



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	16 September 2016

Results information

Result version number	v2 (current)
This version publication date	27 September 2017
First version publication date	09 April 2016
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	MO28107
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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	Final
Date of interim/final analysis	28 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 October 2014
Global end of trial reached?	Yes
Global end of trial date	16 September 2016
Was the trial ended prematurely?	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
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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	230	125
Not completed	139	78
Consent withdrawn by subject	14	14
Treatment failure	1	1
Death	69	34
Lack of compliance	6	1
Reason not specified	20	5
Stable or progressed disease	5	3
Lost to follow-up	20	16
Protocol deviation	4	4

Baseline characteristics

Reporting groups

Reporting group title	Rituximab SC
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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
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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
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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
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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 Complete Response (CR) or Complete Response Unconfirmed (CRu)

End point title	Percentage of Participants with Complete Response (CR) or Complete Response Unconfirmed (CRu)
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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
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End point timeframe:

Up to approximately 4.25 years

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%)	50.6 (45.2 to 56)	42.4 (35 to 50)		

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	= 0.076
Method	Chi-squared
Parameter estimate	Difference in response rates
Point estimate	8.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	17.5

Secondary: Cancer Treatment Satisfaction Questionnaire (CTSQ) Domain Scores

End point title	Cancer Treatment Satisfaction Questionnaire (CTSQ) Domain Scores
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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
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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
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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
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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
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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
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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
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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
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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)	20.6	17.2		
4 to 12 hours (Cycle 1)	69.4	72.4		
More than 12 hours (Cycle 1)	7.3	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	0.6		
30 minutes to 1 hour (Cycle 5)	2.4	0		
1 to 2 hours (Cycle 5)	25.2	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)	3.4	0.6		
30 minutes to 1 hour (Cycle 6)	3.1	0		
1 to 2 hours (Cycle 6)	23	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)	20.3	0.6		
30 minutes to 1 hour (Cycle 8)	6.4	0		
1 to 2 hours (Cycle 8)	29.3	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
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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
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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		
2 to 4 hours (Cycle 1)	3	1.5		
4 to 6 hours (Cycle 1)	19.8	20.7		
6 to 12 hours (Cycle 1)	39	43.8		
12 to 24 hours (Cycle 1)	8.9	6.9		
More than 24 hours (Cycle 1)	26.8	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)	26.4	34.5		
6 to 12 Hours (Cycle 5)	16	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)	39.6	12.6		
4 to 6 Hours (Cycle 6)	26.4	34.1		
6 to 12 Hours (Cycle 6)	16.3	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

End point title	Number of Participants with an Event-Free Survival (EFS) Event
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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
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End point timeframe:

Up to approximately 4.25 years

End point values	Rituximab SC	Rituximab IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	342	177		
Units: participants	116	53		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of EFS

End point title	Duration of EFS
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. ITT Population. 99999 = Median EFS was not reached.	
End point type	Secondary
End point timeframe:	
Up to approximately 4.25 years	

End point values	Rituximab SC	Rituximab IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	342	177		
Units: months				
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)

End point title	Duration of Disease-Free Survival (DFS)
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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. ITT Population (Responder Subpopulation). 99999 = Median DFS was not reached.

End point type	Secondary
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End point timeframe:

Up to approximately 4.25 years

End point values	Rituximab SC	Rituximab IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240	118		
Units: months				
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

End point title	Number of Participants with Progression, Relapse, or Death
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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. ITT Population.

End point type	Secondary
End point timeframe:	
Up to approximately 4.25 years	

End point values	Rituximab SC	Rituximab IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	342	177		
Units: participants	95	38		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Progression-Free Survival (PFS)

End point title	Duration of Progression-Free Survival (PFS)
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. ITT Population. 99999 = Median PFS was not reached.	
End point type	Secondary
End point timeframe:	
Up to approximately 4.25 years	

End point values	Rituximab SC	Rituximab IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	342	177		
Units: months				
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

End point title	Number of Deaths
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End point description:	
ITT Population.	
End point type	Secondary
End point timeframe:	
Up to approximately 4.25 years	

End point values	Rituximab SC	Rituximab IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	342	177		
Units: participants	56	22		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Overall Survival (OS)

End point title	Duration of Overall Survival (OS)
End point description:	
OS was defined as the time from randomization to death from any cause. ITT Population. 99999 = Median OS was not reached.	
End point type	Secondary
End point timeframe:	
Up to approximately 4.25 years	

End point values	Rituximab SC	Rituximab IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	342	177		
Units: months				
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 4.25 years

Adverse event reporting additional description:

Safety Population.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.1
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Reporting groups

Reporting group title	Rituximab SC
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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
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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	155 / 369 (42.01%)	77 / 203 (37.93%)	
number of deaths (all causes)	69	34	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
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	
Invasive ductal breast 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	
Lung adenocarcinoma 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	
Metastatic 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	
Myelodysplastic syndrome 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	
Non-small cell lung cancer 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 / 2	0 / 0	
Prostate 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	
Prostate cancer metastatic 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	
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	0 / 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	
Arterial 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	
Surgical and medical procedures			

Knee arthroplasty			
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	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	7 / 369 (1.90%)	3 / 203 (1.48%)	
occurrences causally related to treatment / all	1 / 8	1 / 3	
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	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 / 2	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 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	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	0 / 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	
Ill-defined 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 / 1	0 / 0	
Immune system disorders			
Cytokine release syndrome			
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	
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			
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	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Dyspnoea			
subjects affected / exposed	0 / 369 (0.00%)	3 / 203 (1.48%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
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	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
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 / 2	0 / 1	
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	
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	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	
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	3 / 369 (0.81%)	3 / 203 (1.48%)	
occurrences causally related to treatment / all	2 / 3	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

White blood cell count decreased 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	
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	0 / 0	0 / 0	
Troponin T increased 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	
Weight decreased 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	
Alanine aminotransferase increased 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	
Blood bilirubin increased 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	
Platelet count 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	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Femur fracture			
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	
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	2 / 2	
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	
Procedural pneumothorax			
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 disorders			

Atrial fibrillation			
subjects affected / exposed	2 / 369 (0.54%)	3 / 203 (1.48%)	
occurrences causally related to treatment / all	0 / 2	0 / 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 / 2	
Atrial flutter			
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	
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	0 / 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	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 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	0 / 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	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 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	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
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 failure congestive			
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 / 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%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
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	
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	
Ischaemic stroke			
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	
Seizure			
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	
Transient ischaemic attack			
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	49 / 369 (13.28%)	24 / 203 (11.82%)	
occurrences causally related to treatment / all	22 / 64	12 / 27	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neutropenia			

subjects affected / exposed	22 / 369 (5.96%)	10 / 203 (4.93%)	
occurrences causally related to treatment / all	13 / 26	8 / 14	
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	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 369 (0.27%)	3 / 203 (1.48%)	
occurrences causally related to treatment / all	1 / 1	6 / 6	
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	0 / 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	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 369 (0.81%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
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	1 / 1	0 / 0	
Vomiting			
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	0 / 0	0 / 0	
Nausea			

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	
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	0 / 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 / 0	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 / 0	0 / 0	
Ileus			
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 / 1	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	0 / 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	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	
Inguinal hernia			

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	
Small intestinal 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	
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	
Cholecystitis			
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	
Hepatic 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	
Skin and subcutaneous tissue disorders			
Eczema			
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	
Haematuria			
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 retention			
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	
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	
Spinal osteoarthritis			
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	
Spondylolisthesis			
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 occurrences causally related to treatment / all deaths causally related to treatment / all	27 / 369 (7.32%) 5 / 28 2 / 6	7 / 203 (3.45%) 3 / 7 1 / 1	
Septic shock subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	3 / 369 (0.81%) 4 / 5 2 / 2	3 / 203 (1.48%) 0 / 3 0 / 3	
Lung infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	4 / 369 (1.08%) 2 / 5 1 / 2	1 / 203 (0.49%) 0 / 1 0 / 0	
Respiratory tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 369 (0.54%) 0 / 2 0 / 1	0 / 203 (0.00%) 0 / 0 0 / 0	
Sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	5 / 369 (1.36%) 0 / 5 0 / 2	0 / 203 (0.00%) 0 / 0 0 / 0	
Cellulitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 369 (0.54%) 1 / 2 0 / 0	0 / 203 (0.00%) 0 / 0 0 / 0	
Infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 369 (0.54%) 2 / 2 0 / 0	0 / 203 (0.00%) 0 / 0 0 / 0	
Lower respiratory tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 369 (0.27%) 1 / 1 0 / 0	1 / 203 (0.49%) 0 / 1 0 / 0	
Urosepsis			

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	
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	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	
Bronchiolitis			
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	
Bronchitis			
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	
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	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	
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	
Tuberculosis			
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	
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	1 / 369 (0.27%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 2	0 / 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	
Lower respiratory tract infection viral			
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	
Intervertebral discitis			
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	
Localised 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	
Gastroenteritis norovirus			
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	
Pneumonia cytomegaloviral			
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	
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	1 / 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	319 / 369 (86.45%)	172 / 203 (84.73%)	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	81 / 369 (21.95%)	43 / 203 (21.18%)	
occurrences (all)	104	63	
Weight decreased			
subjects affected / exposed	28 / 369 (7.59%)	8 / 203 (3.94%)	
occurrences (all)	29	8	
White blood cell count decreased			
subjects affected / exposed	51 / 369 (13.82%)	23 / 203 (11.33%)	
occurrences (all)	85	43	
Lymphocyte count decreased			
subjects affected / exposed	53 / 369 (14.36%)	20 / 203 (9.85%)	
occurrences (all)	73	32	
Platelet count decreased			
subjects affected / exposed	19 / 369 (5.15%)	11 / 203 (5.42%)	
occurrences (all)	28	17	
Nervous system disorders			

Neuropathy peripheral subjects affected / exposed occurrences (all)	44 / 369 (11.92%) 50	24 / 203 (11.82%) 27	
Paraesthesia subjects affected / exposed occurrences (all)	32 / 369 (8.67%) 33	13 / 203 (6.40%) 15	
Headache subjects affected / exposed occurrences (all)	21 / 369 (5.69%) 28	15 / 203 (7.39%) 21	
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all)	104 / 369 (28.18%) 186	54 / 203 (26.60%) 92	
Anaemia subjects affected / exposed occurrences (all)	88 / 369 (23.85%) 110	40 / 203 (19.70%) 49	
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	71 / 369 (19.24%) 76	29 / 203 (14.29%) 38	
Pyrexia subjects affected / exposed occurrences (all)	40 / 369 (10.84%) 50	23 / 203 (11.33%) 31	
Asthenia subjects affected / exposed occurrences (all)	42 / 369 (11.38%) 59	24 / 203 (11.82%) 29	
Mucosal inflammation subjects affected / exposed occurrences (all)	29 / 369 (7.86%) 37	16 / 203 (7.88%) 19	
Oedema peripheral subjects affected / exposed occurrences (all)	27 / 369 (7.32%) 30	9 / 203 (4.43%) 9	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	79 / 369 (21.41%) 112	47 / 203 (23.15%) 65	

Constipation			
subjects affected / exposed	56 / 369 (15.18%)	34 / 203 (16.75%)	
occurrences (all)	65	39	
Diarrhoea			
subjects affected / exposed	52 / 369 (14.09%)	20 / 203 (9.85%)	
occurrences (all)	70	25	
Vomiting			
subjects affected / exposed	40 / 369 (10.84%)	17 / 203 (8.37%)	
occurrences (all)	52	23	
Stomatitis			
subjects affected / exposed	23 / 369 (6.23%)	11 / 203 (5.42%)	
occurrences (all)	28	14	
Abdominal pain			
subjects affected / exposed	24 / 369 (6.50%)	12 / 203 (5.91%)	
occurrences (all)	28	12	
Dyspepsia			
subjects affected / exposed	19 / 369 (5.15%)	14 / 203 (6.90%)	
occurrences (all)	22	16	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	42 / 369 (11.38%)	19 / 203 (9.36%)	
occurrences (all)	52	22	
Dyspnoea			
subjects affected / exposed	22 / 369 (5.96%)	6 / 203 (2.96%)	
occurrences (all)	24	7	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	87 / 369 (23.58%)	48 / 203 (23.65%)	
occurrences (all)	88	48	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	23 / 369 (6.23%)	13 / 203 (6.40%)	
occurrences (all)	23	18	
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed occurrences (all)	18 / 369 (4.88%) 22	11 / 203 (5.42%) 12	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	28 / 369 (7.59%)	18 / 203 (8.87%)	
occurrences (all)	30	23	
Hypokalaemia			
subjects affected / exposed	19 / 369 (5.15%)	5 / 203 (2.46%)	
occurrences (all)	25	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 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