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
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

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/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.

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 (≥) 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 ≥50% in size of previously involved sites, or ≥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 ≥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 ≥50% in size of previously involved sites, or ≥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 ≥50% in size of previously involved sites, or ≥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 ≥50% in size of previously involved sites, or ≥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 ≥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 ≥50% in size of previously involved sites, or ≥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 ≥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 ≥50% in size of previously involved sites, or ≥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/m^2 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/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.

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	27 / 369 (7.32%)	12 / 203 (5.91%)	
occurrences (all)	29	15	
Headache			
subjects affected / exposed	20 / 369 (5.42%)	15 / 203 (7.39%)	
occurrences (all)	28	23	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	122 / 369 (33.06%)	62 / 203 (30.54%)	
occurrences (all)	234	119	
Anaemia			
subjects affected / exposed	77 / 369 (20.87%)	37 / 203 (18.23%)	
occurrences (all)	122	55	
Leukopenia			
subjects affected / exposed	35 / 369 (9.49%)	15 / 203 (7.39%)	
occurrences (all)	69	28	
Lymphopenia			
subjects affected / exposed	25 / 369 (6.78%)	14 / 203 (6.90%)	
occurrences (all)	33	24	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	68 / 369 (18.43%)	29 / 203 (14.29%)	
occurrences (all)	76	39	
Pyrexia			
subjects affected / exposed	40 / 369 (10.84%)	24 / 203 (11.82%)	
occurrences (all)	51	30	
Asthenia			
subjects affected / exposed	40 / 369 (10.84%)	23 / 203 (11.33%)	
occurrences (all)	60	29	
Mucosal inflammation			
subjects affected / exposed	28 / 369 (7.59%)	16 / 203 (7.88%)	
occurrences (all)	38	20	
Oedema peripheral			
subjects affected / exposed	23 / 369 (6.23%)	8 / 203 (3.94%)	
occurrences (all)	27	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 occurrences (all)	26 / 369 (7.05%) 27	18 / 203 (8.87%) 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