2 IV infusion on Day 1 of Cycle 1 then 500 mg/m^2 IV infusions on Day 1 of Cycles 2-6 (28-day cycles) plus chlorambucil 0.5 mg/kg orally on Day 1 and 15 of each 28-day cycle (6 cycles).	
Reporting group title	Stage 2: Obinutuzumab + Chlorambucil (GClb)
Reporting group description:	
Subjects received obinutuzumab 1000 mg IV infusion, on Day 1 [First infusion split 100 mg on Day 1 and 900 mg on Day 2 as per protocol amendment], 8 and 15 in Cycle 1 and Day 1 of Cycles 2-6 (28-day cycles) plus chlorambucil 0.5 mg/kg orally on Day 1 and 15 of each 28-day cycle (6 Cycles).	

Primary: Progression-Free Survival (PFS) in Stage 1

End point title	Progression-Free Survival (PFS) in Stage 1[1]
End point description:	
PFS was defined as time from randomisation to first occurrence of progression, relapse, or death from any cause as assessed by investigator. Progressive disease (PD) required at least one of the following: ≥50% increase in absolute number of lymphocytes, appearance of new palpable lymph nodes (>15 mm in diameter) or new extra nodal lesion, ≥50% increase in diameter of previous site of clinically significant lymphadenopathy, ≥50% increase in enlargement of liver or spleen, transformation to a more aggressive histology or after treatment, progression of any cytopenia (decrease of hemoglobin levels >20 g/L or <10 g/dL or a decrease of platelet counts >50% or <100*10^9/L or by a decrease of neutrophil counts >50% or <1.0*10^9/L). Intent-to-treat population (ITT) included all randomized subjects. Subjects without PFS events were censored.	
End point type	Primary
End point timeframe:	
Randomisation to clinical cutoff date of 10 Oct 2017 (median observation in Stage 1a: 62.5 months and Stage 1b: 57.7 months)	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure only looked at Stage 1 data.

End point values	Stage 1: Rituximab + Chlorambucil (RClb)	Stage 1: Obinutuzumab + Chlorambucil (GClb)	Stage 1: Chlorambucil (Clb)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	233	238	118	
Units: months				
median (confidence interval 95%)	16.5 (14.3 to 17.7)	31.1 (26.5 to 35.6)	11.1 (10.7 to 11.3)	

Statistical analyses

Statistical analysis title	PFS Stage 1a
Statistical analysis description: Stratified by Binet stage at Baseline.	
Comparison groups	Stage 1: Obinutuzumab + Chlorambucil (GClb) v Stage 1: Chlorambucil (Clb)
Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	0.28

Notes:

[2] - Type I error controlled through closed test procedure.

Statistical analysis title	PFS Stage 1b
Statistical analysis description: Stratified by Binet stage at Baseline	
Comparison groups	Stage 1: Chlorambucil (Clb) v Stage 1: Rituximab + Chlorambucil (RClb)
Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	0.59

Notes:

[3] - Type I error controlled through closed test procedure.

Primary: Progression-Free Survival (PFS) Stage 2

End point title	Progression-Free Survival (PFS) Stage 2[4]

End point description:

PFS was defined as time from randomisation to first occurrence of progression, relapse, or death from any cause as assessed by investigator. PD required at least one of the following: ≥50% increase in absolute number of lymphocytes, appearance of new palpable lymph nodes (>15 mm in diameter) or new extra nodal lesion, ≥50% increase in diameter of previous site of clinically significant lymphadenopathy, ≥50% increase in enlargement of liver or spleen, transformation to a more aggressive histology or after treatment, progression of any cytopenia (decrease of hemoglobin levels >20 g/L or <10 g/dL or a decrease of platelet counts >50% or <100*10^9/L or by a decrease of neutrophil counts >50% or <1.0*10^9/L). ITT population. Data for subjects without disease progression or death was censored at time of last response assessment, or, if no response assessments were performed after baseline visit, at time of randomisation +1 day.

End point type	Primary

End point timeframe:

Randomisation to clinical cutoff date of 10 Oct 2017 (median observation 59.4 months)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This outcome measure only looked at Stage 2 data.

End point values	Stage 2: Rituximab + Chlorambucil (RClb)	Stage 2: Obinutuzumab + Chlorambucil (GClb)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	330	333		
Units: months				
median (confidence interval 95%)	15.7 (14.3 to 17.2)	28.9 (26.1 to 32.7)		

Statistical analyses

Statistical analysis title	PFS Stage 2
Comparison groups	Stage 2: Rituximab + Chlorambucil (RClb) v Stage 2: Obinutuzumab + Chlorambucil (GClb)
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Log-rank Test, stratified
Parameter estimate	Hazard ratio (HR)
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	0.58

Notes:

[5] - Stratified by Binet stage at Baseline

Primary: Percentage of Subjects With Progression Free Survival Events in Stage 1

End point title	Percentage of Subjects With Progression Free Survival Events in Stage 1[6][7]

End point description:

Percentage of subjects with progression free survival events: progression, relapse, or death.

End point type	Primary

End point timeframe:

Randomisation to clinical cutoff date of 10 Oct 2017 (median observation in Stage 1a: 62.5 months and Stage 1b: 57.7 months)

Notes:

[6] - 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: This outcome measure only looked at Stage 1 data.

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure only looked at Stage 1 data.

End point values	Stage 1: Rituximab + Chlorambucil (RClb)	Stage 1: Obinutuzumab + Chlorambucil (GClb)	Stage 1: Chlorambucil (Clb)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	233	238	118	
Units: percentage of subjects				
number (not applicable)	90.1	72.7	90.7	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Progression Free Survival Events in Stage 2

End point title	Percentage of Subjects With Progression Free Survival Events in Stage 2[8][9]

End point description:

Percentage of subjects with progression free survival events: disease progression, relapse, or death.

End point type	Primary

End point timeframe:

Randomisation to clinical cutoff date of 10 Oct 2017 (median observation 59.4 months)

Notes:

[8] - 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: This outcome measure only looked at Stage 2 data.

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure only looked at Stage 2 data.

End point values	Stage 2: Rituximab + Chlorambucil (RClb)	Stage 2: Obinutuzumab + Chlorambucil (GClb)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	330	333		
Units: percentage of subject				
number (not applicable)	88.5	73.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival Based on Independent Review Committee (IRC) Data in Stage 1

End point title	Progression Free Survival Based on Independent Review Committee (IRC) Data in Stage 1[10]

End point description:

PFS was defined as the time from randomisation to the first occurrence of progression, relapse, or death from any cause as assessed by Independent Review Committee. PD required at least one of the following: ≥50% increase in absolute number of lymphocytes, appearance of new palpable lymph nodes (>15 mm in diameter) or new extra nodal lesion, ≥50% increase in diameter of previous site of clinically significant lymphadenopathy, ≥50% increase in enlargement of liver or spleen, transformation to a more aggressive histology or after treatment, progression of any cytopenia (decrease of hemoglobin levels >20 g/L or <10 g/dL or a decrease of platelet counts >50% or <100*10^9/L or by a decrease of neutrophil counts >50% or <1.0*10^9/L). ITT population. Subjects without PFS events were censored.

End point type	Secondary

End point timeframe:

Randomisation to clinical cutoff date of 9 May 2013 (median observation for Stage 1a: 22.8 months and Stage 1b: 22.7 months)

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure only looked at Stage 1 data.

End point values	Stage 1: Rituximab + Chlorambucil (RClb)	Stage 1: Obinutuzumab + Chlorambucil (GClb)	Stage 1: Chlorambucil (Clb)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	233	238	118	
Units: months				
median (confidence interval 95%)	16.1 (14.3 to 17.2)	27.2 (23.5 to 33.0)	11.2 (11.0 to 12.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival Based on Independent Review Committee (IRC) Data in Stage 2

End point title	Progression Free Survival Based on Independent Review Committee (IRC) Data in Stage 2[11]

End point description:

PFS was defined as the time from randomisation to the first occurrence of progression, relapse, or death from any cause as assessed by IRC. PD required at least one of the following: ≥50% increase in absolute number of lymphocytes, appearance of new palpable lymph nodes (>15 mm in diameter) or new extra nodal lesion, ≥50% increase in diameter of previous site of clinically significant lymphadenopathy, ≥50% increase in enlargement of liver or spleen, transformation to a more aggressive histology or after treatment, progression of any cytopenia (decrease of hemoglobin levels >20 g/L or <10 g/dL or a decrease of platelet counts >50% or <100*10^9/L or by a decrease of neutrophil counts >50% or <1.0*10^9/L). ITT population. Data for subjects without disease progression or death was censored at time of last response assessment, or, if no response assessments were performed after baseline visit, at time of randomisation +1 day.

End point type	Secondary

End point timeframe:

Randomisation to clinical cutoff date of 09 May 2013 (median observation 18.7 months)

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure only looked at Stage 2 data.

End point values	Stage 2: Rituximab + Chlorambucil (RClb)	Stage 2: Obinutuzumab + Chlorambucil (GClb)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	330	333		
Units: months				
median (confidence interval 95%)	14.9 (14.2 to 17.2)	26.7 (23.2 to 31.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Progression Free Survival Events Based on Independent Review Committee (IRC) Data in Stage 1

End point title	Percentage of Subjects With Progression Free Survival Events Based on Independent Review Committee (IRC) Data in Stage 1[12]

End point description:

Percentage of subjects with progression free survival events: progression, relapse, or death from any cause as assessed by an IRC. ITT population. Subjects without PFS events were censored.

End point type	Secondary

End point timeframe:

Randomization to clinical cutoff date of 9 May 2013 (median observation of Stage 1a: 22.8 months and Stage 1b: 22.7 months)

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure only looked at Stage 1 data.

End point values	Stage 1: Rituximab + Chlorambucil (RClb)	Stage 1: Obinutuzumab + Chlorambucil (GClb)	Stage 1: Chlorambucil (Clb)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	233	238	118	
Units: percentage of subjects				
number (not applicable)	64.8	37.4	76.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Progression Free Survival Events Based on Independent Review Committee (IRC) Data in Stage 2

End point title	Percentage of Subjects With Progression Free Survival Events Based on Independent Review Committee (IRC) Data in Stage 2[13]

End point description:

Percentage of subjects with progression free survival events: progression, relapse, or death from any cause as assessed by an Independent Review Committee.

End point type	Secondary

End point timeframe:

Randomisation to clinical cutoff date of 09 May 2013 (median observation 18.7 months)

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure only looked at Stage 2 data.

End point values	Stage 2: Rituximab + Chlorambucil (RClb)	Stage 2: Obinutuzumab + Chlorambucil (GClb)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	330	333		
Units: percentage of subject				
number (not applicable)	55.5	30.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With End of Treatment Response (EOTR) in Stage 1

End point title	Percentage of Subjects With End of Treatment Response (EOTR) in Stage 1[14]

End point description:

EOTR was first response assessment 56 days from last dose based on International Workshop on Chronic Lymphocytic Leukaemia (IWCLL) guidelines. Complete Response (CR): Peripheral lymphocytes below 4*10^9/L, No lymphadenopathy, No hepatomegaly, No splenomegaly, No disease, Blood counts

as Neutrophils >1.5*10^9/L, Platelets >100*10^9/L, Hemoglobin >11g/dL and Bone marrow at least normocellular for age. CRi was CR with incomplete bone marrow recovery. Partial response (PR): ≥50% decrease in peripheral lymphocyte count from pre-treatment value and Either a ≥50% reduction in lymphadenopathy OR ≥50% reduction of liver enlargement OR ≥50% reduction of spleen enlargement, at least one of following: Neutrophils >1.5*10^9/L or ≥50% increase, Platelets >100*10^9/L, Hemoglobin 11 g/dL or ≥50% increase. Subjects from ITT population with data available for analysis. Subjects who did not reach 3 month Follow-up visit at clinical cutoff are excluded. Here, 99999 indicates that 95% CI not estimated.

End point type	Secondary

End point timeframe:

Randomisation to clinical cutoff date of 10 Oct 2017 (median observation of Stage 1a: 62.5 months and Stage 1b: 57.7 months)

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure only looked at Stage 1 data.

End point values	Stage 1: Rituximab + Chlorambucil (RClb)	Stage 1: Obinutuzumab + Chlorambucil (GClb)	Stage 1: Chlorambucil (Clb)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	233	238	118	
Units: percentage of subject				
number (confidence interval 95%)				
Complete Response (CR)	4.7 (2.4 to 8.3)	17.2 (12.7 to 22.6)	0 (0 to 3.1)	
Complete Response incomplete (CRi)	2.1 (0.7 to 4.9)	4.2 (2 to 7.6)	0 (0 to 3.1)	
Partial Response (PR)	55.4 (48.7 to 61.9)	48.3 (41.8 to 54.9)	28.8 (20.8 to 37.9)	
Nodular Partial Response (nPR)	3.4 (1.5 to 6.7)	7.6 (4.5 to 11.7)	2.5 (0.5 to 7.3)	
Stable Disease	13.7 (9.6 to 18.8)	5 (2.6 to 8.6)	22.9 (15.7 to 31.5)	
Progressive Disease	12.4 (8.5 to 17.4)	4.2 (2.0 to 7.6)	28.8 (20.8 to 37.9)	
No Response Assessment	8.2 (-99999 to 99999)	13.4 (-99999 to 99999)	16.9 (-99999 to 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With End of Treatment Response (EOTR) in Stage 2

End point title	Percentage of Subjects With End of Treatment Response (EOTR) in Stage 2[15]

End point description:

EOTR was first response assessment 56 days from last dose based on International Workshop on Chronic Lymphocytic Leukaemia (IWCLL) guidelines. Complete Response (CR): Peripheral lymphocytes below 4*10^9/L, No lymphadenopathy, No hepatomegaly, No splenomegaly, No disease, Blood counts as Neutrophils >1.5*10^9/L, Platelets >100*10^9/L, Hemoglobin >11g/dL and Bone marrow at least normocellular for age. CRi was CR with incomplete bone marrow recovery. Partial response (PR): ≥50% decrease in peripheral lymphocyte count from pre-treatment value and Either a ≥50% reduction in lymphadenopathy OR ≥50% reduction of liver enlargement OR ≥50% reduction of spleen enlargement, at least one of following: Neutrophils >1.5*10^9/L or ≥50% increase, Platelets >100*10^9/L, Hemoglobin 11 g/dL or ≥50% increase. Subjects from ITT population with data available for analysis.

Subjects who did not reach 3 month Follow-up visit at clinical cutoff are excluded. Here, 99999 indicates that 95% CI not estimated.

End point type	Secondary

End point timeframe:

Randomisation to clinical cutoff date of 10 Oct 2017 (median observation 59.4 months)

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure only looked at Stage 2 data.

End point values	Stage 2: Rituximab + Chlorambucil (RClb)	Stage 2: Obinutuzumab + Chlorambucil (GClb)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	330	333		
Units: percentage of subject				
number (confidence interval 95%)				
Complete Response (CR)	4.8 (2.8 to 7.8)	15.6 (11.9 to 20)		
Complete Response incomplete (CRi)	1.5 (0.5 to 3.5)	3.6 (1.9 to 6.2)		
Partial Response (PR)	53.9 (48.4 to 59.4)	52.0 (46.4 to 57.4)		
Nodular Partial Response (nPR)	5.2 (3 to 8.1)	7.5 (4.9 to 10.9)		
Stable Disease	15.2 (11.5 to 19.5)	4.5 (2.5 to 7.3)		
Progressive Disease	11.2 (8 to 15.1)	4.5 (2.5 to 7.3)		
No Response Assessment	8.2 (-99999 to 99999)	12.3 (-99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Best Overall Response in Stage 1

End point title	Percentage of Subjects With Best Overall Response in Stage

End point description:

Best overall response according to IWCLL guidelines was defined as the percentage of subjects with CR, CRi, PR or nPR. Complete Response (CR): Peripheral lymphocytes below 4*10^9/L, No lymphadenopathy, No hepatomegaly, No splenomegaly, No disease, Blood counts as Neutrophils >1.5*10^9/L, Platelets >100*10^9/L, Hemoglobin >11g/dL and Bone marrow at least normocellular for age. CRi was CR with incomplete bone marrow recovery. Partial response (PR): ≥50% decrease in peripheral lymphocyte count from pre-treatment value and either a ≥50% reduction in lymphadenopathy OR ≥50% reduction of liver enlargement OR ≥50% reduction of spleen enlargement, at least one of following: Neutrophils >1.5*10^9/L or ≥50% increase, Platelets >100*10^9/L, Hemoglobin 11 g/dL or ≥50% increase. Subjects from ITT population with data available for analysis. Subjects who did not reach 3 month Follow-up visit at clinical cutoff are excluded. Here, 99999 indicates that 95% CI was not estimated.

End point type	Secondary

End point timeframe:

Randomisation to clinical cutoff date of 10 Oct 2017 (median observation in Stage 1a: 62.5 months and Stage 1b: 57.7 months)

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure only looked at Stage 1 data.

End point values	Stage 1: Rituximab + Chlorambucil (RClb)	Stage 1: Obinutuzumab + Chlorambucil (GClb)	Stage 1: Chlorambucil (Clb)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	233	238	118	
Units: percentage of subject				
number (confidence interval 95%)				
Complete Response (CR)	7.7 (4.6 to 11.9)	26.5 (21.0 to 32.6)	0 (0 to 3.1)	
Complete Response incomplete (CRi)	1.7 (0.5 to 4.3)	2.5 (0.9 to 5.4)	1.7 (0.2 to 6)	
Partial Response (PR)	54.9 (48.3 to 61.4)	47.1 (40.6 to 53.6)	31.4 (23.1 to 40.5)	
Nodular Partial Response (nPR)	1.7 (0.5 to 4.3)	2.1 (0.7 to 4.8)	0 (0 to 3.1)	
Stable Disease	13.3 (9.2 to 18.4)	4.2 (2.0 to 7.6)	21.2 (14.2 to 29.7)	
Progressive Disease	12.4 (8.5 to 17.4)	4.2 (2.0 to 7.6)	28.8 (20.8 to 37.9)	
No Response Assessment	8.2 (-99999 to 99999)	13.4 (-99999 to 99999)	16.9 (-99999 to 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Best Overall Response in Stage 2

End point title	Percentage of Subjects With Best Overall Response in Stage

End point description:

Best overall response according to IWCLL guidelines was defined as the percentage of subjects with CR, CRi, PR or nPR. Complete Response (CR): Peripheral lymphocytes below 4*10^9/L, No lymphadenopathy, No hepatomegaly, No splenomegaly, No disease, Blood counts as Neutrophils >1.5*10^9/L, Platelets >100*10^9/L, Hemoglobin >11g/dL and Bone marrow at least normocellular for age. CRi was CR with incomplete bone marrow recovery. Partial response (PR): ≥50% decrease in peripheral lymphocyte count from pre-treatment value and either a ≥50% reduction in lymphadenopathy OR ≥50% reduction of liver enlargement OR ≥50% reduction of spleen enlargement, at least one of following: Neutrophils >1.5*10^9/L or ≥50% increase, Platelets >100*10^9/L, Hemoglobin 11 g/dL or ≥50% increase. Subjects from ITT population with data available for analysis. Subjects who did not reach 3 month Follow-up visit at clinical cutoff are excluded. Here, 99999 indicates that 95% CI not estimated.

End point type	Secondary

End point timeframe:

Randomisation to clinical cutoff date of 10 Oct 2017 (median observation 59.4 months)

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure only looked at Stage 2 data.

End point values	Stage 2: Rituximab + Chlorambucil (RClb)	Stage 2: Obinutuzumab + Chlorambucil (GClb)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	330	333		
Units: percentage of subject				
number (confidence interval 95%)				
Complete Response (CR)	7.0 (4.5 to 10.3)	23.7 (19.3 to 28.7)		
Complete Response incomplete (CRi)	1.2 (0.3 to 3.1)	1.8 (0.7 to 3.9)		
Partial Response (PR)	55.5 (49.9 to 60.9)	50.8 (45.2 to 56.2)		
Nodular Partial Response (nPR)	2.7 (1.3 to 5.1)	3.0 (1.4 to 5.5)		
Stable Disease	14.5 (10.9 to 18.8)	3.9 (2.1 to 6.6)		
Progressive Disease	11.5 (8.3 to 15.5)	4.5 (2.5 to 7.3)		
No Response Assessment	7.6 (-99999 to 99999)	12.3 (-99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Event Free Survival (EFS) in Stage 1

End point title	Event Free Survival (EFS) in Stage 1[18]

End point description:

EFS was defined as the time between date of randomization and the date of disease progression/relapse, death, or start of a new anti-leukemic therapy. Progressive disease as per IWCLL criteria required at least one of the following: ≥50% increase in the absolute number of lymphocytes, appearance of new palpable lymph nodes (>15 mm in longest diameter) or any new extra nodal lesion, ≥50% increase in the longest diameter of any previous site of clinically significant lymphadenopathy, ≥50% increase in the enlargement of the liver and/or spleen, Transformation to a more aggressive histology or After treatment, the progression of any cytopenia (a decrease of hemoglobin levels >20 g/L or <10 g/dL or a decrease of platelet counts >50% or <100*10^9/L or by a decrease of neutrophil counts >50% or <1.0*10^9/L). ITT population. Subjects without EFS events were censored.

End point type	Secondary

End point timeframe:

Randomisation to clinical cutoff date of 10 Oct 2017 (median observation in Stage 1a: 62.5 months and 1b: 57.7 months)

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure only looked at Stage 1 data.

End point values	Stage 1: Rituximab + Chlorambucil (RClb)	Stage 1: Obinutuzumab + Chlorambucil (GClb)	Stage 1: Chlorambucil (Clb)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	233	238	118	
Units: months				
median (confidence interval 95%)	15.7 (14.2 to 17.2)	28.7 (23.9 to 32.9)	10.8 (8 to 11.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Event Free Survival (EFS) in Stage 2

End point title	Event Free Survival (EFS) in Stage 2[19]

End point description:

EFS was defined as the time between date of randomisation and the date of disease progression/relapse, death, or start of a new anti-leukemic therapy. Progressive disease as per IWCLL criteria required at least one of the following: ≥50% increase in the absolute number of lymphocytes, appearance of new palpable lymph nodes (>15 mm in longest diameter) or any new extra nodal lesion, ≥50% increase in the longest diameter of any previous site of clinically significant lymphadenopathy, ≥50% increase in the enlargement of the liver and/or spleen, Transformation to a more aggressive histology or After treatment, the progression of any cytopenia (a decrease of hemoglobin levels >20 g/L or <10 g/dL or a decrease of platelet counts >50% or <100*10^9/L or by a decrease of neutrophil counts >50% or <1.0*10^9/L). ITT population. Subjects without EFS events were censored.

End point type	Secondary

End point timeframe:

Randomisation to clinical cutoff date of 10 Oct 2017 (median observation 59.4 months)

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure only looked at Stage 2 data.

End point values	Stage 2: Rituximab + Chlorambucil (RClb)	Stage 2: Obinutuzumab + Chlorambucil (GClb)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	330	333		
Units: months				
median (confidence interval 95%)	15 (14.2 to 17.1)	26.5 (24.8 to 30.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival in Stage 1

End point title	Overall Survival in Stage 1[20]

End point description:

Overall Survival (OS) was defined as the time between the date of randomization and the date of death due to any cause. ITT population. Subjects without OS events were censored. Here, 99999 indicates that median survival time and 95% CI could not be estimated due to a low number of deaths.

End point type	Secondary

End point timeframe:

Randomisation to clinical cutoff date of 10 Oct 2017 (median observation in Stage 1a: 62.5 months and Stage 1b: 57.7 months)

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure only looked at Stage 1 data.

End point values	Stage 1: Rituximab + Chlorambucil (RClb)	Stage 1: Obinutuzumab + Chlorambucil (GClb)	Stage 1: Chlorambucil (Clb)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	233	238	118	
Units: months				
median (confidence interval 95%)	74.9 (60.8 to 99999)	99999 (74.2 to 99999)	66.7 (50.9 to 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival in Stage 2

End point title	Overall Survival in Stage 2[21]

End point description:

Overall Survival (OS) was defined as the time between the date of randomization and the date of death due to any cause. ITT population. Subjects who were not reported as having died at the time of the analysis were censored at the date when they were last known to be alive. Here, the median survival time and upper limit of 95% CI could not be estimated due to a low number of deaths

End point type	Secondary

End point timeframe:

Randomisation to clinical cutoff date of 10 Oct 2017 (median observation 59.4 months)

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure only looked at Stage 2 data.

End point values	Stage 2: Rituximab + Chlorambucil (RClb)	Stage 2: Obinutuzumab + Chlorambucil (GClb)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	330	333		
Units: months				
median (confidence interval 95%)	73.1 (60.8 to 99999)	99999 (74.6 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response in Stage 1

End point title	Duration of Response in Stage 1[22]

End point description:

Duration of Response was defined as the date the response [either Complete Response (CR) or Partial Response (PR)] was first recorded until the date of Disease Progression or death due to any cause. Response was assessed according IWCLL guidelines. Subjects from the ITT population with response. Subjects from the ITT population with CR or PR. Subject without response were censored.

End point type	Secondary

End point timeframe:

Randomisation to clinical cutoff date of 10 Oct 2017 (median observation in Stage 1a: 62.5 months and Stage 1b: 57.7 months)

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure only looked at Stage 1 data.

End point values	Stage 1: Rituximab + Chlorambucil (RClb)	Stage 1: Obinutuzumab + Chlorambucil (GClb)	Stage 1: Chlorambucil (Clb)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	155	191	41	
Units: months				
median (confidence interval 95%)	12.2 (9.5 to 14.5)	24.8 (22.1 to 33.5)	5.1 (3.3 to 6.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response in Stage 2

End point title	Duration of Response in Stage 2[23]

End point description:

Duration of Response was defined as the date the response [either Complete Response (CR) or Partial Response (PR)] was first recorded until the date of Disease Progression or death due to any cause. Response was assessed according IWCLL guidelines. Subjects from the ITT population with CR or PR. Subject without response were censored.

End point type	Secondary

End point timeframe:

Randomisation to clinical cutoff date of 10 Oct 2017 (median observation 59.4 months)

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure only looked at Stage 2 data.

End point values	Stage 2: Rituximab + Chlorambucil (RClb)	Stage 2: Obinutuzumab + Chlorambucil (GClb)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	220	271		
Units: months				
median (confidence interval 95%)	11.8 (9.5 to 12.6)	23.8 (19.1 to 30.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Molecular Remission at the End of Treatment in Stage 1

End point title	Percentage of Subjects With Molecular Remission at the End of Treatment in Stage 1[24]

End point description:

Molecular remission was defined as a minimal residual disease (MRD)-negative result at the end of treatment (assessment that occurred between 56 days and 6 months of last treatment). Molecular remission was assessed for all subjects using a blood sample. Additionally, a bone marrow sample was obtained from subjects whom the investigator assumed to have a complete response, consistent with the IWCLL guidelines. A combined analysis of blood and bone marrow results was conducted. A subject was considered MRD negative if result was less than 1 chronic lymphocytic leukemia (CLL) cell in 10000 leukocytes (MRD value < 0.0001) based on the method of allele specific polymerase chain reaction (ASO-PCR). Subjects from ITT population with data available for analysis. Subjects who did not reach 3 month Follow-up visit at clinical cutoff are excluded.

End point type	Secondary

End point timeframe:

Randomisation to clinical cutoff date of 10 Oct 2017 (median observation in Stage 1a: 62.5 months and Stage 1b: 57.7 months)

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure only looked at Stage 1 data.

End point values	Stage 1: Rituximab + Chlorambucil (RClb)	Stage 1: Obinutuzumab + Chlorambucil (GClb)	Stage 1: Chlorambucil (Clb)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	170	166	90	
Units: percentage of subject				
number (confidence interval 95%)	2 (0.6 to 5.9)	25 (18.9 to 32.6)	0 (0.0 to 4.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Molecular Remission at the End of

Treatment in Stage 2

End point title	Percentage of Subjects With Molecular Remission at the End of Treatment in Stage 2[25]

End point description:

Molecular remission was defined as a minimal residual disease (MRD)-negative result at the end of treatment (assessment that occurred between 56 days and 6 months of last treatment). Molecular remission was assessed for all subjects using a blood sample. Additionally, a bone marrow sample was obtained from subjects whom the investigator assumed to have a complete response, consistent with the IWCLL guidelines. A combined analysis of blood and bone marrow results was conducted. A subject was considered MRD negative if result was less than 1 chronic lymphocytic leukemia (CLL) cell in 10000 leukocytes (MRD value < 0.0001) based on the method of allele specific polymerase chain reaction (ASO-PCR). Subjects from ITT population with data available for analysis. Subjects who did not reach 3 month Follow-up visit at clinical cutoff are excluded.

End point type	Secondary

End point timeframe:

Randomisation to clinical cutoff date of 10 Oct 2017 (median observation 59.4 months)

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure only looked at Stage 2 data.

End point values	Stage 2: Rituximab + Chlorambucil (RClb)	Stage 2: Obinutuzumab + Chlorambucil (GClb)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246	237		
Units: percentage of subjects				
number (confidence interval 95%)	2 (0.9 to 5.2)	24 (18.8 to 30.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Re-Treatment/New-antileukemic Therapy in Stage 1

End point title	Time to Re-Treatment/New-antileukemic Therapy in Stage 1[26]

End point description:

Time to re-treatment/new anti-leukemic therapy was defined as time between the date of randomization and the date of first intake of re-treatment or new anti-leukemic therapy. ITT population. Subjects without events (re-treatment or new anti-leukemic therapy) were censored. Here, 99999 indicates that the upper limit 95% CI was not reached.

End point type	Secondary

End point timeframe:

Randomisation to clinical cutoff date of 10 Oct 2017 (median observation in Stage 1a: 62.5 months and Stage 1b: 57.7 months)

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure only looked at Stage 1 data.

End point values	Stage 1: Rituximab + Chlorambucil (RClb)	Stage 1: Obinutuzumab + Chlorambucil (GClb)	Stage 1: Chlorambucil (Clb)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	233	238	118	
Units: months				
median (confidence interval 95%)	33.2 (27.8 to 44.4)	55.7 (47.4 to 99999)	15.1 (11.7 to 18.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Re-Treatment/New-antileukemic Therapy in Stage 2

End point title	Time to Re-Treatment/New-antileukemic Therapy in Stage 2[27]

End point description:

Time to re-treatment/new anti-leukemic therapy was defined as time between the date of randomization and the date of first intake of re-treatment or new anti-leukemic therapy. ITT population. Subjects who were reported as not having started re-treatment or new anti−leukemic therapy were censored at the last visit date they were assessed with regard to start of new treatment or the date of death. Here, 99999 indicates that the upper limit of 95% CI was not reached.

End point type	Secondary

End point timeframe:

Randomisation to clinical cutoff date of 10 Oct 2017 (median observation 59.4 months)

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure only looked at Stage 2 data.

End point values	Stage 2: Rituximab + Chlorambucil (RClb)	Stage 2: Obinutuzumab + Chlorambucil (GClb)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	330	333		
Units: months				
median (confidence interval 95%)	34.9 (29.1 to 41.6)	56.4 (48.3 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) of Obinutuzumab (RO5072759) in Combination With Chlorambucil (Clb)

End point title	Pharmacokinetics (PK) of Obinutuzumab (RO5072759) in Combination With Chlorambucil (Clb)[28]

End point description:

Blood samples were collected from all subjects allocated to the GClb treatment arm pre- and post-dose Day 1 of Cycles 1 to 6 and were sent to a laboratory. The concentration of obinutzumab in serum was

determined using a validated enzyme-linked immunosorbent assay (ELISA) and was reported in micrograms/milliliter (µg/mL). PK population includes all subjects with PK data available at the given time-point.

End point type	Secondary

End point timeframe:

Pre- and post-dose sampling on day 1 of cycles 1-6 (Up to 26.8 months)

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure only looked at the PK data of obinutuzumab and chlorambucil arm.

End point values	Stage 1: Obinutuzumab + Chlorambucil (GClb)			
Subject group type	Reporting group			
Number of subjects analysed	220			
Units: µg/mL				
geometric mean (geometric coefficient of variation)				
Post-dose Cycle 1 (n=201)	247 (± 41.6)			
Pre-dose Cycle 2 (n=198)	227 (± 57.9)			
Post-dose Cycle 2 (n=197)	587 (± 36.5)			
Pre-dose Cycle 3 (n=193)	165 (± 68.7)			
Post-dose Cycle 3 (n=192)	527 (± 39.7)			
Pre-dose Cycle 4 (n=191)	156 (± 74.3)			
Post-dose Cycle 4 (n=189)	535 (± 41)			
Pre-dose Cycle 5 (n=185)	163 (± 72.4)			
Post-dose Cycle 5 (n=181)	534 (± 39.1)			
Pre-dose Cycle 6 (n=185)	181 (± 69)			
Post-dose Cycle 6 (n=183)	525 (± 39.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 Questionnaire in Stage 1

End point title	European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 Questionnaire in Stage 1[29]

End point description:

The EORTC Quality of Life Questionnaire (QLQ-C30) was used to assess patient-reported outcomes (PRO) and symptom burden. The QLQ-C30 contains 30 items including the functional scales of physical functioning (5 items), role functioning (2 items), emotional functioning (4 items), cognitive functioning (2 items), social functioning (2 items) and symptom scales including fatigue (3 items), nausea and vomiting (2 items), and pain (4 items) and six single item scales on dyspnea, sleep disturbance, appetite loss, constipation, diarrhea and financial impact. Final scores are transformed such that they range from 0 − 100, whereby higher scores indicate greater functioning, greater quality of life, or a greater degree of symptoms, with changes of 5 − 10 points considered to be of minimally important difference to subjects. A positive change from Baseline indicated improvement.

End point type	Secondary

End point timeframe:

Baseline and Cycle 4 Day 1 (Cy4D1)

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This outcome measure only looked at Stage 1 data.

End point values	Stage 1: Rituximab + Chlorambucil (RClb)	Stage 1: Obinutuzumab + Chlorambucil (GClb)	Stage 1: Chlorambucil (Clb)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	233	238	118	
Units: unit on a scale				
arithmetic mean (standard deviation)				
Appetite Loss: Baseline (n=226, 111, 220)	15.8 (± 27.11)	18.1 (± 28.46)	19.8 (± 29.26)	
Appetite Loss: Cy4D1(n=189,92,196)	10.9 (± 21.50)	10.2 (± 21.77)	14.5 (± 24.36)	
Cognitive Functioning: Baseline (n=227, 111, 221)	82.7 (± 20.77)	80.6 (± 21.35)	81.8 (± 22.76)	
Cognitive Functioning: Cy4D1 (n=190,93,196)	83.0 (± 17.86)	83.9 (± 20.31)	85.8 (± 18.54)	
Constipation: Baseline (n=225, 111, 219)	15.1 (± 25.37)	14.8 (± 23.94)	16.8 (± 26.92)	
Constipation: Cy4D1 (n=188, 93, 195)	13.3 (± 22.04)	15.1 (± 25.16)	12.5 (± 23.53)	
Diarrhoea: Baseline (n=226, 110, 220)	7.6 (± 18.66)	9.3 (± 20.05)	8.8 (± 18.98)	
Diarrhoea: Cy4D1 (n=189, 93, 195)	9.2 (± 20.45)	9.3 (± 19.47)	6.5 (± 14.95)	
Dyspnoea: Baseline (n=225, 109, 220)	26.1 (± 28.09)	27.1 (± 29.89)	23.9 (± 27.63)	
Dyspnoea: Cy4D1 (n=189, 91, 196)	19.7 (± 25.19)	15.9 (± 23.71)	22.3 (± 26.78)	
Emotional Functioning: Baseline (n=226, 111, 221)	77.3 (± 21.23)	73.8 (± 23.45)	72.9 (± 25.7)	
Emotional Functioning: Cy4D1(n=190,93,196)	82.8 (± 17.52)	82.5 (± 18.62)	80.6 (± 18.48)	
Fatigue: Baseline (n=226, 111, 221)	35.8 (± 24.60)	38 (± 25.72)	36.9 (± 27.01)	
Fatigue: Cy4D1(n=189, 93, 197)	29.6 (± 22.24)	29.2 (± 20.39)	30.8 (± 23.00)	
Financial Difficulties: Baseline (n=224,110, 220)	10.9 (± 22.12)	8.9 (± 20.69)	13.6 (± 25.26)	
Financial Difficulty: Cy4D1(n=189,93, 193)	10.2 (± 20.26)	7.4 (± 17.64)	9.3 (± 19.88)	
Nausea, Vomiting: Baseline (n=227, 111, 221)	4.4 (± 12.04)	5 (± 11.18)	7.4 (± 18.49)	
Nausea, Vomiting: Cy4D1 (n=189,93, 197)	3.6 (± 8.99)	5.5 (± 11.51)	7.5 (± 17.81)	
Pain: Baseline (n=228, 111, 221)	21.5 (± 27.37)	22.9 (± 27.57)	21.5 (± 25.66)	
Pain: Cy4D1 (n=190, 93, 197)	15.1 (± 22.41)	17.9 (± 24.09)	17.7 (± 25.98)	
Physical Functioning: Baseline (n=228, 111, 221)	76.1 (± 18.95)	73.7 (± 19.86)	77.3 (± 18.87)	
Physical Functioning: Cy4D1(n=189,93,197)	77.6 (± 18.27)	78.6 (± 18.71)	80.9 (± 16.24)	
Global Health Status: Baseline (n=226, 111, 219)	58.7 (± 22.28)	58.4 (± 22.8)	57.4 (± 22.9)	
Global Health Status: Cy4D1(n=189,93, 195)	65.7 (± 20.13)	66.7 (± 20.03)	63.4 (± 20.56)	
Role Functioning: Baseline(n=227,110, 221)	76.9 (± 28.70)	76.1 (± 26.18)	74.7 (± 28.35)	
Role Functioning: Cy4D1(n=189,93,197)	79.4 (± 25.97)	79.7 (± 23.64)	81.5 (± 21.35)	
Social Functioning:Baseline(n=226,110, 221)	82.1 (± 24.49)	86.3 (± 22.52)	83.3 (± 25.34)	

Social Functioning: Cy4D1(n=190,93,195)	85.5 (± 20.79)	87.8 (± 19.97)	85.5 (± 19.38)	
Insomina: Baseline (n=228,111,220)	24.8 (± 30.03)	29.4 (± 31.12)	31.5 (± 32.98)	
Insomina: Cy4D1(n=189,93,195)	18.8 (± 25.77)	20.6 (± 27.13)	24.4 (± 29.13)	

Statistical analyses

No statistical analyses for this end point

Secondary: European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 Questionnaire in Stage 2

End point title	European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 Questionnaire in Stage 2[30]

End point description:

The EORTC quality of life questionnaire (QLQ-C30) was used to assess patient-reported outcomes (PRO) and symptom burden. The QLQ-C30 contains 30 items including the functional scales of physical functioning (5 items), role functioning (2 items), emotional functioning (4 items), cognitive functioning (2 items), social functioning (2 items) and symptom scales including fatigue (3 items), nausea and vomiting (2 items), and pain (4 items) and six single item scales on dyspnea, sleep disturbance, appetite loss, constipation, diarrhea and financial impact. Final scores are transformed such that they range from 0 − 100, whereby higher scores indicate greater functioning, greater quality of life, or a greater degree of symptoms, with changes of 5 − 10 points considered to be of minimally important difference to subjects.

End point type	Secondary

End point timeframe:

Baseline and Cycle 4 Day 1 (Cy4D1)

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure only looked at Stage 2 data.

End point values	Stage 2: Rituximab + Chlorambucil (RClb)	Stage 2: Obinutuzumab + Chlorambucil (GClb)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	330	333		
Units: unit on a scale				
arithmetic mean (standard deviation)				
Appetite Loss Scale: Baseline (n=314, 312)	15.4 (± 26.02)	19 (± 29.37)		
Appetite Loss Scale: Cy4D1 (n=277, 258)	12 (± 23.22)	10.9 (± 21.47)		
Cognitive Functioning Scale: Baseline(n=312, 315)	83 (± 20.02)	80.4 (± 22.52)		
Cognitive Functioning Scale: Cy4D1 (n=277, 259)	83.6 (± 17.26)	83.9 (± 20.25)		
Constipation Scale: Baseline (n=311, 312)	15.2 (± 24.62)	14.9 (± 23.54)		
Constipation Scale: Cy4D1 (n=276,256)	14.3 (± 23.05)	15.3 (± 25.16)		
Diarrhoea Scale: Baseline (n=311,313)	8.4 (± 18.78)	9.5 (± 19.58)		
Diarrhoea Scale: Cy4D1 (n=276,257)	8.8 (± 19.66)	9.2 (± 20.32)		
Dyspnoea Scale: Baseline (n=312,312)	27.5 (± 28.62)	27.8 (± 29.97)		
Dyspnoea: Cy4D1 (n=277,258)	20.8 (± 26.69)	16.5 (± 23.75)		

Emotional Functioning Scale: Baseline (n=312,314)	77.1 (± 21.32)	73.9 (± 23.14)		
Emotional Functioning Scale: Cy4D1 (n=277,259)	82.7 (± 18.29)	82.5 (± 19.18)		
Fatigue Scale: Baseline (n=313,312)	36.9 (± 25.86)	38.5 (± 26.05)		
Fatigue Scale: Cy4D1 (n=278,258)	30.4 (± 22.32)	29.8 (± 21.43)		
Financial Difficulties Scale: Baseline (n=309,312)	10.5 (± 21.53)	10.5 (± 22.14)		
Financial Difficulties Scale Cy4D1(n=273,258)	9.6 (± 20.02)	8.4 (± 19.35)		
Nausea, Vomiting Scale: Baseline (n=313,315)	4.5 (± 12.66)	5.3 (± 12.9)		
Nausea, Vomiting Scale: Cy4D1 (n=278,258)	4.1 (± 10.18)	5.2 (± 10.96)		
Pain scale: Baseline (n=313,316)	22.5 (± 27.59)	22.9 (± 27.73)		
Pain scale: Cy4D1 (n=278,259)	15.6 (± 22.48)	18.1 (± 24.60)		
Physical Functioning Scale: Baseline (n=313,316)	75.8 (± 19.34)	73.3 (± 20.77)		
Physical Functioning Scale: Cy4D1 (n=278,258)	77.8 (± 18.5)	78.5 (± 18.90)		
Global Health Status Scale: Baseline (n=310,313)	58.1 (± 22.74)	58 (± 23.81)		
Global Health Status Scale: Cy4D1 (n=257,256)	65.8 (± 20.22)	66.7 (± 20.27)		
Role Functioning Scale: Baseline (n=313,315)	76.4 (± 28.68)	74.3 (± 27.62)		
Role Functioning Scale: Cy4D1 (n=277,258)	79.9 (± 25.4)	78.7 (± 24.56)		
Social Functioning Scale: Baseline (n=312,314)	82.9 (± 23.81)	83.7 (± 24.96)		
Social Functioning Scale: Cy4D1(n=276,259)	85.4 (± 21)	86.6 (± 20.71)		
Insomnia: Baseline (n=312,316)	25.6 (± 30.91)	29.9 (± 31.18)		
Insomnia: Cy4D1(n=276,258)	20.9 (± 26.71)	21.6 (± 27.97)		

Statistical analyses

No statistical analyses for this end point

Secondary: European Organization for Research and Treatment of Cancer (EORTC) QLQ-CLL16 Questionnaire Score in Stage 1

End point title	European Organization for Research and Treatment of Cancer (EORTC) QLQ-CLL16 Questionnaire Score in Stage 1[31]

End point description:

EORTC Quality of Life Questionnaire (QLQ-CLL16) module was used to assess patient-reported outcomes and symptom burden. The QLQ-CLL16 module includes three multi-item scales assessing fatigue (2 items), treatment side effects and disease symptoms (8 items), infection (4 items) and two single item scales on social activities and future health worries. Final scores are transformed such that they range from 0 − 100, whereby higher scores indicate greater functioning, greater quality of life, or a greater degree of symptoms, with changes of 5 − 10 points considered to be of minimally important difference to subjects. A positive change from Baseline indicated improvement.

End point type	Secondary

End point timeframe:

Baseline and Cycle 4 Day 1 (Cy4D1)

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This outcome measure only looked at Stage 1 data.

End point values	Stage 1: Rituximab + Chlorambucil (RClb)	Stage 1: Obinutuzumab + Chlorambucil (GClb)	Stage 1: Chlorambucil (Clb)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	233	238	118	
Units: unit on a scale				
arithmetic mean (standard deviation)				
Disease Effects: Baseline (n=209, 102, 198)	22.7 (± 18.21)	23 (± 18.89)	23.7 (± 20.18)	
Disease Effects: Cy4D1 (n=176, 86, 173)	14.1 (± 13.71)	15.0 (± 15.12)	15.9 (± 14.16)	
Fatigue: Baseline (n=209, 102, 198)	27.8 (± 23.39)	31.2 (± 25.83)	27.6 (± 24.65)	
Fatigue: Cy4D1 (n=176, 86, 173)	20.0 (± 20.25)	20.9 (± 21.51)	23.4 (± 22.20)	
Future Health: Baseline (n=206, 101, 197)	45.9 (± 31.24)	47.7 (± 32.14)	50.8 (± 33.53)	
Future Health: Cy4D1 (n=175, 86, 171)	33.1 (± 28.12)	29.5 (± 31.74)	39.1 (± 30.33)	
Infection: Baseline (n=209, 102, 197)	9.7 (± 14.45)	12 (± 15.91)	14.6 (± 17.97)	
Infection: Cy4D1 (n=176, 86, 173)	8.9 (± 13.08)	8.9 (± 11.65)	8.5 (± 10.70)	
Social Problems: Baseline (n=206, 100, 195)	25.1 (± 31.40)	24.3 (± 31.99)	26.3 (± 33.26)	
Social Problems: Cy4D1 (n=175, 85, 173)	19.3 (± 25.94)	19.4 (± 27.75)	22.0 (± 27.00)	
Treatment Side Effects: Baseline (n=209,102, 198)	17.5 (± 14.98)	19.8 (± 17.7)	17.2 (± 15.27)	
Treatment Side Effect: Cy4D1(n=176, 86, 173)	13.9 (± 12.42)	14.7 (± 14.68)	15.6 (± 16.11)	

Statistical analyses

No statistical analyses for this end point

Secondary: European Organization for Research and Treatment of Cancer (EORTC) QLQ-CLL16 Questionnaire in Stage 2

End point title	European Organization for Research and Treatment of Cancer (EORTC) QLQ-CLL16 Questionnaire in Stage 2[32]

End point description:

EORTC Quality of Life Questionnaire (QLQ-CLL16) module was used to assess patient-reported outcomes and symptom burden. The QLQ-CLL16 module includes three multi-item scales assessing fatigue (2 items), treatment side effects and disease symptoms (8 items), infection (4 items) and two single item scales on social activities and future health worries. Final scores are transformed such that they range from 0 − 100, whereby higher scores indicate greater functioning, greater quality of life, or a greater degree of symptoms, with changes of 5 − 10 points considered to be of minimally important difference to subjects.

End point type	Secondary

End point timeframe:

Baseline and Cycle 4 Day 1 (Cy4D1)

Notes:

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This outcome measure only looked at Stage 2 data.

End point values	Stage 2: Rituximab + Chlorambucil (RClb)	Stage 2: Obinutuzumab + Chlorambucil (GClb)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	330	333		
Units: unit on a scale				
arithmetic mean (standard deviation)				
Disease Effects Scale: Baseline (n=276,284)	22.8 (± 17.94)	22.7 (± 18.49)		
Disease Effects Scale: Cy4D1 (n=243, 233)	15.4 (± 15)	14.7 (± 15.34)		
Fatigue Scale: Baseline (n=276, 284)	27.7 (± 23.48)	31.1 (± 25.32)		
Fatigue Scale: Cy4D1 (n=243, 233)	21 (± 20.52)	20.6 (± 20.82)		
Future Health: Baseline (n=275, 280)	47.5 (± 32.17)	49.8 (± 32.79)		
Future Health: Cy4D1 (n=240, 231)	33.9 (± 29.72)	30.3 (± 31.17)		
Infection Scale: Baseline (n=275, 284)	11.8 (± 15.83)	12.7 (± 16.67)		
Infection Scale: Cy4D1 (n=243, 233)	9.4 (± 13.94)	9 (± 12.2)		
Social Problems: Baseline (n=271, 281)	25.2 (± 32.45)	23.6 (± 31.12)		
Social Problems: Cy4D1 (n=242, 232)	19.3 (± 26.03)	19.5 (± 27.94)		
Treatment Side Effects Scale: Baseline(n=276, 284)	17.9 (± 15.69)	19.9 (± 17.59)		
Treatment Side Effect Scale: Cy4D1(n=243, 243)	14.2 (± 13.57)	14.6 (± 14.89)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomisation up to 5.5 years

Adverse event reporting additional description:

Adverse events were reported as per the treatment received by the subjects, not as per the stages (i.e. Stage 1a [GClb vs Clb], Stage 1b [RClb vs Clb] and Stage 2 [GClb vs RClb]) of analysis.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Rituximab + Chlorambucil (RClb)

Reporting group description:

Subject received 375 mg/m^2 rituximab IV infusion on Day 1 of Cycle 1 then 500 mg/m^2 IV infusions on Day 1 of Cycles 2-6 (28-day cycles) plus chlorambucil 0.5 mg/kg orally on Day 1 and 15 of each 28-day cycle (6 cycles).

Reporting group title	Obinutuzumab + Chlorambucil (GClb)

Reporting group description:

Subjects received 1000 mg obinutuzumab IV infusion, on Day 1 [First infusion split 100 mg on Day 1 and 900 mg on Day 2 as per protocol amendment], 8 and 15 in Cycle 1 and Day 1 of Cycles 2-6 (28-day cycles) plus chlorambucil 0.5 milligram per kilogram of body weight (mg/kg) orally on Day 1 and 15 of each 28-day cycle (6 Cycles).

Reporting group title	Crossover subjects: Obinutuzumab + Chlorambucil (GClb)

Reporting group description:

Subjects in Clb arm who progressed during/within 6 months after end of Clb treatment had opportunity to cross over to GClb arm at discretion of investigator. Subjects received 1000 mg obinutuzumab IV infusion, on Day 1 [First infusion split 100 mg on Day 1 and 900 mg on Day 2 as per protocol amendment], 8 and 15 in Cycle 1 and Day 1 of Cycles 2-6 (28-day cycles) plus chlorambucil 0.5 milligram per kilogram of body weight (mg/kg) orally on Day 1 and 15 of each 28-day cycle (6 Cycles).

Reporting group title	Chlorambucil (Clb)

Reporting group description:

Subjects received chlorambucil 0.5 mg/kg orally on Day 1 and 15 of each 28-day cycle (6 Cycles). Subjects with Progressive Disease or within 6 months of follow-up were allowed to cross over to receive obinutuzumab + chlorambucil.

Serious adverse events	Rituximab + Chlorambucil (RClb)	Obinutuzumab + Chlorambucil (GClb)	Crossover subjects: Obinutuzumab + Chlorambucil (GClb)
Total subjects affected by serious adverse events			
subjects affected / exposed	124 / 321 (38.63%)	150 / 336 (44.64%)	8 / 30 (26.67%)
number of deaths (all causes)	144	123	2
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of skin			

subjects affected / exposed	6 / 321 (1.87%)	6 / 336 (1.79%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 8	0 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	2 / 321 (0.62%)	2 / 336 (0.60%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Pancreatic carcinoma			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Plasma cell myeloma			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Prostate cancer			
subjects affected / exposed	3 / 321 (0.93%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	7 / 321 (2.18%)	4 / 336 (1.19%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	2 / 7	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma gastric			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Choroid melanoma			

subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	1 / 321 (0.31%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Gastrointestinal stromal tumour			
subjects affected / exposed	0 / 321 (0.00%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular carcinoma			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Intraocular melanoma			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Keratoacanthoma			
subjects affected / exposed	1 / 321 (0.31%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelodysplastic syndrome			
subjects affected / exposed	3 / 321 (0.93%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	1 / 3	0 / 1	0 / 0
Non-small cell lung cancer			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal adenocarcinoma			

subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Rectal cancer			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cell carcinoma			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Schwannoma			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of lung			
subjects affected / exposed	1 / 321 (0.31%)	2 / 336 (0.60%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Superficial spreading melanoma stage unspecified			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transitional cell carcinoma			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Oropharyngeal cancer			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic malignant melanoma			

subjects affected / exposed	2 / 321 (0.62%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Intracranial tumour haemorrhage			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Diffuse large B-cell lymphoma			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchial carcinoma			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Breast cancer			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bowen's disease			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Acute myeloid leukaemia			

subjects affected / exposed	2 / 321 (0.62%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Skin cancer			
subjects affected / exposed	2 / 321 (0.62%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic squamous cell carcinoma			
subjects affected / exposed	2 / 321 (0.62%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Colon adenoma			
subjects affected / exposed	1 / 321 (0.31%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	4 / 321 (1.25%)	8 / 336 (2.38%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	1 / 4	0 / 8	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of colon			
subjects affected / exposed	1 / 321 (0.31%)	2 / 336 (0.60%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Gastric cancer			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Malignant melanoma in situ			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cancer			

subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic neoplasm			
subjects affected / exposed	0 / 321 (0.00%)	0 / 336 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Lung neoplasm			
subjects affected / exposed	0 / 321 (0.00%)	0 / 336 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic stenosis			
subjects affected / exposed	0 / 321 (0.00%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Capillary leak syndrome			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic macroangiopathy			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dry gangrene			
subjects affected / exposed	0 / 321 (0.00%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			

subjects affected / exposed	0 / 321 (0.00%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery thrombosis			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis superficial			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Circulatory collapse			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant hypertension			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis			

subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Fracture treatment			
subjects affected / exposed	0 / 321 (0.00%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	2 / 321 (0.62%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	1 / 321 (0.31%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	3 / 321 (0.93%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 3	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	3 / 321 (0.93%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Impaired healing			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Malaise			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	2 / 321 (0.62%)	2 / 336 (0.60%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	2 / 321 (0.62%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adhesion			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Prostatic obstruction			
subjects affected / exposed	0 / 321 (0.00%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Testicular hypertrophy			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 321 (0.00%)	2 / 336 (0.60%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 321 (0.31%)	2 / 336 (0.60%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 321 (0.62%)	2 / 336 (0.60%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pulmonary alveolar haemorrhage			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Interstitial lung disease			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Dyspnoea			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute pulmonary oedema			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disorientation			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mania			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Major depression			
subjects affected / exposed	0 / 321 (0.00%)	0 / 336 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Platelet count decreased			
subjects affected / exposed	0 / 321 (0.00%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General physical condition abnormal			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin decreased			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	5 / 321 (1.56%)	34 / 336 (10.12%)	2 / 30 (6.67%)
occurrences causally related to treatment / all	6 / 6	36 / 36	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 321 (0.31%)	3 / 336 (0.89%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	3 / 321 (0.93%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 321 (0.00%)	2 / 336 (0.60%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	1 / 321 (0.31%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture displacement			
subjects affected / exposed	0 / 321 (0.00%)	2 / 336 (0.60%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Spinal fracture			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Subdural haemorrhage			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shunt thrombosis			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pubis fracture			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laceration			

subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	2 / 321 (0.62%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 321 (0.00%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Hereditary non-polyposis colorectal cancer syndrome			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phimosis			
subjects affected / exposed	0 / 321 (0.00%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 321 (0.00%)	4 / 336 (1.19%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Cardiac failure			
subjects affected / exposed	2 / 321 (0.62%)	4 / 336 (1.19%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 3	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0

Atrial fibrillation			
subjects affected / exposed	1 / 321 (0.31%)	2 / 336 (0.60%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute coronary syndrome			
subjects affected / exposed	1 / 321 (0.31%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial thrombosis			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nodal rhythm			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachyarrhythmia			
subjects affected / exposed	0 / 321 (0.00%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	3 / 321 (0.93%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 3	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	2 / 321 (0.62%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			

subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve stenosis			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure chronic			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular extrasystoles			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	2 / 321 (0.62%)	3 / 336 (0.89%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Syncope			

subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Central nervous system haemorrhage			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 321 (0.00%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic encephalopathy			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haematoma			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Depressed level of consciousness			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoaesthesia			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures			

subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	3 / 321 (0.93%)	6 / 336 (1.79%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	3 / 3	6 / 6	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	2 / 321 (0.62%)	3 / 336 (0.89%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	2 / 5	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune haemolytic anaemia			
subjects affected / exposed	1 / 321 (0.31%)	2 / 336 (0.60%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	2 / 321 (0.62%)	4 / 336 (1.19%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	2 / 2	5 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 321 (0.31%)	4 / 336 (1.19%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolysis			

subjects affected / exposed	0 / 321 (0.00%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolytic anaemia			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune thrombocytopenic purpura			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	2 / 321 (0.62%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytopenia			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 321 (0.00%)	3 / 336 (0.89%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			

subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 321 (0.31%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 321 (0.00%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 321 (0.00%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis mesenteric vessel			
subjects affected / exposed	0 / 321 (0.00%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Food poisoning			

subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proctitis			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varices oesophageal			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fistula			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			

subjects affected / exposed	0 / 321 (0.00%)	0 / 336 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 321 (0.00%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver disorder			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	0 / 321 (0.00%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin disorder			

subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Cystitis haemorrhagic			
subjects affected / exposed	0 / 321 (0.00%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	3 / 321 (0.93%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute prerenal failure			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephritic syndrome			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	1 / 321 (0.31%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal column stenosis			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gouty arthritis			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	19 / 321 (5.92%)	14 / 336 (4.17%)	2 / 30 (6.67%)
occurrences causally related to treatment / all	9 / 25	9 / 17	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	2 / 321 (0.62%)	3 / 336 (0.89%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 2	3 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	3 / 321 (0.93%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 321 (0.31%)	3 / 336 (0.89%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			

subjects affected / exposed	1 / 321 (0.31%)	3 / 336 (0.89%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	3 / 321 (0.93%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 321 (0.31%)	3 / 336 (0.89%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	3 / 321 (0.93%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	3 / 321 (0.93%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	2 / 321 (0.62%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 321 (0.31%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	1 / 321 (0.31%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			

subjects affected / exposed	0 / 321 (0.00%)	2 / 336 (0.60%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia infection			
subjects affected / exposed	1 / 321 (0.31%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis B			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	2 / 321 (0.62%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 321 (0.31%)	1 / 336 (0.30%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 321 (0.00%)	2 / 336 (0.60%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Streptococcal sepsis			
subjects affected / exposed	1 / 321 (0.31%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella			
subjects affected / exposed	2 / 321 (0.62%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			

subjects affected / exposed	1 / 321 (0.31%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dacryocystitis			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related sepsis			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epididymitis			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Furuncle			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gangrene			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			

subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis clostridial			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes simplex			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected skin ulcer			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious colitis			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of bronchiectasis			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral discitis			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngitis			

subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver abscess			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ophthalmic herpes zoster			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia influenzal			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Septic arthritis staphylococcal			

subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superinfection bacterial			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth abscess			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic infection			
subjects affected / exposed	0 / 321 (0.00%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral candidiasis			
subjects affected / exposed	0 / 321 (0.00%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			

subjects affected / exposed	0 / 321 (0.00%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stenotrophomonas sepsis			
subjects affected / exposed	0 / 321 (0.00%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis B reactivation			
subjects affected / exposed	1 / 321 (0.31%)	0 / 336 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Tumour lysis syndrome			
subjects affected / exposed	0 / 321 (0.00%)	5 / 336 (1.49%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	5 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 321 (0.00%)	1 / 336 (0.30%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Chlorambucil (Clb)		
Total subjects affected by serious adverse events			
subjects affected / exposed	45 / 116 (38.79%)		
number of deaths (all causes)	57		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of skin			

subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung adenocarcinoma				
subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Malignant melanoma				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatic carcinoma				
subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Plasma cell myeloma				
subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Prostate cancer				
subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Squamous cell carcinoma				
subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Adenocarcinoma gastric				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Choroid melanoma				

subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colon cancer			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal stromal tumour			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatocellular carcinoma			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intraocular melanoma			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Keratoacanthoma			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myelodysplastic syndrome			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Non-small cell lung cancer			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rectal adenocarcinoma			

subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rectal cancer				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal cell carcinoma				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Schwannoma				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of lung				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Superficial spreading melanoma stage unspecified				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Transitional cell carcinoma				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oropharyngeal cancer				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastatic malignant melanoma				

subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung neoplasm malignant				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intracranial tumour haemorrhage				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diffuse large B-cell lymphoma				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchial carcinoma				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Breast cancer				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bowen's disease				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Adenocarcinoma				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute myeloid leukaemia				

subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin cancer				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastatic squamous cell carcinoma				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colon adenoma				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Basal cell carcinoma				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Adenocarcinoma of colon				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric cancer				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Malignant melanoma in situ				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal cancer				

subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastatic neoplasm				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung neoplasm				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Deep vein thrombosis				
subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Aortic stenosis				
subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Capillary leak syndrome				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diabetic macroangiopathy				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dry gangrene				
subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Orthostatic hypotension				

subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral artery thrombosis				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thrombophlebitis superficial				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Circulatory collapse				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypertension				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypertensive crisis				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Malignant hypertension				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peripheral ischaemia				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Venous thrombosis				

subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Fracture treatment			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Asthenia			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Impaired healing			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Malaise				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Adhesion				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chills				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Anaphylactic reaction				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Prostatic obstruction				
subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Testicular hypertrophy				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary oedema			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Pulmonary alveolar haemorrhage			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Interstitial lung disease			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Dyspnoea				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Asthma				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute pulmonary oedema				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Delirium				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Disorientation				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mania				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Major depression				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Platelet count decreased				
subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

General physical condition abnormal				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemoglobin decreased				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Infusion related reaction				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tibia fracture				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Femoral neck fracture				
subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fracture displacement				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Spinal fracture				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subdural haematoma				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subdural haemorrhage				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tendon rupture				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal compression fracture				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Shunt thrombosis				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pubis fracture				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower limb fracture				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Laceration				

subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post procedural haemorrhage				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Radius fracture				
subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Congenital, familial and genetic disorders				
Hereditary non-polyposis colorectal cancer syndrome				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Phimosis				
subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Myocardial infarction				
subjects affected / exposed	2 / 116 (1.72%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	2 / 116 (1.72%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			

Atrial fibrillation				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute coronary syndrome				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial thrombosis				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nodal rhythm				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tachyarrhythmia				
subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Angina pectoris				

subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aortic valve stenosis				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arrhythmia				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure chronic				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial ischaemia				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ventricular extrasystoles				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebrovascular accident				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				

subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Central nervous system haemorrhage				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral haemorrhage				
subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Haemorrhage intracranial				
subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Metabolic encephalopathy				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral haematoma				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Depressed level of consciousness				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoaesthesia				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Partial seizures				

subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Presyncope				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Encephalopathy				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Febrile neutropenia				
subjects affected / exposed	5 / 116 (4.31%)			
occurrences causally related to treatment / all	5 / 5			
deaths causally related to treatment / all	0 / 0			
Anaemia				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Autoimmune haemolytic anaemia				
subjects affected / exposed	2 / 116 (1.72%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemolysis				

subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Haemolytic anaemia				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune thrombocytopenic purpura				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancytopenia				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cytopenia				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Leukopenia				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Diarrhoea				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ascites				

subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Enterocolitis				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Inguinal hernia				
subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pancreatitis acute				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thrombosis mesenteric vessel				
subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Food poisoning				

subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Proctitis				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Varices oesophageal				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anal fistula				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileus				

subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Liver disorder			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatitis			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rash maculo-papular			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin disorder			

subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Cystitis haemorrhagic			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Acute kidney injury			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute prerenal failure			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nephritic syndrome			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			

Back pain				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal chest pain				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal column stenosis				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gouty arthritis				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Pneumonia				
subjects affected / exposed	4 / 116 (3.45%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 2			
Respiratory tract infection				
subjects affected / exposed	3 / 116 (2.59%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	1 / 1			
Bronchitis				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Neutropenic sepsis				

subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchopneumonia				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Endocarditis				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Erysipelas				

subjects affected / exposed	2 / 116 (1.72%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Escherichia infection				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatitis B				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infective exacerbation of chronic obstructive airways disease				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	4 / 116 (3.45%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 2			
Septic shock				
subjects affected / exposed	2 / 116 (1.72%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Streptococcal sepsis				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Varicella				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Wound infection				

subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cystitis				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dacryocystitis				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device related sepsis				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Epididymitis				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Escherichia sepsis				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Furuncle				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gangrene				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				

subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis clostridial			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Herpes simplex			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infected skin ulcer			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infectious colitis			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infective exacerbation of bronchiectasis			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intervertebral discitis			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Laryngitis			

subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Liver abscess				
subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ophthalmic herpes zoster				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumocystis jirovecii pneumonia				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia influenzal				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary sepsis				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Septic arthritis staphylococcal				

subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Staphylococcal infection				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subcutaneous abscess				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Superinfection bacterial				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tooth abscess				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	0 / 116 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutropenic infection				
subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oral candidiasis				
subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal sepsis				

subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Stenotrophomonas sepsis			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatitis B reactivation			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Tumour lysis syndrome			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Rituximab + Chlorambucil (RClb)	Obinutuzumab + Chlorambucil (GClb)	Crossover subjects: Obinutuzumab + Chlorambucil (GClb)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	279 / 321 (86.92%)	299 / 336 (88.99%)	23 / 30 (76.67%)
Injury, poisoning and procedural complications			
Infusion related reaction			

subjects affected / exposed	118 / 321 (36.76%)	197 / 336 (58.63%)	15 / 30 (50.00%)
occurrences (all)	168	288	21
Nervous system disorders			
Headache			
subjects affected / exposed	18 / 321 (5.61%)	23 / 336 (6.85%)	0 / 30 (0.00%)
occurrences (all)	20	28	0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	104 / 321 (32.40%)	128 / 336 (38.10%)	12 / 30 (40.00%)
occurrences (all)	164	250	28
Anaemia			
subjects affected / exposed	34 / 321 (10.59%)	33 / 336 (9.82%)	3 / 30 (10.00%)
occurrences (all)	43	34	3
Thrombocytopenia			
subjects affected / exposed	20 / 321 (6.23%)	46 / 336 (13.69%)	7 / 30 (23.33%)
occurrences (all)	25	61	10
Leukopenia			
subjects affected / exposed	7 / 321 (2.18%)	21 / 336 (6.25%)	5 / 30 (16.67%)
occurrences (all)	7	28	5
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	30 / 321 (9.35%)	26 / 336 (7.74%)	1 / 30 (3.33%)
occurrences (all)	32	30	1
Pyrexia			
subjects affected / exposed	22 / 321 (6.85%)	28 / 336 (8.33%)	2 / 30 (6.67%)
occurrences (all)	24	35	2
Asthenia			
subjects affected / exposed	25 / 321 (7.79%)	23 / 336 (6.85%)	1 / 30 (3.33%)
occurrences (all)	27	24	1
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	42 / 321 (13.08%)	40 / 336 (11.90%)	3 / 30 (10.00%)
occurrences (all)	52	48	4
Diarrhoea			
subjects affected / exposed	24 / 321 (7.48%)	31 / 336 (9.23%)	3 / 30 (10.00%)
occurrences (all)	25	43	3

Constipation			
subjects affected / exposed	16 / 321 (4.98%)	27 / 336 (8.04%)	2 / 30 (6.67%)
occurrences (all)	16	28	2
Vomiting			
subjects affected / exposed	22 / 321 (6.85%)	19 / 336 (5.65%)	0 / 30 (0.00%)
occurrences (all)	25	21	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	19 / 321 (5.92%)	24 / 336 (7.14%)	4 / 30 (13.33%)
occurrences (all)	22	31	4
Dyspnoea			
subjects affected / exposed	13 / 321 (4.05%)	9 / 336 (2.68%)	2 / 30 (6.67%)
occurrences (all)	13	11	2
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	19 / 321 (5.92%)	8 / 336 (2.38%)	0 / 30 (0.00%)
occurrences (all)	20	9	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	13 / 321 (4.05%)	12 / 336 (3.57%)	2 / 30 (6.67%)
occurrences (all)	16	19	2
Urinary tract infection			
subjects affected / exposed	6 / 321 (1.87%)	17 / 336 (5.06%)	0 / 30 (0.00%)
occurrences (all)	12	19	0
Viral upper respiratory tract infection			
subjects affected / exposed	8 / 321 (2.49%)	16 / 336 (4.76%)	0 / 30 (0.00%)
occurrences (all)	9	20	0
Herpes zoster			
subjects affected / exposed	5 / 321 (1.56%)	5 / 336 (1.49%)	2 / 30 (6.67%)
occurrences (all)	5	5	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	9 / 321 (2.80%)	10 / 336 (2.98%)	2 / 30 (6.67%)
occurrences (all)	10	10	2

Non-serious adverse events	Chlorambucil (Clb)		
Total subjects affected by non-serious adverse events			

subjects affected / exposed	89 / 116 (76.72%)		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 116 (6.90%)		
occurrences (all)	10		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	21 / 116 (18.10%)		
occurrences (all)	35		
Anaemia			
subjects affected / exposed	12 / 116 (10.34%)		
occurrences (all)	14		
Thrombocytopenia			
subjects affected / exposed	9 / 116 (7.76%)		
occurrences (all)	10		
Leukopenia			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	12 / 116 (10.34%)		
occurrences (all)	16		
Pyrexia			
subjects affected / exposed	8 / 116 (6.90%)		
occurrences (all)	14		
Asthenia			
subjects affected / exposed	8 / 116 (6.90%)		
occurrences (all)	12		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	29 / 116 (25.00%)		
occurrences (all)	47		
Diarrhoea			

subjects affected / exposed	13 / 116 (11.21%)		
occurrences (all)	16		
Constipation			
subjects affected / exposed	12 / 116 (10.34%)		
occurrences (all)	14		
Vomiting			
subjects affected / exposed	14 / 116 (12.07%)		
occurrences (all)	15		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 116 (6.90%)		
occurrences (all)	10		
Dyspnoea			
subjects affected / exposed	8 / 116 (6.90%)		
occurrences (all)	10		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 116 (2.59%)		
occurrences (all)	3		
Infections and infestations			
Bronchitis			
subjects affected / exposed	8 / 116 (6.90%)		
occurrences (all)	8		
Urinary tract infection			
subjects affected / exposed	2 / 116 (1.72%)		
occurrences (all)	2		
Viral upper respiratory tract infection			
subjects affected / exposed	6 / 116 (5.17%)		
occurrences (all)	7		
Herpes zoster			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	9 / 116 (7.76%)		
occurrences (all)	9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 August 2009	• A wet signature page has been included.
03 November 2009	• 6 subject safety run-in to three cycles was extended while allowing the randomised part of the study to initiate after cycle one provided these patients do not meet the stopping criteria as currently defined in the protocol. An additional safety review after the 6 run-in subjects had completed three (3 cycles) of treatment was introduced as specified below.
14 January 2010	• Modification of the exclusion criteria to prevent subjects who were recently vaccinated with live virus from entering the study • Entry criteria were modified so that subjects with the following could participate in the study 1. Positive HCV serology but RNA negative 2. Certain malignancies with good prognosis 3. Autoimmune hemolytic anemia • Inconsistencies in the definition of partial response were amended • Small clarifications to laboratory processes • Updated information to warnings and precautions section because of new safety information providing recommendations for the monitoring of HBV reactivation • The frequency of the DSMB review of safety data was changed from every three months to monthly (until 50 subjects had been randomised) • In response to feedback from investigators, various changes to study drug administration were made including the dose of chlorambucil was capped at a maximum dose associated with a body mass index of 35, antibiotic prophylaxis was strongly recommended; clarified that for subjects with a high circulating lymphocyte count (as opposed to subjects with a WBC ≥100*10^9/L) the infusion (of obinutuzumab or rituximab) could be given more slowly over a longer period of time, or the dose could be split over 2 consecutive days. • Second malignancies were to be reported irrespective of time elapsed since study completion
26 November 2010	• The DSMB recommendation to define a clear and consistent cutoff for high circulating lymphocyte count (>25*10^9/L) was implemented and it was recommended that all subjects above this level received corticosteroids as premedication • HBsAg negative/anti-HBc positive subjects with undetectable serum HBV DNA were to be followed at monthly intervals for 12 months for HBV DNA (instead of 3-monthly intervals for 6 months) • Events that required permanent discontinuation of study therapy were clarified • Clarifications were made to the response section to avoid ambiguity and also the IRC section was aligned with the IRC charter • Refinement of the CIRS eligibility criteria (subjects with CIRS grade 4 for Eyes, Ears, Nose, Throat and Larynx organ system became eligible for the study) • Clarification of lab procedures and study assessments
12 June 2011	• Premedication requirements were modified to include corticosteroids (100 mg prednisolone or 20 mg dexamethasone or 80 mg methylprednisolone) for all subjects during the first infusion in an effort to reduce the risk of IRRs. Consideration to withholding of antihypertensives on day of infusion was included in the dosing schedule. • Duration of follow-up for B-cell recovery and monitoring of infection was extended to 2 years after the end of treatment • Clarified that not all NCI CTC Grade 4 laboratory parameters are considered serious adverse events since they are not always considered 'life−threatening-at immediate risk of death" • Dose modification criteria were clarified
09 December 2011	• To further reduce the risk and severity of IRRs and on the recommendation of the DSMB, the first infusion of obinutuzumab was to be given over two days (100 mg on Day 1 and 900 mg on Day 2) with a reduced rate of infusion during the first day, and hypertensive drugs were not to be given on the morning of and throughout all infusions • Two additional urinalysis samples were added to obtain long term information on proteinuria

04 September 2012	• Clarification of Stage 1a and Stage 1b data release • Documentation of the implemented process for assigning response at Cycle 4 Day 1 and follow-up Day 28 when imaging and bone marrow are not available. Specifically, at 2 visits the eCRF captures response data CR, nCR, PR, SD and PD but according to IWCLL guidelines, imaging and bone marrow examination data are required for a full assessment of response (CR/PR). The problem arose how to complete the eCRF response assessment fields in the absence of the information. The team agreed to follow a standard approach that at these visits, response would be assessed according to the assessments planned; laboratory values, and physical examination. As a result of those changes the definition of disease free survival and duration of response was clarified to exclude those early responses. • Use of the stored plasma sample obtained at baseline for the obinutuzumab PK analysis to determine HAHA at baseline
07 June 2013	• Schedule of assessments was updated to include additional HAHA and pharmacokinetic assessments, and additional lymphocyte immunophenotyping and immunoglobulin assessment as well as provision of information on the diagnosis, evaluation and guidance should any subject be diagnosed with progressive mulitifocal leukoencephalopathy.
01 December 2016	• End of Study/Study Closure was revised to the date of LPLV, which occurred on 23 August 2017 • Duration of the 6-month follow-up visit period was changed to 5 years from date of last patient randomization, or end of study, whichever occurred first. • Duration of the annual follow-up visit period was changed to a maximum of 5 years from last patient enrollment, or end of study, whichever occurred first • Overview of study design was revised for the end-of-study period • Schedule of assessments was revised

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported