

**Clinical trial results:**

A COMPARATIVE, RANDOMIZED, PARALLEL-GROUP, MULTI-CENTER, PHASE IIIB STUDY TO INVESTIGATE THE EFFICACY OF SUBCUTANEOUS (SC) RITUXIMAB VERSUS INTRAVENOUS (IV) RITUXIMAB BOTH IN COMBINATION WITH CHOP (R-CHOP) IN PREVIOUSLY UNTREATED PATIENTS WITH CD20-POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

Summary

| | |
|--------------------------|----------------------------------|
| EudraCT number | 2012-000669-19 |
| Trial protocol | ES FI NL GR GB IT IE FR BE BG PT |
| Global end of trial date | |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 |
| This version publication date | 09 April 2016 |
| First version publication date | 09 April 2016 |

Trial information**Trial identification**

| | |
|-----------------------|---------|
| Sponsor protocol code | MO28107 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01649856 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | F. Hoffmann-La Roche AG |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070 |
| Public contact | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |
| Scientific contact | Roche Trial Information Hotline, 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 | Interim |
| Date of interim/final analysis | 28 August 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 21 October 2014 |
| Global end of trial reached? | No |

Notes:

General information about the trial

Main objective of the trial:

This multicenter, randomized, open-label parallel-group study evaluated the efficacy and safety of subcutaneous (SC) versus intravenous (IV) rituximab, both in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), in participants with previously untreated cluster of differentiation (CD) 20-positive diffuse large B-cell lymphoma (DLBCL). Participants were randomized 2:1 to receive either SC or IV rituximab on Day 1 of each cycle for 8 cycles, in combination with 6 to 8 cycles of CHOP chemotherapy. Cycle length (14 or 21 days) was decided by the individual study center.

Protection of trial subjects:

The study was conducted in full conformance with the International Conference on Harmonisation (ICH)-E6 Guideline for Good Clinical Practice (GCP) and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research was conducted, whichever afforded greater protection to the participant. The study has complied with requirements of the ICH-E2A Guideline for Clinical Safety Data Management, and for study sites in the European Union (EU)/European Economic Area (EEA), the study has also complied with the EU Clinical Trial Directive (2001/20/EC).

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 22 August 2012 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 2 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------|
| Country: Number of subjects enrolled | Argentina: 3 |
| Country: Number of subjects enrolled | Belgium: 17 |
| Country: Number of subjects enrolled | Brazil: 7 |
| Country: Number of subjects enrolled | Bulgaria: 10 |
| Country: Number of subjects enrolled | Canada: 30 |
| Country: Number of subjects enrolled | Colombia: 13 |
| Country: Number of subjects enrolled | Finland: 21 |
| Country: Number of subjects enrolled | France: 30 |
| Country: Number of subjects enrolled | Greece: 30 |
| Country: Number of subjects enrolled | Ireland: 11 |
| Country: Number of subjects enrolled | Israel: 30 |
| Country: Number of subjects enrolled | Italy: 74 |
| Country: Number of subjects enrolled | Netherlands: 43 |
| Country: Number of subjects enrolled | Peru: 6 |
| Country: Number of subjects enrolled | Poland: 13 |

| | |
|--------------------------------------|--------------------------------------|
| Country: Number of subjects enrolled | Portugal: 12 |
| Country: Number of subjects enrolled | Russian Federation: 37 |
| Country: Number of subjects enrolled | Serbia: 7 |
| Country: Number of subjects enrolled | South Africa: 3 |
| Country: Number of subjects enrolled | Spain: 40 |
| Country: Number of subjects enrolled | Thailand: 21 |
| Country: Number of subjects enrolled | Turkey: 74 |
| Country: Number of subjects enrolled | Ukraine: 20 |
| Country: Number of subjects enrolled | United Kingdom: 18 |
| Country: Number of subjects enrolled | Venezuela, Bolivarian Republic of: 2 |
| Worldwide total number of subjects | 572 |
| EEA total number of subjects | 319 |

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) | 306 |
| From 65 to 84 years | 266 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 662 individuals were screened for entry into the study, and 86 failed the screening procedure. Overall, 576 participants were randomized; 572 received treatment and were included in the analyses.

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? | Yes |
| Arm title | Rituximab SC |

Arm description:

Participants with previously untreated, CD20-positive DLBCL received up to 8 cycles of rituximab in combination with CHOP. Treatment was given on Day 1 of each cycle, and the cycle length (14 or 21 days) was decided by the study center. For Cycle 1, rituximab was administered at a dose of 375 milligrams per meter-squared (mg/m^2) via IV infusion; subsequent doses were given as 1400 milligrams (mg) via SC injection. Tumor response was assessed after 4 cycles according to criteria published by Cheson et al (1999), which are presented in Endpoint 1. The duration of CHOP therapy could be reduced from 8 to 6 cycles for those who achieved complete response (CR) or complete response unconfirmed (CRu) after 4 cycles, but all participants received a full 8 cycles of rituximab.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Rituximab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection, Concentrate and solvent for solution for infusion |
| Routes of administration | Subcutaneous use, Intravenous use |

Dosage and administration details:

Rituximab was administered as 1400 mg via SC injection or as 375 mg/m^2 via IV infusion, depending upon treatment assignment, on Day 1 of each cycle. During the first cycle, all participants received the IV formulation regardless of treatment assignment.

| | |
|------------------|--------------|
| Arm title | Rituximab IV |
|------------------|--------------|

Arm description:

Participants with previously untreated, CD20-positive DLBCL received up to 8 cycles of rituximab in combination with CHOP. Treatment was given on Day 1 of each cycle, and the cycle length (14 or 21 days) was decided by the study center. For all cycles, rituximab was administered at a dose of 375 mg/m^2 via IV infusion. Tumor response was assessed after 4 cycles according to criteria published by Cheson et al (1999), which are presented in Endpoint 1. The duration of CHOP therapy could be reduced from 8 to 6 cycles for those who achieved CR or CRu after 4 cycles, but all participants received a full 8 cycles of rituximab.

| | |
|--|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Rituximab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for infusion, Solution for injection |
| Routes of administration | Intravenous use, Subcutaneous use |

Dosage and administration details:

Rituximab was administered as 1400 mg via SC injection or as 375 mg/m^2 via IV infusion, depending

upon treatment assignment, on Day 1 of each cycle. During the first cycle, all participants received the IV formulation regardless of treatment assignment.

| Number of subjects in period 1 | Rituximab SC | Rituximab IV |
|---------------------------------------|--------------|--------------|
| Started | 369 | 203 |
| Completed | 0 | 0 |
| Not completed | 369 | 203 |
| Consent withdrawn by subject | 6 | 9 |
| Treatment failure | 4 | 1 |
| Death | 37 | 26 |
| Not specified | 1 | - |
| Lack of compliance | - | 1 |
| Stable or progressed disease | 5 | 3 |
| Lost to follow-up | 9 | 7 |
| Ongoing in follow-up | 303 | 152 |
| Protocol deviation | 4 | 4 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | Rituximab SC |
|-----------------------|--------------|

Reporting group description:

Participants with previously untreated, CD20-positive DLBCL received up to 8 cycles of rituximab in combination with CHOP. Treatment was given on Day 1 of each cycle, and the cycle length (14 or 21 days) was decided by the study center. For Cycle 1, rituximab was administered at a dose of 375 milligrams per meter-squared (mg/m²) via IV infusion; subsequent doses were given as 1400 milligrams (mg) via SC injection. Tumor response was assessed after 4 cycles according to criteria published by Cheson et al (1999), which are presented in Endpoint 1. The duration of CHOP therapy could be reduced from 8 to 6 cycles for those who achieved complete response (CR) or complete response unconfirmed (CRu) after 4 cycles, but all participants received a full 8 cycles of rituximab.

| | |
|-----------------------|--------------|
| Reporting group title | Rituximab IV |
|-----------------------|--------------|

Reporting group description:

Participants with previously untreated, CD20-positive DLBCL received up to 8 cycles of rituximab in combination with CHOP. Treatment was given on Day 1 of each cycle, and the cycle length (14 or 21 days) was decided by the study center. For all cycles, rituximab was administered at a dose of 375 mg/m² via IV infusion. Tumor response was assessed after 4 cycles according to criteria published by Cheson et al (1999), which are presented in Endpoint 1. The duration of CHOP therapy could be reduced from 8 to 6 cycles for those who achieved CR or CRu after 4 cycles, but all participants received a full 8 cycles of rituximab.

| Reporting group values | Rituximab SC | Rituximab IV | Total |
|------------------------------------|--------------|--------------|-------|
| Number of subjects | 369 | 203 | 572 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|-----------------|---------------|-----|
| Age continuous Units: years arithmetic mean standard deviation | 60.4 ± 13.78 | 61 ± 12.63 | - |
| Gender categorical Units: Subjects | | | |
| Female | 165 | 100 | 265 |
| Male | 204 | 103 | 307 |

End points

End points reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | Rituximab SC |
|-----------------------|--------------|

Reporting group description:

Participants with previously untreated, CD20-positive DLBCL received up to 8 cycles of rituximab in combination with CHOP. Treatment was given on Day 1 of each cycle, and the cycle length (14 or 21 days) was decided by the study center. For Cycle 1, rituximab was administered at a dose of 375 milligrams per meter-squared (mg/m^2) via IV infusion; subsequent doses were given as 1400 milligrams (mg) via SC injection. Tumor response was assessed after 4 cycles according to criteria published by Cheson et al (1999), which are presented in Endpoint 1. The duration of CHOP therapy could be reduced from 8 to 6 cycles for those who achieved complete response (CR) or complete response unconfirmed (CRu) after 4 cycles, but all participants received a full 8 cycles of rituximab.

| | |
|-----------------------|--------------|
| Reporting group title | Rituximab IV |
|-----------------------|--------------|

Reporting group description:

Participants with previously untreated, CD20-positive DLBCL received up to 8 cycles of rituximab in combination with CHOP. Treatment was given on Day 1 of each cycle, and the cycle length (14 or 21 days) was decided by the study center. For all cycles, rituximab was administered at a dose of 375 mg/m^2 via IV infusion. Tumor response was assessed after 4 cycles according to criteria published by Cheson et al (1999), which are presented in Endpoint 1. The duration of CHOP therapy could be reduced from 8 to 6 cycles for those who achieved CR or CRu after 4 cycles, but all participants received a full 8 cycles of rituximab.

Primary: Percentage of Participants With CR or CRu at the Time of Primary Analysis

| | |
|-----------------|---|
| End point title | Percentage of Participants With CR or CRu at the Time of Primary Analysis |
|-----------------|---|

End point description:

Tumor response was assessed per criteria published by Cheson et al (1999). According to consensus recommendations, CR was defined as complete disappearance of all clinical and radiographic evidence of disease and disease-related symptoms, regression of lymph nodes to normal size, absence of splenomegaly, and absence of bone marrow involvement. CRu was defined as disappearance of clinical and radiographic evidence of disease and absence of splenomegaly, with regression of lymph nodes by greater than (>) 75 percent (%) but still >1.5 centimeters (cm) in size, and indeterminate bone marrow assessment. The percentage of participants with either response at the end of induction (EOI) was determined with corresponding 95% Pearson-Clopper confidence interval (CI). Intent-to-Treat (ITT) Population: All participants who completed Baseline and at least one on-treatment efficacy assessment.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to approximately 7 months (assessed at Baseline, Cycle 4, and 30 days after the start of the last rituximab cycle [maximum 8 cycles; each cycle was 14 or 21 days])

| End point values | Rituximab SC | Rituximab IV | | |
|-----------------------------------|-------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 342 | 177 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 52 (46.8 to 57.3) | 50.8 (43.5 to 58.2) | | |

Statistical analyses

| | |
|---|------------------------------|
| Statistical analysis title | Difference in response rates |
| Comparison groups | Rituximab SC v Rituximab IV |
| Number of subjects included in analysis | 519 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.796 |
| Method | Chi-squared |
| Parameter estimate | Difference in response rates |
| Point estimate | 1.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.9 |
| upper limit | 10.3 |

Secondary: Cancer Treatment Satisfaction Questionnaire (CTSQ) Domain Scores

| | |
|-----------------|--|
| End point title | Cancer Treatment Satisfaction Questionnaire (CTSQ) Domain Scores |
|-----------------|--|

End point description:

The CTSQ is a validated 16-item questionnaire that measures three domains related to satisfaction with cancer therapy. These include expectations of therapy, feelings about side effects, and satisfaction with therapy. Each domain is scored on a scale of 0 to 100, with higher scores indicative of more positive feelings toward therapy. The score for each domain was averaged among all participants. ITT Population (CTSQ Subpopulation): All participants who completed the CTSQ at Cycles 3 and 7.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At Cycle 7 (each cycle was 14 or 21 days)

| End point values | Rituximab SC | Rituximab IV | | |
|---|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 280 ^[1] | 141 ^[2] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Expectations of Therapy (n=280,141) | 79.35 (± 17.422) | 82.94 (± 16.536) | | |
| Feelings about Side Effects (n=276,141) | 60.69 (± 21.594) | 57.62 (± 23.339) | | |
| Satisfaction with Therapy (n=278,141) | 85.92 (± 11.428) | 83.6 (± 13.451) | | |

Notes:

[1] - number (n) = number of participants in the analysis for the specified domain.

[2] - n = number of participants in the analysis for the specified domain.

Statistical analyses

No statistical analyses for this end point

Secondary: Rituximab Administration Satisfaction Questionnaire (RASQ) Domain

Scores

| | |
|-----------------|---|
| End point title | Rituximab Administration Satisfaction Questionnaire (RASQ) Domain Scores |
|-----------------|---|

End point description:

The RASQ is a 20-item questionnaire that measures five domains related to the impact of treatment administration. These include physical impact, psychological impact, impact on activities of daily living (ADLs), convenience, and satisfaction. Each domain is scored on a scale of 0 to 100, with higher scores indicative of more positive feelings toward therapy. The score for each domain was averaged among all participants. ITT Population (RASQ Subpopulation): All participants who completed the RASQ at Cycles 3 and 7.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At Cycle 7 (each cycle was 14 or 21 days)

| End point values | Rituximab SC | Rituximab IV | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 284 ^[3] | 144 ^[4] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Physical Impact (n=278,140) | 86.24 (± 14.012) | 81.49 (± 16.848) | | |
| Psychological Impact (n=277,141) | 85.65 (± 13.92) | 78.65 (± 18.233) | | |
| Impact on ADLs (n=266,140) | 83.77 (± 16.117) | 57.38 (± 19.23) | | |
| Convenience (n=279,143) | 82.32 (± 13.428) | 60.14 (± 17.473) | | |
| Satisfaction (n=282,141) | 89.58 (± 12.051) | 77.39 (± 18.232) | | |

Notes:

[3] - n = number of participants in the analysis for the specified domain.

[4] - n = number of participants in the analysis for the specified domain.

Statistical analyses

No statistical analyses for this end point

Secondary: Median Duration of Rituximab Administration for Each Treatment Cycle

| | |
|-----------------|--|
| End point title | Median Duration of Rituximab Administration for Each Treatment Cycle |
|-----------------|--|

End point description:

Duration of rituximab administration was defined as the time from start to end of the SC injection or IV infusion. The median duration was reported. Safety Population: All participants who received at least one dose of study drug according to treatment received.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Cycles 1, 2, 3, 4, 5, 6, 7, and 8 (each cycle was 14 or 21 days)

| End point values | Rituximab SC | Rituximab IV | | |
|-------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 369 ^[5] | 203 ^[6] | | |
| Units: hours | | | | |
| median (full range (min-max)) | | | | |
| Cycle 1 (n=346,190) | 4 (0.1 to 11) | 4 (1.2 to 10) | | |
| Cycle 2 (n=361,178) | 0.1 (0.1 to 23.1) | 3 (0.5 to 10) | | |
| Cycle 3 (n=349,177) | 0.1 (0.1 to 5.5) | 2.8 (1 to 21.4) | | |
| Cycle 4 (n=346,173) | 0.1 (0 to 2.5) | 2.7 (0.5 to 8) | | |
| Cycle 5 (n=332,165) | 0.1 (0 to 2.5) | 2.6 (0.1 to 8.1) | | |
| Cycle 6 (n=319,162) | 0.1 (0 to 2.5) | 2.7 (0.1 to 20) | | |
| Cycle 7 (n=304,156) | 0.1 (0 to 23.6) | 2.7 (0.5 to 6.7) | | |
| Cycle 8 (n=305,152) | 0.1 (0 to 2.5) | 2.55 (0.1 to 17.9) | | |
| Overall (n=368,201) | 4.7 (0.1 to 28.7) | 19 (1.2 to 57.4) | | |

Notes:

[5] - n = number of participants in the analysis for the specified timepoint.

[6] - n = number of participants in the analysis for the specified timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants by Time Spent in the Infusion Chair/Bed for Each Treatment Cycle

| | |
|-----------------|---|
| End point title | Percentage of Participants by Time Spent in the Infusion Chair/Bed for Each Treatment Cycle |
|-----------------|---|

End point description:

Chair time was defined as the amount of time the participant occupied an infusion chair/bed for a single treatment cycle of rituximab + CHOP chemotherapy. Where the chair time was not documented for a given cycle, it was reported as "Missing". Safety Population.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Cycles 1, 2, 3, 4, 5, 6, 7, and 8 (each cycle was 14 or 21 days)

| End point values | Rituximab SC | Rituximab IV | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 369 | 203 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Less than 30 minutes (Cycle 1) | 0 | 0 | | |
| 30 minutes to 1 hour (Cycle 1) | 0 | 0.5 | | |
| 1 to 2 hours (Cycle 1) | 1.4 | 0 | | |
| 2 to 4 hours (Cycle 1) | 20.3 | 17.2 | | |
| 4 to 12 hours (Cycle 1) | 69.4 | 72.4 | | |
| More than 12 hours (Cycle 1) | 7.6 | 7.9 | | |
| Missing (Cycle 1) | 1.4 | 2 | | |
| Less than 30 minutes (Cycle 2) | 7.3 | 0 | | |

| | | | | |
|--------------------------------|------|------|--|--|
| 30 minutes to 1 hour (Cycle 2) | 2.4 | 0 | | |
| 1 to 2 hours (Cycle 2) | 17.1 | 1.1 | | |
| 2 to 4 hours (Cycle 2) | 56.1 | 36.2 | | |
| 4 to 12 hours (Cycle 2) | 12.2 | 60.1 | | |
| More than 12 hours (Cycle 2) | 0.3 | 1.1 | | |
| Missing (Cycle 2) | 4.6 | 1.6 | | |
| Less than 30 minutes (Cycle 3) | 5.6 | 0 | | |
| 30 minutes to 1 hour (Cycle 3) | 2 | 0 | | |
| 1 to 2 hours (Cycle 3) | 22.1 | 0.5 | | |
| 2 to 4 hours (Cycle 3) | 55.9 | 38.9 | | |
| 4 to 12 hours (Cycle 3) | 12.6 | 58.4 | | |
| More than 12 hours (Cycle 3) | 0.3 | 0.5 | | |
| Missing (Cycle 3) | 1.7 | 1.6 | | |
| Less than 30 minutes (Cycle 4) | 5.1 | 0 | | |
| 30 minutes to 1 hour (Cycle 4) | 2.8 | 0 | | |
| 1 to 2 hours (Cycle 4) | 21.8 | 1.1 | | |
| 2 to 4 hours (Cycle 4) | 55 | 36.7 | | |
| 4 to 12 hours (Cycle 4) | 13.9 | 60.6 | | |
| More than 12 hours (Cycle 4) | 0.3 | 0.6 | | |
| Missing (Cycle 4) | 1.1 | 1.1 | | |
| Less than 30 minutes (Cycle 5) | 5.3 | 0.6 | | |
| 30 minutes to 1 hour (Cycle 5) | 2.4 | 0 | | |
| 1 to 2 hours (Cycle 5) | 24.9 | 1.1 | | |
| 2 to 4 hours (Cycle 5) | 53.4 | 40.2 | | |
| 4 to 12 hours (Cycle 5) | 12.8 | 56.3 | | |
| More than 12 hours (Cycle 5) | 0 | 0.6 | | |
| Missing (Cycle 5) | 1.2 | 1.1 | | |
| Less than 30 minutes (Cycle 6) | 3.7 | 0.6 | | |
| 30 minutes to 1 hour (Cycle 6) | 3.1 | 0 | | |
| 1 to 2 hours (Cycle 6) | 22.7 | 1.8 | | |
| 2 to 4 hours (Cycle 6) | 56.7 | 42.5 | | |
| 4 to 12 hours (Cycle 6) | 12.3 | 53.3 | | |
| More than 12 hours (Cycle 6) | 0 | 0 | | |
| Missing (Cycle 6) | 1.5 | 1.8 | | |
| Less than 30 minutes (Cycle 7) | 18.7 | 0 | | |
| 30 minutes to 1 hour (Cycle 7) | 7 | 0 | | |
| 1 to 2 hours (Cycle 7) | 26.9 | 4.9 | | |
| 2 to 4 hours (Cycle 7) | 40.2 | 48.8 | | |
| 4 to 12 hours (Cycle 7) | 6 | 44.4 | | |
| More than 12 hours (Cycle 7) | 0 | 0 | | |
| Missing (Cycle 7) | 1.3 | 1.9 | | |
| Less than 30 minutes (Cycle 8) | 19.9 | 0.6 | | |
| 30 minutes to 1 hour (Cycle 8) | 6.4 | 0 | | |
| 1 to 2 hours (Cycle 8) | 29.6 | 4.4 | | |
| 2 to 4 hours (Cycle 8) | 36.7 | 50.9 | | |
| 4 to 12 hours (Cycle 8) | 5.8 | 43.4 | | |
| More than 12 hours (Cycle 8) | 0 | 0 | | |
| Missing (Cycle 8) | 1.6 | 0.6 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants by Time Spent in the Hospital for Each Treatment Cycle

| | |
|-----------------|---|
| End point title | Percentage of Participants by Time Spent in the Hospital for Each Treatment Cycle |
|-----------------|---|

End point description:

Hospital time was defined as the amount of time the participant was in the hospital for the course of one cycle of rituximab + CHOP chemotherapy. Where the hospital time was not documented for a given cycle, it was reported as "Missing". Safety Population.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Cycles 1, 2, 3, 4, 5, 6, 7, and 8 (each cycle was 14 or 21 days)

| End point values | Rituximab SC | Rituximab IV | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 369 | 203 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Less than 2 hours (Cycle 1) | 0.3 | 0.5 | | |
| 2 to 4 hours (Cycle 1) | 3.5 | 1.5 | | |
| 4 to 6 hours (Cycle 1) | 19.2 | 20.7 | | |
| 6 to 12 hours (Cycle 1) | 38.8 | 43.8 | | |
| 12 to 24 hours (Cycle 1) | 8.9 | 6.4 | | |
| More than 24 hours (Cycle 1) | 27.1 | 24.1 | | |
| Missing (Cycle 1) | 2.2 | 3 | | |
| Less than 2 hours (Cycle 2) | 3.8 | 0 | | |
| 2 to 4 hours (Cycle 2) | 33.1 | 10.1 | | |
| 4 to 6 Hours (Cycle 2) | 27.9 | 33.5 | | |
| 6 to 12 Hours (Cycle 2) | 16.3 | 38.8 | | |
| 12 to 24 Hours (Cycle 2) | 3.8 | 1.1 | | |
| More than 24 Hours (Cycle 2) | 10.3 | 11.7 | | |
| Missing (Cycle 2) | 4.9 | 4.8 | | |
| Less Than 2 Hours (Cycle 3) | 3.6 | 0.5 | | |
| 2 to 4 Hours (Cycle 3) | 37.2 | 11.9 | | |
| 4 to 6 Hours (Cycle 3) | 30.2 | 30.8 | | |
| 6 to 12 Hours (Cycle 3) | 14.5 | 41.6 | | |
| 12 to 24 Hours (Cycle 3) | 2.8 | 2.2 | | |
| More than 24 Hours (Cycle 3) | 9.8 | 10.3 | | |
| Missing (Cycle 3) | 2 | 2.7 | | |
| Less Than 2 Hours (Cycle 4) | 4.5 | 0 | | |
| 2 to 4 Hours (Cycle 4) | 36.3 | 10 | | |
| 4 to 6 Hours (Cycle 4) | 27.5 | 31.1 | | |
| 6 to 12 Hours (Cycle 4) | 17.6 | 42.2 | | |
| 12 to 24 Hours (Cycle 4) | 2 | 2.8 | | |
| More than 24 Hours (Cycle 4) | 10.2 | 10.6 | | |
| Missing (Cycle 4) | 2 | 3.3 | | |
| Less Than 2 Hours (Cycle 5) | 5 | 0.6 | | |

| | | | | |
|------------------------------|------|------|--|--|
| 2 to 4 Hours (Cycle 5) | 39.5 | 11.5 | | |
| 4 to 6 Hours (Cycle 5) | 26.7 | 34.5 | | |
| 6 to 12 Hours (Cycle 5) | 15.7 | 37.4 | | |
| 12 to 24 Hours (Cycle 5) | 2.1 | 1.7 | | |
| More than 24 Hours (Cycle 5) | 8.9 | 10.9 | | |
| Missing (Cycle 5) | 2.1 | 3.4 | | |
| Less Than 2 Hours (Cycle 6) | 4.3 | 0.6 | | |
| 2 to 4 Hours (Cycle 6) | 39.9 | 12.6 | | |
| 4 to 6 Hours (Cycle 6) | 26.7 | 34.1 | | |
| 6 to 12 Hours (Cycle 6) | 15.6 | 38.3 | | |
| 12 to 24 Hours (Cycle 6) | 2.5 | 2.4 | | |
| More than 24 Hours (Cycle 6) | 8.6 | 9 | | |
| Missing (Cycle 6) | 2.5 | 3 | | |
| Less Than 2 Hours (Cycle 7) | 17.7 | 0 | | |
| 2 to 4 Hours (Cycle 7) | 40.8 | 23.5 | | |
| 4 to 6 Hours (Cycle 7) | 19.9 | 36.4 | | |
| 6 to 12 Hours (Cycle 7) | 10.4 | 30.9 | | |
| 12 to 24 Hours (Cycle 7) | 2.8 | 2.5 | | |
| More than 24 Hours (Cycle 7) | 5.7 | 3.7 | | |
| Missing (Cycle 7) | 2.5 | 3.1 | | |
| Less Than 2 Hours (Cycle 8) | 18 | 0 | | |
| 2 to 4 Hours (Cycle 8) | 40.5 | 25.8 | | |
| 4 to 6 Hours (Cycle 8) | 21.9 | 34 | | |
| 6 to 12 Hours (Cycle 8) | 8.7 | 30.8 | | |
| 12 to 24 Hours (Cycle 8) | 2.6 | 1.3 | | |
| More than 24 Hours (Cycle 8) | 5.8 | 5 | | |
| Missing (Cycle 8) | 2.6 | 3.1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with an Event-Free Survival (EFS) Event at the Time of Primary Analysis

| | |
|-----------------|--|
| End point title | Number of Participants with an Event-Free Survival (EFS) Event at the Time of Primary Analysis |
|-----------------|--|

End point description:

EFS events included disease progression, relapse, initiation of other anti-lymphoma therapy, or death. Tumor response was assessed according to criteria published by Cheson et al (1999). Progression was defined as greater than or equal to (\geq) 50% increase in the sum of products of greatest diameters of any previously identified abnormal lymph node or the appearance of any new lesion. Relapse was defined as a new lesion or increase by \geq 50% in size of previously involved sites, or \geq 50% increase in greatest diameter of any previously identified node >1 cm, following an earlier assessment of CR or CRu. ITT Population.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to approximately 2 years (assessed at Baseline, Day 1 of each cycle [maximum 8 cycles; each cycle was 14 to 21 days]; every 3 months thereafter; and/or 4 weeks after early termination)

| End point values | Rituximab SC | Rituximab IV | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 342 | 177 | | |
| Units: participants | 80 | 40 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of EFS at the Time of Primary Analysis

| | |
|-----------------|---|
| End point title | Duration of EFS at the Time of Primary Analysis |
|-----------------|---|

End point description:

EFS was defined as the time from randomization to first occurrence of disease progression, relapse, initiation of other anti-lymphoma therapy, or death, whichever occurred first. Tumor response was assessed according to criteria published by Cheson et al (1999). Progression was defined as a $\geq 50\%$ increase in the sum of products of greatest diameters of any previously identified abnormal lymph node or the appearance of any new lesion. Relapse was defined as a new lesion or increase by $\geq 50\%$ in size of previously involved sites, or $\geq 50\%$ increase in greatest diameter of any previously identified node > 1 cm, following an earlier assessment of CR or CRu. The duration of EFS was to be determined at the time of clinical cut-off (October 2014) using Kaplan-Meier analysis. ITT Population. 99999 = estimate not available due to insufficient follow-up.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to approximately 2 years (assessed at Baseline, Day 1 of each cycle [maximum 8 cycles; each cycle was 14 to 21 days]; every 3 months thereafter; and/or 4 weeks after early termination)

| End point values | Rituximab SC | Rituximab IV | | |
|-------------------------------|-------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 342 | 177 | | |
| Units: weeks | | | | |
| median (full range (min-max)) | 99999 (-99999 to 99999) | 99999 (-99999 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Relapse or Death at the Time of Primary Analysis

| | |
|-----------------|--|
| End point title | Number of Participants with Relapse or Death at the Time of Primary Analysis |
|-----------------|--|

End point description:

Tumor response was assessed according to criteria published by Cheson et al (1999). Relapse was defined as a new lesion or increase by $\geq 50\%$ in size of previously involved sites, or $\geq 50\%$ increase in greatest diameter of any previously identified node > 1 cm, following an earlier assessment of CR or CRu. The number of participants who had experienced relapse or death prior to the clinical cut-off date (October 2014) was determined. ITT Population (Responder Subpopulation): All participants who achieved CR or CRu after 4 cycles.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 2 years (assessed at Baseline, Day 1 of each cycle [maximum 8 cycles; each cycle was 14 to 21 days], every 3 months thereafter, and/or 4 weeks after early termination) | |

| End point values | Rituximab SC | Rituximab IV | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 178 | 90 | | |
| Units: participants | 12 | 5 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Disease-Free Survival (DFS) at the Time of Primary Analysis

| | |
|-----------------|---|
| End point title | Duration of Disease-Free Survival (DFS) at the Time of Primary Analysis |
|-----------------|---|

End point description:

DFS was defined as the time from date of initial CR/CRu to the date of relapse or death from any cause. Tumor response was assessed according to criteria published by Cheson et al (1999). Relapse was defined as a new lesion or increase by $\geq 50\%$ in size of previously involved sites, or $\geq 50\%$ increase in greatest diameter of any previously identified node >1 cm, following an earlier assessment of CR or CRu. The duration of DFS was to be determined at the time of clinical cut-off (October 2014) using Kaplan-Meier analysis. ITT Population (Responder Subpopulation). 99999 = estimate not available due to insufficient follow-up.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to approximately 2 years (assessed at Baseline, Day 1 of each cycle [maximum 8 cycles; each cycle was 14 to 21 days], every 3 months thereafter, and/or 4 weeks after early termination)

| End point values | Rituximab SC | Rituximab IV | | |
|-------------------------------|-------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 178 | 90 | | |
| Units: weeks | | | | |
| median (full range (min-max)) | 99999 (-99999 to 99999) | 99999 (-99999 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Progression, Relapse, or Death at the Time of Primary Analysis

| | |
|-----------------|--|
| End point title | Number of Participants with Progression, Relapse, or Death at the Time of Primary Analysis |
|-----------------|--|

End point description:

Tumor response was assessed according to criteria published by Cheson et al (1999). Progression was defined as $\geq 50\%$ increase in the sum of products of greatest diameters of any previously identified abnormal lymph node or the appearance of any new lesion. Relapse was defined as a new lesion or increase by $\geq 50\%$ in size of previously involved sites, or $\geq 50\%$ increase in greatest diameter of any previously identified node > 1 cm, following an earlier assessment of CR or CRu. The number of participants who had experienced progression, relapse, or death prior to the clinical cut-off date (October 2014) was determined. ITT Population.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to approximately 2 years (assessed at Baseline, Day 1 of each cycle [maximum 8 cycles; each cycle was 14 to 21 days], every 3 months thereafter, and/or 4 weeks after early termination)

| End point values | Rituximab SC | Rituximab IV | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 342 | 177 | | |
| Units: participants | 54 | 28 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Progression-Free Survival (PFS) at the Time of Primary Analysis

| | |
|-----------------|---|
| End point title | Duration of Progression-Free Survival (PFS) at the Time of Primary Analysis |
|-----------------|---|

End point description:

PFS was defined as the time from randomization to first occurrence of disease progression, relapse, or death from any cause. Tumor response was assessed according to criteria published by Cheson et al (1999). Progression was defined as $\geq 50\%$ increase in the sum of products of greatest diameters of any previously identified abnormal lymph node or the appearance of any new lesion. Relapse was defined as a new lesion or increase by $\geq 50\%$ in size of previously involved sites, or $\geq 50\%$ increase in greatest diameter of any previously identified node > 1 cm, following an earlier assessment of CR or CRu. The duration of PFS was to be determined using Kaplan-Meier analysis. ITT Population. 99999 = estimate not available due to insufficient follow-up.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to approximately 2 years (assessed at Baseline, Day 1 of each cycle [maximum 8 cycles; each cycle was 14 to 21 days], every 3 months thereafter, and/or 4 weeks after early termination)

| End point values | Rituximab SC | Rituximab IV | | |
|-------------------------------|-------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 342 | 177 | | |
| Units: weeks | | | | |
| median (full range (min-max)) | 99999 (-99999 to 99999) | 99999 (-99999 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Deaths at the Time of Primary Analysis

| | |
|--|--|
| End point title | Number of Deaths at the Time of Primary Analysis |
| End point description: The number of participants who had experienced death prior to the clinical cut-off date (October 2014) was determined. ITT Population. | |
| End point type | Secondary |
| End point timeframe: Up to approximately 2 years (survival followed from randomization until death) | |

| End point values | Rituximab SC | Rituximab IV | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 342 | 177 | | |
| Units: participants | 25 | 15 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Overall Survival (OS) at the Time of Primary Analysis

| | |
|---|---|
| End point title | Duration of Overall Survival (OS) at the Time of Primary Analysis |
| End point description: OS was defined as the time from randomization to death from any cause. The duration of OS was to be determined using Kaplan-Meier analysis. ITT Population. 99999 = estimate not available due to insufficient follow-up. | |
| End point type | Secondary |
| End point timeframe: Up to approximately 2 years (survival followed from randomization until death) | |

| | | | | |
|-------------------------------|-------------------------|-------------------------|--|--|
| End point values | Rituximab SC | Rituximab IV | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 342 | 177 | | |
| Units: weeks | | | | |
| median (full range (min-max)) | 99999 (-99999 to 99999) | 99999 (-99999 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 2 years (from Baseline up to 4 weeks after end of study)

Adverse event reporting additional description:

Safety Population. The adverse event terms "lumbar spondylosis" and "lung separation with small pleural effusion" were entered into an uncoded System Organ Class (SOC) at the time of reporting. The best possible option for SOC was selected for the purposes of clinical trial disclosure.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | Rituximab SC |
|-----------------------|--------------|

Reporting group description:

Participants with previously untreated, CD20-positive DLBCL received up to 8 cycles of rituximab in combination with CHOP. Treatment was given on Day 1 of each cycle, and the cycle length (14 or 21 days) was decided by the study center. For Cycle 1, rituximab was administered at a dose of 375 mg/m² via IV infusion; subsequent doses were given as 1400 mg via SC injection. Tumor response was assessed after 4 cycles according to criteria published by Cheson et al (1999), which are presented in Endpoint 1. The duration of CHOP therapy could be reduced from 8 to 6 cycles for those who achieved CR or CRu after 4 cycles, but all participants received a full 8 cycles of rituximab.

| | |
|-----------------------|--------------|
| Reporting group title | Rituximab IV |
|-----------------------|--------------|

Reporting group description:

Participants with previously untreated, CD20-positive DLBCL received up to 8 cycles of rituximab in combination with CHOP. Treatment was given on Day 1 of each cycle, and the cycle length (14 or 21 days) was decided by the study center. For all cycles, rituximab was administered at a dose of 375 mg/m² via IV infusion. Tumor response was assessed after 4 cycles according to criteria published by Cheson et al (1999), which are presented in Endpoint 1. The duration of CHOP therapy could be reduced from 8 to 6 cycles for those who achieved CR or CRu after 4 cycles, but all participants received a full 8 cycles of rituximab.

| Serious adverse events | Rituximab SC | Rituximab IV | |
|---|--------------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 142 / 369 (38.48%) | 71 / 203 (34.98%) | |
| number of deaths (all causes) | 37 | 26 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Central nervous system lymphoma | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Papillary thyroid cancer | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal cell carcinoma | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transitional cell carcinoma | | | |
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Embolism venous | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Flushing | | | |
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subclavian vein thrombosis | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombosis | | | |
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 8 / 369 (2.17%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 3 / 9 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chills | | | |
| subjects affected / exposed | 2 / 369 (0.54%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Influenza like illness | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injection site hypertrophy | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Localised oedema | | | |
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden death | | | |
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Reproductive system and breast disorders | | | |
| Prostatitis | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumonitis | | | |
| subjects affected / exposed | 4 / 369 (1.08%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 3 / 203 (1.48%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 369 (0.00%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 2 / 369 (0.54%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Cough | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Organising pneumonia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleurisy | | | |
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary fibrosis | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung separation with small pleural effusion | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Adjustment disorder | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Confusional state | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depression | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 7 / 369 (1.90%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 10 / 10 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 4 / 369 (1.08%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 4 / 4 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Troponin T increased | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Multiple fractures | | | |
| subjects affected / exposed | 2 / 369 (0.54%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Femur fracture | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infusion related reaction | | | |
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower limb fracture | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transfusion reaction | | | |
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fracture | | | |
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 369 (0.54%) | 3 / 203 (1.48%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 369 (0.27%) | 3 / 203 (1.48%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 3 | |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 369 (0.00%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Congestive cardiomyopathy | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Left ventricular failure | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tachycardia induced cardiomyopathy | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Syncope | | | |
| subjects affected / exposed | 2 / 369 (0.54%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 2 / 369 (0.54%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Presyncope | | | |
| subjects affected / exposed | 2 / 369 (0.54%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Convulsion | | | |

| | | | |
|---|-------------------|-------------------|--|
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysarthria | | | |
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 48 / 369 (13.01%) | 23 / 203 (11.33%) | |
| occurrences causally related to treatment / all | 58 / 61 | 26 / 26 | |
| deaths causally related to treatment / all | 0 / 0 | 2 / 2 | |
| Neutropenia | | | |
| subjects affected / exposed | 17 / 369 (4.61%) | 11 / 203 (5.42%) | |
| occurrences causally related to treatment / all | 19 / 19 | 11 / 12 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 369 (0.54%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile bone marrow aplasia | | | |
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 369 (0.81%) | 2 / 203 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 369 (0.81%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 3 / 369 (0.81%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal fissure | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal haemorrhage | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric perforation | | | |
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Haematemesis | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine perforation | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic colitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Obstruction gastric | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Bile duct obstruction | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Proteinuria | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Bone pain | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myalgia | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|------------------|-----------------|--|
| Osteonecrosis | | | |
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pathological fracture | | | |
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tendonitis | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar spondylosis | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 17 / 369 (4.61%) | 6 / 203 (2.96%) | |
| occurrences causally related to treatment / all | 10 / 18 | 3 / 6 | |
| deaths causally related to treatment / all | 2 / 3 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 3 / 369 (0.81%) | 3 / 203 (1.48%) | |
| occurrences causally related to treatment / all | 4 / 5 | 0 / 3 | |
| deaths causally related to treatment / all | 2 / 2 | 0 / 3 | |
| Lung infection | | | |
| subjects affected / exposed | 2 / 369 (0.54%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 3 / 369 (0.81%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 3 / 369 (0.81%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 2 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 3 / 369 (0.81%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 2 / 369 (0.54%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 2 / 369 (0.54%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal abscess | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchiolitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| H1N1 influenza | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes oesophagitis | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes simplex hepatitis | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Klebsiella sepsis | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic infection | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral herpes | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pneumocystis jirovecii infection | | | |
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinusitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tuberculosis | | | |
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral infection | | | |
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 369 (0.54%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 369 (0.27%) | 0 / 203 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypernatraemia | | | |
| subjects affected / exposed | 0 / 369 (0.00%) | 1 / 203 (0.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Rituximab SC | Rituximab IV | |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 305 / 369 (82.66%) | 165 / 203 (81.28%) | |
| Investigations | | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 24 / 369 (6.50%) | 16 / 203 (7.88%) | |
| occurrences (all) | 56 | 33 | |
| Weight decreased | | | |
| subjects affected / exposed | 28 / 369 (7.59%) | 8 / 203 (3.94%) | |
| occurrences (all) | 32 | 8 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 15 / 369 (4.07%) | 13 / 203 (6.40%) | |
| occurrences (all) | 30 | 44 | |
| Nervous system disorders | | | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 42 / 369 (11.38%) | 24 / 203 (11.82%) | |
| occurrences (all) | 54 | 33 | |

| | | | |
|--|---------------------------|--------------------------|--|
| Paraesthesia subjects affected / exposed occurrences (all) | 27 / 369 (7.32%) 29 | 12 / 203 (5.91%) 15 | |
| Headache subjects affected / exposed occurrences (all) | 20 / 369 (5.42%) 28 | 15 / 203 (7.39%) 23 | |
| Blood and lymphatic system disorders | | | |
| Neutropenia subjects affected / exposed occurrences (all) | 122 / 369 (33.06%) 234 | 62 / 203 (30.54%) 119 | |
| Anaemia subjects affected / exposed occurrences (all) | 77 / 369 (20.87%) 122 | 37 / 203 (18.23%) 55 | |
| Leukopenia subjects affected / exposed occurrences (all) | 35 / 369 (9.49%) 69 | 15 / 203 (7.39%) 28 | |
| Lymphopenia subjects affected / exposed occurrences (all) | 25 / 369 (6.78%) 33 | 14 / 203 (6.90%) 24 | |
| General disorders and administration site conditions | | | |
| Fatigue subjects affected / exposed occurrences (all) | 68 / 369 (18.43%) 76 | 29 / 203 (14.29%) 39 | |
| Pyrexia subjects affected / exposed occurrences (all) | 40 / 369 (10.84%) 51 | 24 / 203 (11.82%) 30 | |
| Asthenia subjects affected / exposed occurrences (all) | 40 / 369 (10.84%) 60 | 23 / 203 (11.33%) 29 | |
| Mucosal inflammation subjects affected / exposed occurrences (all) | 28 / 369 (7.59%) 38 | 16 / 203 (7.88%) 20 | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 23 / 369 (6.23%) 27 | 8 / 203 (3.94%) 8 | |
| Gastrointestinal disorders | | | |

| | | | |
|---|-------------------|-------------------|--|
| Nausea | | | |
| subjects affected / exposed | 78 / 369 (21.14%) | 48 / 203 (23.65%) | |
| occurrences (all) | 116 | 70 | |
| Constipation | | | |
| subjects affected / exposed | 53 / 369 (14.36%) | 34 / 203 (16.75%) | |
| occurrences (all) | 63 | 43 | |
| Diarrhoea | | | |
| subjects affected / exposed | 50 / 369 (13.55%) | 20 / 203 (9.85%) | |
| occurrences (all) | 74 | 29 | |
| Vomiting | | | |
| subjects affected / exposed | 38 / 369 (10.30%) | 17 / 203 (8.37%) | |
| occurrences (all) | 50 | 22 | |
| Stomatitis | | | |
| subjects affected / exposed | 23 / 369 (6.23%) | 11 / 203 (5.42%) | |
| occurrences (all) | 32 | 14 | |
| Abdominal pain | | | |
| subjects affected / exposed | 22 / 369 (5.96%) | 11 / 203 (5.42%) | |
| occurrences (all) | 24 | 11 | |
| Dyspepsia | | | |
| subjects affected / exposed | 18 / 369 (4.88%) | 14 / 203 (6.90%) | |
| occurrences (all) | 21 | 16 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 39 / 369 (10.57%) | 18 / 203 (8.87%) | |
| occurrences (all) | 46 | 21 | |
| Dyspnoea | | | |
| subjects affected / exposed | 21 / 369 (5.69%) | 7 / 203 (3.45%) | |
| occurrences (all) | 23 | 7 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 87 / 369 (23.58%) | 48 / 203 (23.65%) | |
| occurrences (all) | 97 | 57 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 23 / 369 (6.23%) | 12 / 203 (5.91%) | |
| occurrences (all) | 23 | 16 | |

| | | | |
|------------------------------------|------------------|------------------|--|
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 26 / 369 (7.05%) | 18 / 203 (8.87%) | |
| occurrences (all) | 27 | 25 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|--|
| 02 May 2012 | The protocol was amended to clarify reporting requirements for certain events, and also to specify the procedure for submitting protocol amendments to the Institutional Review Board (IRB)/Ethics Committee (EC) and to regulatory authorities in accordance with local requirements. |
| 20 March 2013 | The protocol was amended to clarify and correct several sections including the defined patient population (with the added exclusion of pregnant women), study treatment schedules, timing of study assessments, and description of the statistical analysis plan. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported