



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 (RCIb) 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/m² rituximab IV infusion on Day 1 of Cycle 1 then 500 mg/m² 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/m² by IV infusion on Days 1 of Cycle 1 then 500 mg/m² 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 (RCIb) |
|------------------|--|

Arm description:

Subjects received rituximab 375 mg/m² IV infusion on Day 1 of Cycle 1 then 500 mg/m² 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/m² by IV infusion on Days 1 of Cycle 1 then 500 mg/m² IV infusion on Day 1 of Cycles 2-6 (28-day cycles).

| | |
|------------------|---|
| Arm title | Stage 2: Obinutuzumab + Chlorambucil (GCIb) |
|------------------|---|

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 (RCIb) | Stage 1: Obinutuzumab + Chlorambucil (GCIb) | Stage 1: Chlorambucil (CIb) |
|---------------------------------------|--|---|-----------------------------|
| 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 (RCIb) | Stage 2: Obinutuzumab + Chlorambucil (GCIb) |
|---------------------------------------|--|---|
| 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 (RCIb) |
|-----------------------|--|

Reporting group description:

Subjects received 375 mg/m² rituximab IV infusion on Day 1 of Cycle 1 then 500 mg/m² 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 (GCIb) |
|-----------------------|---|

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 (CIb) |
|-----------------------|-----------------------------|

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 (RCIb) |
|-----------------------|--|

Reporting group description:

Subjects received rituximab 375 mg/m² IV infusion on Day 1 of Cycle 1 then 500 mg/m² 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 (GCIb) |
|-----------------------|---|

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 GCIb vs RCIb vs CIb, study was split into two Stages for analysis: Stage 1 (Stage 1a - GCIb vs CIb, and Stage 1b - RCIb vs CIb) and Stage 2 (RCIb vs GCIb). In Stage 2, randomization continued in the GCIb and RCIb arms only. Stage 1 and Stage 2 are not temporally consecutive, but rather compare different treatment arms. All patients enrolled in GCIb and RCIb 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 (RCIb) | Stage 1: Obinutuzumab + Chlorambucil (GCIb) | Stage 1: Chlorambucil (CIb) |
|--|--|---|-----------------------------|
| 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 (RCIb) | Stage 2: Obinutuzumab + Chlorambucil (GCIb) | 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 (RCIb) |
| 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 (GCIb) |
| 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 (CIb) |
| 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 (RCIb) |
| 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 (GCIb) |
| 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 (RCIb) | Stage 1: Obinutuzumab + Chlorambucil (GCIb) | Stage 1: Chlorambucil (CIb) | |
|----------------------------------|---|--|-----------------------------------|--|
| 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 (GCIb) v Stage 1: Chlorambucil (CIb) |
| 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 (CIb) v Stage 1: Rituximab + Chlorambucil (RCIb) |
| 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: $\geq 50\%$ increase in absolute number of lymphocytes, appearance of new palpable lymph nodes (>15 mm in diameter) or new extra nodal lesion, $\geq 50\%$ increase in diameter of previous site of clinically significant lymphadenopathy, $\geq 50\%$ 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 $<100 \times 10^9/L$ or by a decrease of neutrophil counts $>50\%$ or $<1.0 \times 10^9/L$). 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 (RCIb) | Stage 1: Obinutuzumab + Chlorambucil (GCIb) | Stage 1: Chlorambucil (CIb) | |
|-------------------------------|---|--|-----------------------------------|--|
| 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 (RCIb) | Stage 2: Obinutuzumab + Chlorambucil (GCIb) | | |
|------------------------------|---|--|--|--|
| 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: $\geq 50\%$ increase in absolute number of lymphocytes, appearance of new palpable lymph nodes (>15 mm in diameter) or new extra nodal lesion, $\geq 50\%$ increase in diameter of previous site of clinically significant lymphadenopathy, $\geq 50\%$ 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 $<100 \times 10^9/L$ or by a decrease of neutrophil counts $>50\%$ or $<1.0 \times 10^9/L$). 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 (RCIb) | Stage 1: Obinutuzumab + Chlorambucil (GCIb) | Stage 1: Chlorambucil (CIb) | |
|----------------------------------|---|--|-----------------------------------|--|
| 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: $\geq 50\%$ increase in absolute number of lymphocytes, appearance of new palpable lymph nodes (>15 mm in diameter) or new extra nodal lesion, $\geq 50\%$ increase in diameter of previous site of clinically significant lymphadenopathy, $\geq 50\%$ 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 $<100 \times 10^9/L$ or by a decrease of neutrophil counts $>50\%$ or $<1.0 \times 10^9/L$). 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 (RCIb) | Stage 1: Obinutuzumab + Chlorambucil (GCIb) | Stage 1: Chlorambucil (CIb) | |
|-------------------------------|---|--|-----------------------------------|--|
| 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 (RCIb) | Stage 2: Obinutuzumab + Chlorambucil (GCIb) | | |
|------------------------------|---|--|--|--|
| 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 $4 \times 10^9/L$, No lymphadenopathy, No hepatomegaly, No splenomegaly, No disease, Blood counts

as Neutrophils $>1.5 \times 10^9/L$, Platelets $>100 \times 10^9/L$, Hemoglobin $>11g/dL$ and Bone marrow at least normocellular for age. CRi was CR with incomplete bone marrow recovery. Partial response (PR): $\geq 50\%$ decrease in peripheral lymphocyte count from pre-treatment value and Either a $\geq 50\%$ reduction in lymphadenopathy OR $\geq 50\%$ reduction of liver enlargement OR $\geq 50\%$ reduction of spleen enlargement, at least one of following: Neutrophils $>1.5 \times 10^9/L$ or $\geq 50\%$ increase, Platelets $>100 \times 10^9/L$, Hemoglobin $11 g/dL$ or $\geq 50\%$ 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 (RCIb) | Stage 1: Obinutuzumab + Chlorambucil (GCIb) | Stage 1: Chlorambucil (CIb) | |
|------------------------------------|---|--|-----------------------------------|--|
| 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 $4 \times 10^9/L$, No lymphadenopathy, No hepatomegaly, No splenomegaly, No disease, Blood counts as Neutrophils $>1.5 \times 10^9/L$, Platelets $>100 \times 10^9/L$, Hemoglobin $>11g/dL$ and Bone marrow at least normocellular for age. CRi was CR with incomplete bone marrow recovery. Partial response (PR): $\geq 50\%$ decrease in peripheral lymphocyte count from pre-treatment value and Either a $\geq 50\%$ reduction in lymphadenopathy OR $\geq 50\%$ reduction of liver enlargement OR $\geq 50\%$ reduction of spleen enlargement, at least one of following: Neutrophils $>1.5 \times 10^9/L$ or $\geq 50\%$ increase, Platelets $>100 \times 10^9/L$, Hemoglobin $11 g/dL$ or $\geq 50\%$ 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 (RCIb) | Stage 2: Obinutuzumab + Chlorambucil (GCIb) | | |
|------------------------------------|---|--|--|--|
| 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 $4 \times 10^9/L$, No lymphadenopathy, No hepatomegaly, No splenomegaly, No disease, Blood counts as Neutrophils $>1.5 \times 10^9/L$, Platelets $>100 \times 10^9/L$, Hemoglobin $>11g/dL$ and Bone marrow at least normocellular for age. CRi was CR with incomplete bone marrow recovery. Partial response (PR): $\geq 50\%$ decrease in peripheral lymphocyte count from pre-treatment value and either a $\geq 50\%$ reduction in lymphadenopathy OR $\geq 50\%$ reduction of liver enlargement OR $\geq 50\%$ reduction of spleen enlargement, at least one of following: Neutrophils $>1.5 \times 10^9/L$ or $\geq 50\%$ increase, Platelets $>100 \times 10^9/L$, Hemoglobin $11 g/dL$ or $\geq 50\%$ 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 $4 \times 10^9/L$, No lymphadenopathy, No hepatomegaly, No splenomegaly, No disease, Blood counts as Neutrophils $>1.5 \times 10^9/L$, Platelets $>100 \times 10^9/L$, Hemoglobin $>11g/dL$ and Bone marrow at least normocellular for age. CRi was CR with incomplete bone marrow recovery. Partial response (PR): $\geq 50\%$ decrease in peripheral lymphocyte count from pre-treatment value and either a $\geq 50\%$ reduction in lymphadenopathy OR $\geq 50\%$ reduction of liver enlargement OR $\geq 50\%$ reduction of spleen enlargement, at least one of following: Neutrophils $>1.5 \times 10^9/L$ or $\geq 50\%$ increase, Platelets $>100 \times 10^9/L$, Hemoglobin $11 g/dL$ or $\geq 50\%$ 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 (RCIb) | Stage 2: Obinutuzumab + Chlorambucil (GCIb) | | |
|------------------------------------|---|--|--|--|
| 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: $\geq 50\%$ increase in the absolute number of lymphocytes, appearance of new palpable lymph nodes (>15 mm in longest diameter) or any new extra nodal lesion, $\geq 50\%$ increase in the longest diameter of any previous site of clinically significant lymphadenopathy, $\geq 50\%$ 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 $<100 \times 10^9/L$ or by a decrease of neutrophil counts $>50\%$ or $<1.0 \times 10^9/L$). 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 (RCIb) | Stage 1: Obinutuzumab + Chlorambucil (GCIb) | Stage 1: Chlorambucil (CIb) | |
|----------------------------------|---|--|-----------------------------------|--|
| 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: $\geq 50\%$ increase in the absolute number of lymphocytes, appearance of new palpable lymph nodes (>15 mm in longest diameter) or any new extra nodal lesion, $\geq 50\%$ increase in the longest diameter of any previous site of clinically significant lymphadenopathy, $\geq 50\%$ 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 $<100 \times 10^9/L$ or by a decrease of neutrophil counts $>50\%$ or $<1.0 \times 10^9/L$). 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 (RCIb) | Stage 2: Obinutuzumab + Chlorambucil (GCIb) | | |
|----------------------------------|---|--|--|--|
| 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 (RCIb) | Stage 1: Obinutuzumab + Chlorambucil (GCIb) | Stage 1: Chlorambucil (CIb) | |
|----------------------------------|---|--|-----------------------------------|--|
| 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 (RCIb) | Stage 2: Obinutuzumab + Chlorambucil (GCIb) | | |
|----------------------------------|---|--|--|--|
| 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 (RCIb) | Stage 2: Obinutuzumab + Chlorambucil (GCIb) | | |
|----------------------------------|---|--|--|--|
| 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 (RCIb) | Stage 1: Obinutuzumab + Chlorambucil (GCIb) | Stage 1: Chlorambucil (CIb) | |
|----------------------------------|---|--|-----------------------------------|--|
| 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 (RCIb) | Stage 2: Obinutuzumab + Chlorambucil (GCIb) | | |
|----------------------------------|---|--|--|--|
| 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 obinutuzumab 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 (RCIb) | Stage 2: Obinutuzumab + Chlorambucil (GCIb) | | |
|---|---|--|--|--|
| 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/m² rituximab IV infusion on Day 1 of Cycle 1 then 500 mg/m² 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 occurrences (all) | 118 / 321 (36.76%) 168 | 197 / 336 (58.63%) 288 | 15 / 30 (50.00%) 21 |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 18 / 321 (5.61%) 20 | 23 / 336 (6.85%) 28 | 0 / 30 (0.00%) 0 |
| Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all) | 104 / 321 (32.40%) 164 | 128 / 336 (38.10%) 250 | 12 / 30 (40.00%) 28 |
| Anaemia subjects affected / exposed occurrences (all) | 34 / 321 (10.59%) 43 | 33 / 336 (9.82%) 34 | 3 / 30 (10.00%) 3 |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 20 / 321 (6.23%) 25 | 46 / 336 (13.69%) 61 | 7 / 30 (23.33%) 10 |
| Leukopenia subjects affected / exposed occurrences (all) | 7 / 321 (2.18%) 7 | 21 / 336 (6.25%) 28 | 5 / 30 (16.67%) 5 |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) | 30 / 321 (9.35%) 32 | 26 / 336 (7.74%) 30 | 1 / 30 (3.33%) 1 |
| Pyrexia subjects affected / exposed occurrences (all) | 22 / 321 (6.85%) 24 | 28 / 336 (8.33%) 35 | 2 / 30 (6.67%) 2 |
| Asthenia subjects affected / exposed occurrences (all) | 25 / 321 (7.79%) 27 | 23 / 336 (6.85%) 24 | 1 / 30 (3.33%) 1 |
| Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) | 42 / 321 (13.08%) 52 | 40 / 336 (11.90%) 48 | 3 / 30 (10.00%) 4 |
| Diarrhoea subjects affected / exposed occurrences (all) | 24 / 321 (7.48%) 25 | 31 / 336 (9.23%) 43 | 3 / 30 (10.00%) 3 |

| | | | |
|--|------------------------|------------------------|----------------------|
| Constipation subjects affected / exposed occurrences (all) | 16 / 321 (4.98%) 16 | 27 / 336 (8.04%) 28 | 2 / 30 (6.67%) 2 |
| Vomiting subjects affected / exposed occurrences (all) | 22 / 321 (6.85%) 25 | 19 / 336 (5.65%) 21 | 0 / 30 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 19 / 321 (5.92%) 22 | 24 / 336 (7.14%) 31 | 4 / 30 (13.33%) 4 |
| Dyspnoea subjects affected / exposed occurrences (all) | 13 / 321 (4.05%) 13 | 9 / 336 (2.68%) 11 | 2 / 30 (6.67%) 2 |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) | 19 / 321 (5.92%) 20 | 8 / 336 (2.38%) 9 | 0 / 30 (0.00%) 0 |
| Infections and infestations Bronchitis subjects affected / exposed occurrences (all) | 13 / 321 (4.05%) 16 | 12 / 336 (3.57%) 19 | 2 / 30 (6.67%) 2 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 6 / 321 (1.87%) 12 | 17 / 336 (5.06%) 19 | 0 / 30 (0.00%) 0 |
| Viral upper respiratory tract infection subjects affected / exposed occurrences (all) | 8 / 321 (2.49%) 9 | 16 / 336 (4.76%) 20 | 0 / 30 (0.00%) 0 |
| Herpes zoster subjects affected / exposed occurrences (all) | 5 / 321 (1.56%) 5 | 5 / 336 (1.49%) 5 | 2 / 30 (6.67%) 2 |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 9 / 321 (2.80%) 10 | 10 / 336 (2.98%) 10 | 2 / 30 (6.67%) 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 | <ul style="list-style-type: none"> • A wet signature page has been included. |
| 03 November 2009 | <ul style="list-style-type: none"> • 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 | <ul style="list-style-type: none"> • 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 $WBC \geq 100 \times 10^9/L$) 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 | <ul style="list-style-type: none"> • The DSMB recommendation to define a clear and consistent cutoff for high circulating lymphocyte count ($>25 \times 10^9/L$) 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 | <ul style="list-style-type: none"> • 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 | <ul style="list-style-type: none"> • 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 | <ul style="list-style-type: none"> • 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 HABA at baseline |
| 07 June 2013 | <ul style="list-style-type: none"> • Schedule of assessments was updated to include additional HABA 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 multifocal leukoencephalopathy. |
| 01 December 2016 | <ul style="list-style-type: none"> • 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