Clinical trial results:
A RANDOMIZED, OPEN-LABEL, MULTI-CENTRE STUDY TO EVALUATE PATIENT PREFERENCE WITH SUBCUTANEOUS ADMINISTRATION OF RITUXIMAB VERSUS INTRAVENOUS RITUXIMAB IN PREVIOUSLY UNTREATED PATIENTS WITH CD20+ DIFFUSE LARGE B-CELL LYMPHOMA OR CD20+ FOLLICULAR NON-HODGKIN'S LYMPHOMA GRADES 1, 2, OR 3A

Summary

EudraCT number	2012-003230-17
Trial protocol	DE HU NL IT PT SE AT DK HR
Global end of trial date	

Results information

Result version number	v1
This version publication date	19 May 2016
First version publication date	19 May 2016

Trial information

Trial identification

Sponsor protocol code	MO28457

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01724021
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hoffman La-Roche
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland,
Public contact	Head of Clin. Ops Italy, Roche S.p.A., +39 039 247 5070, ITALY.INFO_CTA@ROCHE.COM
Scientific contact	Head of Clin. Ops Italy, Roche S.p.A., +39 039 247 5070, ITALY.INFO_CTA@ROCHE.COM

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	03 December 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the proportion of subjects indicating an overall preference via a Patient Preference Questionnaire (PPQ) for either the subcutaneous (SC) or the intravenous (IV) route of rituximab administration.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 December 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 12
Country: Number of subjects enrolled	Portugal: 10
Country: Number of subjects enrolled	Romania: 31
Country: Number of subjects enrolled	Sweden: 17
Country: Number of subjects enrolled	Croatia: 2
Country: Number of subjects enrolled	Austria: 15
Country: Number of subjects enrolled	Denmark: 13
Country: Number of subjects enrolled	Germany: 201
Country: Number of subjects enrolled	Hungary: 24
Country: Number of subjects enrolled	Italy: 60
Country: Number of subjects enrolled	Argentina: 10
Country: Number of subjects enrolled	Australia: 49
Country: Number of subjects enrolled	Brazil: 26
Country: Number of subjects enrolled	Canada: 20
Country: Number of subjects enrolled	Chile: 10
Country: Number of subjects enrolled	Colombia: 3
Country: Number of subjects enrolled	Dominican Republic: 4
Country: Number of subjects enrolled	Egypt: 10
Country: Number of subjects enrolled	El Salvador: 11
Country: Number of subjects enrolled	Guatemala: 8

Country: Number of subjects enrolled	Hong Kong: 8
Country: Number of subjects enrolled	Indonesia: 23
Country: Number of subjects enrolled	Korea, Republic of: 31
Country: Number of subjects enrolled	Malaysia: 20
Country: Number of subjects enrolled	New Zealand: 5
Country: Number of subjects enrolled	Panama: 22
Country: Number of subjects enrolled	Peru: 10
Country: Number of subjects enrolled	Philippines: 18
Country: Number of subjects enrolled	Taiwan: 16
Country: Number of subjects enrolled	Thailand: 30
Country: Number of subjects enrolled	Turkey: 15
Country: Number of subjects enrolled	Vietnam: 6
Worldwide total number of subjects	740
EEA total number of subjects	385

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)	459
From 65 to 84 years	281
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 743 subjects were enrolled across all the sites. Three subjects were enrolled but died before receiving study medication, therefore the safety population consisted of 740 subjects.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Subjects in Arm A received one cycle of rituximab 375 milligram per metre square (mg/m^2) intravenously (IV), then three cycles of rituximab 1400mg subcutaneously (SC), followed by four cycles of rituximab 375 mg/m^2 IV in combination with a standard chemotherapy of cyclophosphamide, hydroxydaunorubicin, Oncovin, prednisone/prednisolone (CHOP), cyclcophosphamie, vincristine, prednisone/prednisolone (CVP), or bendamustine. Rituximab was administered on Day 1 of each treatment cycle followed by administration of the preselected chemotherapy. Cycles were repeated every 14, 21, or 28 days, depending on the combination chemotherapy regimen selected by the investigator.

Arm type	Experimental
Investigational medicinal product name	Rituximab IV
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received one cycle of rituximab 375 mg/m^2 IV, and four cycles of rituximab 375 mg/m^2 IV n Day 1 of each treatment cycle. Cycles were repeated every 14, 21, or 28 days, depending on the combination chemotherapy regimen selected by the investigator.

Investigational medicinal product name	Rituximab SC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received three cycles of rituximab 1400 mg SC on Day 1 of each treament cycle. Cycles were repeated every 14, 21, or 28 days, depending on the combination chemotherapy regimen selected by the investigator.

Arm title	Arm B

Arm description:

Subjects in Arm B received four cycles of rituximab 375 mg/m^2 IV followed by four cycles of rituximab 1400 mg SC in combination with a standard chemotherapy of CHOP, CVP, or bendamustine. Rituximab was
administered on Day 1 of each treatment cycle followed by administration of the preselected chemotherapy. Cycles were repeated every 14, 21, or 28 days, depending on the combination chemotherapy regimen selected by the investigator.

Arm type	Experimental
Investigational medicinal product name	Rituximab IV
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received four cycles of rituximab 375 mg/m^2 IV n Day 1 of each treatment cycle. Cycles were repeated every 14, 21, or 28 days, depending on the combination chemotherapy regimen selected by the investigator.

Investigational medicinal product name	Rituximab SC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received four cycles of rituximab 1400 mg SC on Day 1 of each treament cycle. Cycles were repeated every 14, 21, or 28 days, depending on the combination chemotherapy regimen selected by the investigator.

Number of subjects in period 1	Arm A	Arm B
Started	371	369
Completed	323	309
Not completed	48	60
Lack of Compliance	-	1
Adverse Event	5	4
Death	24	29
Subject request/ Withdrew consent	13	10
Reason Not Specified	6	9
Lost to follow-up	-	7

Baseline characteristics

Reporting groups	
Reporting group title	Arm A

Reporting group description:

Subjects in Arm A received one cycle of rituximab 375 milligram per metre square (mg/m^2) intravenously (IV), then three cycles of rituximab 1400mg subcutaneously (SC), followed by four cycles of rituximab 375 mg/m^2 IV in combination with a standard chemotherapy of cyclophosphamide, hydroxydaunorubicin, Oncovin, prednisone/prednisolone (CHOP), cyclcophosphamie, vincristine, prednisone/prednisolone (CVP), or bendamustine. Rituximab was administered on Day 1 of each treatment cycle followed by administration of the preselected chemotherapy. Cycles were repeated every 14, 21, or 28 days, depending on the combination chemotherapy regimen selected by the investigator.

Reporting group title	Arm B

Reporting group description:

Subjects in Arm B received four cycles of rituximab 375 mg/m^2 IV followed by four cycles of rituximab 1400 mg SC in combination with a standard chemotherapy of CHOP, CVP, or bendamustine. Rituximab was
administered on Day 1 of each treatment cycle followed by administration of the preselected chemotherapy. Cycles were repeated every 14, 21, or 28 days, depending on the combination chemotherapy regimen selected by the investigator.

Reporting group values	Arm A	Arm B	Total
Number of subjects	371	369	740
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	58.2	59.4	
standard deviation	± 13.18	± 12.64	-
Gender categorical Units: Subjects			
Female	187	180	367
Male	184	189	373

End points

End points reporting groups

Reporting group title	Arm A

Reporting group description:

Subjects in Arm A received one cycle of rituximab 375 milligram per metre square (mg/m^2) intravenously (IV), then three cycles of rituximab 1400mg subcutaneously (SC), followed by four cycles of rituximab 375 mg/m^2 IV in combination with a standard chemotherapy of cyclophosphamide, hydroxydaunorubicin, Oncovin, prednisone/prednisolone (CHOP), cyclcophosphamie, vincristine, prednisone/prednisolone (CVP), or bendamustine. Rituximab was administered on Day 1 of each treatment cycle followed by administration of the preselected chemotherapy. Cycles were repeated every 14, 21, or 28 days, depending on the combination chemotherapy regimen selected by the investigator.

Reporting group title	Arm B

Reporting group description:

Subjects in Arm B received four cycles of rituximab 375 mg/m^2 IV followed by four cycles of rituximab 1400 mg SC in combination with a standard chemotherapy of CHOP, CVP, or bendamustine. Rituximab was
administered on Day 1 of each treatment cycle followed by administration of the preselected chemotherapy. Cycles were repeated every 14, 21, or 28 days, depending on the combination chemotherapy regimen selected by the investigator.

Subject analysis set title	Rituximab Intravenous (IV)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Rituximab was administered at a dose of 375 mg/m2 body surface area (BSA) as a single IV infusion, followed by administration of chemotherapy. At Cycle 1, Day 1, the first rituximab dose for both Arms A and B was always administered as a slow IV infusion, according to local standard practice. Faster infusion rates were permitted after Cycle 1, according to local practice. Cycles were repeated every 14, 21, or 28 days, depending on the combination chemotherapy regimen selected by the investigator.

Subject analysis set title	Rituximab Subcutaneous (SC)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Each treatment cycle consisted of a single SC injection of rituximab administered at a fixed dose of 1400 mg. Rituximab was administered on Day 1 of each treatment cycle followed by administration of the preselected chemotherapy. Cycles were repeated every 14, 21, or 28 days, depending on the combination chemotherapy regimen selected by the investigator.

Subject analysis set title	Arm A (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects received one cycle of rituximab 375 mg/m^2 IV, then three cycles of rituximab 1400mg SC, followed by four cycles of rituximab 375 mg/m^2 IV in combination with a standard chemotherapy of CHOP, CVP, or bendamustine. Rituximab was administered on Day 1 of each treatment cycle followed by administration of the preselected chemotherapy. Cycles were repeated every 14, 21, or 28 days, depending on the combination chemotherapy regimen selected by the investigator. The analysed intent-to treat (ITT) population included all subjects who were randomised in the study.

Subject analysis set title	Arm B (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects received four cycles of rituximab 375 mg/m^2 IV followed by four cycles of rituximab 1400mg SC in combination with a standard chemotherapy of CHOP, CVP, or bendamustine. Rituximab was
administered on Day 1 of each treatment cycle followed by administration of the preselected chemotherapy. Cycles were repeated every 14, 21, or 28 days, depending on the combination chemotherapy regimen selected by the investigator. The analysed ITT population included all subjects who were randomised in the study.

Primary: Percentage of Subjects Indicating a Preference for Rituximab Subcutaneous (SC) Over Rituximab Intravenously (IV) at Cycle 6

End point title	Percentage of Subjects Indicating a Preference for Rituximab Subcutaneous (SC) Over Rituximab Intravenously (IV) at Cycle 6[1]

End point description:

Subjects who preferred rituximab SC over rituximab IV, along with the corresponding 95% confidence interval (CI), were estimated using the patient preference questionnaire (PPQ) after completing cycle 6. Intent-to treat (ITT) population included all subjects who were randomised in the study.

End point type	Primary

End point timeframe:

Cycle 6

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported.

End point values	Arm A (ITT)	Arm B (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	372	371		
Units: percentage of subjects				
number (confidence interval 95%)	79.1 (74.2 to 83.5)	80.6 (75.7 to 84.8)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Indicating a Preference for Rituximab Subcutaneous (SC) Over Rituximab Intravenously (IV) at Cycle 8

End point title	Percentage of Subjects Indicating a Preference for Rituximab Subcutaneous (SC) Over Rituximab Intravenously (IV) at Cycle 8[2]

End point description:

Subjects who preferred rituximab SC over rituximab IV, along with the corresponding 95% CI, were estimated using the patient preference questionnaire (PPQ) after completing cycle 8. ITT population included all subjects who were randomised in the study.

End point type	Primary

End point timeframe:

Cycle 8

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported.

End point values	Arm A (ITT)	Arm B (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	372	371		
Units: percentage of subjects				
number (confidence interval 95%)	77.1 (71.9 to 81.8)	84.2 (79.6 to 88.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment Emergent Adverse Events (AEs)

End point title	Number of Subjects With Treatment Emergent Adverse Events (AEs)

End point description:

An AE was defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. The safety population included all subjects who received at least one dose of rituximab.

End point type	Secondary

End point timeframe:

Randomization of first participant to clinical cutoff (approximately 25 months)

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	371	369		
Units: subjects	344	340		

Statistical analyses

No statistical analyses for this end point

Secondary: Time Required for Rituximab Administration (Subcutaneous [SC] or Intravenous [IV])

End point title	Time Required for Rituximab Administration (Subcutaneous [SC] or Intravenous [IV])

End point description:

Administration time was defined as the time from start to end of the SC injection or from start to end of the IV infusion. ITT population included all subjects who were randomised in the study.

End point type	Secondary

End point timeframe:

Cycle 2-4, cycle 5-8 for both SC and IV

End point values	Rituximab Intravenous (IV)	Rituximab Subcutaneous (SC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	740	687		
Units: minutes				
median (full range (min-max))	838 (0 to 3967)	22 (0 to 1242)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cancer Therapy Satisfaction Questionnaire (CTQS) Score

End point title	Cancer Therapy Satisfaction Questionnaire (CTQS) Score

End point description:

CTSQ is a 16-item questionnaire measuring three domains related to subjects' satisfaction with cancer therapy: expectations of therapy, feelings about side effects, and satisfaction with therapy. The maximum score in each domain is 100. ITT population included all subjects who were randomized in the study. Here, n specifies the number of participants who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

During cycle 4, 8 of treatment

End point values	Rituximab Intravenous (IV)	Rituximab Subcutaneous (SC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	740	687		
Units: units on a scale				
arithmetic mean (standard deviation)				
Expectations of therapy domain (n=631, 627)	80.84 (± 18.365)	81.96 (± 17.856)		
Feelings about side effects domain (n=630, 624)	60.69 (± 22.266)	61.62 (± 22.323)		
Satisfaction with therapy domain (n=619, 623)	84.58 (± 12.207)	85.38 (± 11.284)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rituximab Administration Satisfaction Questionnaire (RASQ) Score

End point title	Rituximab Administration Satisfaction Questionnaire (RASQ) Score

End point description:

RASQ is a 20-item questionnaire measuring the impact of the mode of treatment administration on five domains: physical impact, psychological impact, impact on activities of daily living, convenience, and satisfaction. The maximum score in each domain was 100. ITT population included all subjects who were randomized in the study. Here, n specifies the number of subjects who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

During cycle 4, 8 of treatment

End point values	Rituximab Intravenous (IV)	Rituximab Subcutaneous (SC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	740	687		
Units: units on a scale				
arithmetic mean (standard deviation)				
Physical impact domain (n=622,619)	82.26 (± 15.584)	82.07 (± 15.85)		
Psychological Impact domain (n=614,612)	77.7 (± 16.377)	84.01 (± 14.356)		
Impact on activities of daily living (n=433,461)	57.66 (± 25.148)	83.95 (± 16.537)		
Convenience domain (n=619,599)	59.03 (± 20.75)	81.02 (± 13.119)		
Satisfaction domain (n=617,624)	74.86 (± 19.368)	87.28 (± 14.964)		

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Response (CR) Rate

End point title	Complete Response (CR) Rate

End point description:

Complete Response (CR) rate was defined as CR and CR unconfirmed (CRu). ITT population included all subjects who were randomised in the study.

End point type	Secondary

End point timeframe:

28 (± 3 days) after Day 1 of the last dose of induction treatment

End point values	Arm A (ITT)	Arm B (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	310[3]	315[4]		
Units: percentage of subjects				
number (confidence interval 95%)	51.3 (45.6 to 57)	52.4 (46.7 to 58)		

Notes:

[3] - Number of subjects analysed specifies number of subjects who were evaluable for this endpoint.

[4] - Number of subjects analysed specifies number of subjects who were evaluable for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Event-free Survival (EFS)

End point title	Event-free Survival (EFS)

End point description:

EFS was defined as the time from randomisation to first occurrence of progression or relapse accounting to International Working Group (IWG) response criteria. ITT population included all subjects who were randomised in the study. Here, 99999 indicates median and upper and lower limits of CI (99999 and -99999) since they were not reached for this endpoint.

End point type	Secondary

End point timeframe:

From the time of randomisation until disease progression or 24 months post treatment follow up or which ever occur first (approximately 4 years)

End point values	Arm A (ITT)	Arm B (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	372	371		
Units: months				
median (confidence interval 95%)	99999 (-99999 to 99999)	99999 (-99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-free Survival (DFS)

End point title	Disease-free Survival (DFS)

End point description:

DFS was defined as the period from the data of the initial CR/CRu until the date of relapse or death from any cause, whichever occurred first. ITT population included all subjects who were randomised in the study. Here, 99999 indicates median and upper and lower limits of CI (99999 and -99999) since they were not reached for this endpoint.

End point type	Secondary

End point timeframe:

From the time of randomisation until disease progression or 24 months post treatment follow up or which ever occur first (approximately 4 years)

End point values	Arm A (ITT)	Arm B (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	372	371		
Units: months				
median (confidence interval 95%)	99999 (-99999 to 99999)	99999 (-99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)

End point description:

PFS was defined as the time from randomization to the first occurrence of progression or relapse, according to the IWG response criteria. ITT population included all subjects who were randomised in the study. Here, 99999 indicates median and upper and lower limits of CI (99999 and -99999) since they were not reached for this endpoint.

End point type	Secondary

End point timeframe:

From the time of randomisation until disease progression or 24 months post treatment follow up or which ever occur first (approximately 4 years)

End point values	Arm A (ITT)	Arm B (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	372	371		
Units: months				
median (confidence interval 95%)	99999 (-99999 to 99999)	99999 (-99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from randomization to death from any cause. ITT population included all subjects who were randomised in the study. Here, 99999 indicates median and upper and lower limits of CI (99999 and -99999) since they were not reached for this endpoint.

End point type	Secondary

End point timeframe:

From the time of randomisation until disease progression or 24 months post treatment follow up or which ever occur first (approximately 4 years)

End point values	Arm A (ITT)	Arm B (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	372	371		
Units: months				
median (confidence interval 95%)	99999 (-99999 to 99999)	99999 (-99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Anti-Rituximab Antibodies Over Time

End point title	Percentage of Subjects With Anti-Rituximab Antibodies Over Time

End point description:

The safety population included all subjects who received at least one dose of rituximab. Here, n specifies the number of subjects who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

pre-dose Cycle 1 to 8, interim staging, final staging, 6, 12 months follow-up, end of study

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	371	369		
Units: percentage of subjects				
number (not applicable)				
Cycle 1 (n=332,330)	2.1	3		
Cycle 2 (n=324,322)	2.2	2.2		
Cycle 3 (n=319,318)	0.3	0.3		
Cycle 4 (n=315,315)	0	0.3		
Interim staging (n=271,268)	0	0		
Cycle 5 (n=234,248)	0	0		
Cycle 6 (n=281,281)	0	0		
Cycle 7 (n=263,279)	0	0		
Cycle 8 (n=247,267)	0	0		
Final staging (n=219,234)	0	0		
Follow-up, 6 months (n=75,84)	0	0		
Follow-up, 12 months (n=16,8)	0	0		

End of study/early treatment termination (n=22,17)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Anti-Recombinant Human Hyaluronidase (rHuPH20) Antibodies Over Time

End point title	Percentage of Subjects With Anti-Recombinant Human Hyaluronidase (rHuPH20) Antibodies Over Time

End point description:

The safety population included all subjects who received at least one dose of rituximab. Here, n specifies the number of subjects who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

pre-dose Cycle 2 to 8, interim staging, final staging, 6, 12 months follow-up, end of study

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	371	369		
Units: percentage of subjects				
number (not applicable)				
Cycle 2 (n=302,3)	7	33.3		
Cycle 3 (n=294,1)	6.5	100		
Cycle 4 (n=280,1)	7.1	100		
Interim staging (n=240,233)	9.2	10.7		
Cycle 5 (n=0,229)	0	10		
Cycle 6 (n=2,263)	0	11		
Cycle 7 (n=2,260)	50	11.2		
Cycle 8 (n=0,253)	0	11.5		
Final staging (n=200,221)	10	14		
Follow-up, 6 months (n=72,81)	8.3	13.6		
Follow-up, 12 months (n=15,8)	6.7	0		
End of study/early treatment termination (n=20,19)	15	5.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Observed Serum Rituximab Concentration

End point title	Summary of Observed Serum Rituximab Concentration

End point description:

The safety population included all subjects who received at least one dose of rituximab. Here, n specifies the number of subjects who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

pre-dose Cycle 1 to 8, interim staging, final staging, 6, 12 months follow-up, end of study

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	371	369		
Units: microgram per millilitre				
arithmetic mean (standard deviation)				
Cycle 1 (n=283,279)	3850.3 (± 21522.14)	1464.4 (± 9399.08)		
Cycle 2 (n=282,278)	25104.2 (± 19533.34)	24325.2 (± 18222.16)		
Cycle 3 (n=279,280)	63001.4 (± 29726.55)	45897.9 (± 31362.32)		
Cycle 4 (n=281,281)	88888.5 (± 41266.45)	59001.4 (± 59001.4)		
Interim staging (n=243,245)	118022.6 (± 51063.31)	77004.9 (± 28952.1)		
Cycle 5 (n=213,228)	108828 (± 54263.69)	69654.5 (± 30207.29)		
Cycle 6 (n=266,261)	102664.3 (± 48904.9)	98704.6 (± 39910.07)		
Cycle 7 (n=252,259)	97646.4 (± 45647.06)	116129.7 (± 44374.87)		
Cycle 8 (n=237,251)	107452.3 (± 49909.38)	136598.4 (± 53529.14)		
Final staging (n=211,219)	89052.3 (± 43629.85)	121032.9 (± 60682.31)		
Follow-up, 6 months (n=74,84)	8153.2 (± 12744.38)	9732.2 (± 15570.33)		
Follow-up, 12 months (n=16,8)	4458.9 (± 8792.36)	5605 (± 12353.68)		
End of study/early treatment termination (n=23,21)	53774.7 (± 49446.12)	63783.3 (± 57845.33)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Randomization of first participant to clinical cutoff (approximately 25 months)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups	
Reporting group title	Arm A

Reporting group description:

Subjects in Arm A received one cycle of rituximab 375 milligram per metre square (mg/m^2) intravenously (IV), then three cycles of rituximab 1400mg subcutaneously (SC), followed by four cycles of rituximab 375 mg/m^2 IV in combination with a standard chemotherapy of cyclophosphamide, hydroxydaunorubicin, Oncovin, prednisone/prednisolone (CHOP), cyclcophosphamie, vincristine, prednisone/prednisolone (CVP), or bendamustine. Rituximab was administered on Day 1 of each treatment cycle followed by administration of the preselected chemotherapy. Cycles were repeated every 14, 21, or 28 days, depending on the combination chemotherapy regimen selected by the investigator.

Reporting group title	Arm B

Reporting group description:

Subjects in Arm B received four cycles of rituximab 375 mg/m^2 IV followed by four cycles of rituximab 1400 mg SC in combination with a standard chemotherapy of CHOP, CVP, or bendamustine. Rituximab was
administered on Day 1 of each treatment cycle followed by administration of the preselected chemotherapy. Cycles were repeated every 14, 21, or 28 days, depending on the combination chemotherapy regimen selected by the investigator.

Serious adverse events	Arm A	Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	126 / 371 (33.96%)	118 / 369 (31.98%)	
number of deaths (all causes)	8	9	
number of deaths resulting from adverse events	2	4	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Papillary thyroid cancer			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell cancer			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Circulatory collapse			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 371 (0.00%)	3 / 369 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasculitis			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 371 (1.08%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	1 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

General physical health deterioration			
subjects affected / exposed	2 / 371 (0.54%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site warmth			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	11 / 371 (2.96%)	6 / 369 (1.63%)	
occurrences causally related to treatment / all	8 / 13	1 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytokine release syndrome			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 371 (0.00%)	2 / 369 (0.54%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Bronchospasm			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 371 (0.54%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	2 / 371 (0.54%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 371 (0.00%)	2 / 369 (0.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 371 (0.81%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Depression			

subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocyte count decreased			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	11 / 371 (2.96%)	9 / 369 (2.44%)	
occurrences causally related to treatment / all	10 / 14	7 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	3 / 371 (0.81%)	2 / 369 (0.54%)	
occurrences causally related to treatment / all	0 / 7	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 371 (0.54%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infusion related reaction			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial Infarction			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Acute coronary syndrome			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	2 / 371 (0.54%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 371 (0.00%)	2 / 369 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Depressed level of consciousness			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	2 / 371 (0.54%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	1 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive encephalopathy			

subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neuropathy peripheral			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 371 (0.27%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vith nerve paralysis			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile Neutropenia			
subjects affected / exposed	29 / 371 (7.82%)	28 / 369 (7.59%)	
occurrences causally related to treatment / all	16 / 36	16 / 36	
deaths causally related to treatment / all	1 / 1	0 / 0	
Anaemia			

subjects affected / exposed	3 / 371 (0.81%)	4 / 369 (1.08%)	
occurrences causally related to treatment / all	1 / 3	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	3 / 371 (0.81%)	2 / 369 (0.54%)	
occurrences causally related to treatment / all	4 / 8	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	17 / 371 (4.58%)	16 / 369 (4.34%)	
occurrences causally related to treatment / all	13 / 30	7 / 19	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pancytopenia			
subjects affected / exposed	0 / 371 (0.00%)	2 / 369 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 371 (0.54%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Pain lower			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			

subjects affected / exposed	2 / 371 (0.54%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 371 (0.27%)	3 / 369 (0.81%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal obstruction			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal perforation			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall haematoma			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			

subjects affected / exposed	1 / 371 (0.27%)	2 / 369 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haemorrhage			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 371 (0.54%)	2 / 369 (0.54%)	
occurrences causally related to treatment / all	0 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis Acute			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			

subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Purpura			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 371 (0.27%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stevens-Johnson syndrome			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephropathy toxic			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	1 / 371 (0.27%)	2 / 369 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary tract pain			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			

Diabetes insipidus			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gouty arthritis			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myofascial pain syndrome			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myopathy			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	1 / 371 (0.27%)	2 / 369 (0.54%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 1	

Lung Infection			
subjects affected / exposed	2 / 371 (0.54%)	4 / 369 (1.08%)	
occurrences causally related to treatment / all	2 / 2	3 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	
Oropharyngeal Candidiasis			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Septic Shock			
subjects affected / exposed	2 / 371 (0.54%)	2 / 369 (0.54%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 1	1 / 1	
Anal abscess			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (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 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis Perforated			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	1 / 371 (0.27%)	2 / 369 (0.54%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 371 (0.27%)	2 / 369 (0.54%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary Aspergillosis			

subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 371 (0.27%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 371 (0.27%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal infection			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (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 / 371 (0.27%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis Bacterial			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes Zoster			

subjects affected / exposed	2 / 371 (0.54%)	3 / 369 (0.81%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	3 / 371 (0.81%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	2 / 371 (0.54%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site abscess			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (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	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymph node abscess			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal infection			

subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral fungal infection			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillitis			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis Jirovecii Pneumonia			
subjects affected / exposed	2 / 371 (0.54%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	11 / 371 (2.96%)	5 / 369 (1.36%)	
occurrences causally related to treatment / all	2 / 11	1 / 5	
deaths causally related to treatment / all	0 / 2	0 / 0	
Post procedural infection			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Progressive multifocal leukoencephalopathy			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyoderma			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Tract Infection			

subjects affected / exposed	0 / 371 (0.00%)	2 / 369 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	3 / 371 (0.81%)	6 / 369 (1.63%)	
occurrences causally related to treatment / all	1 / 3	3 / 6	
deaths causally related to treatment / all	0 / 1	0 / 1	
Skin infection			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	0 / 371 (0.00%)	2 / 369 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 371 (0.27%)	2 / 369 (0.54%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			

subjects affected / exposed	3 / 371 (0.81%)	2 / 369 (0.54%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 371 (0.00%)	2 / 369 (0.54%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 371 (0.27%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 371 (0.27%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 371 (0.00%)	2 / 369 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypernataemia			

subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 371 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumor lysis syndrome			
subjects affected / exposed	1 / 371 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A	Arm B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	301 / 371 (81.13%)	302 / 369 (81.84%)	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	24 / 371 (6.47%)	22 / 369 (5.96%)	
occurrences (all)	41	31	
White blood cell count decreased			
subjects affected / exposed	21 / 371 (5.66%)	18 / 369 (4.88%)	
occurrences (all)	43	37	
Nervous system disorders			
Headache			
subjects affected / exposed	27 / 371 (7.28%)	29 / 369 (7.86%)	
occurrences (all)	36	33	
Neuropathy peripheral			
subjects affected / exposed	36 / 371 (9.70%)	46 / 369 (12.47%)	
occurrences (all)	41	51	
Paraesthesia			
subjects affected / exposed	17 / 371 (4.58%)	34 / 369 (9.21%)	
occurrences (all)	18	38	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	67 / 371 (18.06%)	62 / 369 (16.80%)	
occurrences (all)	90	90	
Leukopenia			
subjects affected / exposed	40 / 371 (10.78%)	30 / 369 (8.13%)	
occurrences (all)	80	64	
Neutropenia			
subjects affected / exposed	66 / 371 (17.79%)	90 / 369 (24.39%)	
occurrences (all)	131	175	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	28 / 371 (7.55%)	15 / 369 (4.07%)	
occurrences (all)	33	21	
Fatigue			
subjects affected / exposed	67 / 371 (18.06%)	87 / 369 (23.58%)	
occurrences (all)	90	118	
Mucosal inflammation			
subjects affected / exposed	26 / 371 (7.01%)	26 / 369 (7.05%)	
occurrences (all)	32	34	
Pyrexia			
subjects affected / exposed	52 / 371 (14.02%)	45 / 369 (12.20%)	
occurrences (all)	63	61	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	20 / 371 (5.39%)	19 / 369 (5.15%)	
occurrences (all)	24	19	
Abdominal pain upper			
subjects affected / exposed	17 / 371 (4.58%)	22 / 369 (5.96%)	
occurrences (all)	18	22	
Constipation			
subjects affected / exposed	58 / 371 (15.63%)	59 / 369 (15.99%)	
occurrences (all)	75	75	
Diarrhoea			
subjects affected / exposed	42 / 371 (11.32%)	47 / 369 (12.74%)	
occurrences (all)	67	55	
Nausea			

subjects affected / exposed	81 / 371 (21.83%)	99 / 369 (26.83%)	
occurrences (all)	119	144	
Stomatitis			
subjects affected / exposed	21 / 371 (5.66%)	20 / 369 (5.42%)	
occurrences (all)	26	21	
Vomiting			
subjects affected / exposed	40 / 371 (10.78%)	55 / 369 (14.91%)	
occurrences (all)	56	64	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	41 / 371 (11.05%)	38 / 369 (10.30%)	
occurrences (all)	47	44	
Dyspnoea			
subjects affected / exposed	19 / 371 (5.12%)	21 / 369 (5.69%)	
occurrences (all)	19	22	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	58 / 371 (15.63%)	53 / 369 (14.36%)	
occurrences (all)	60	53	
Pruritus			
subjects affected / exposed	27 / 371 (7.28%)	15 / 369 (4.07%)	
occurrences (all)	28	15	
Rash			
subjects affected / exposed	20 / 371 (5.39%)	20 / 369 (5.42%)	
occurrences (all)	20	27	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	24 / 371 (6.47%)	29 / 369 (7.86%)	
occurrences (all)	24	31	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	20 / 371 (5.39%)	19 / 369 (5.15%)	
occurrences (all)	25	22	
Upper respiratory tract infection			
subjects affected / exposed	20 / 371 (5.39%)	18 / 369 (4.88%)	
occurrences (all)	24	20	

Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	29 / 371 (7.82%) 38	31 / 369 (8.40%) 38	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 February 2013	1. For each anti-rituximab sample taken, drug-concentration analysis was added as a requirement at each scheduled time point. 2. The 30-minute postdose anti-rHuPH20 samples were removed from every cycle. 3. Additional anti-rituximab and anti-rHuPH20 samples were required during the follow up period (i.e., at 6 and 12 months). 4. The screening/baseline anti-rituximab sample was removed (because the Cycle 1 predose sample could also act as the baseline sample). 5. The Schedule of Assessments and applicable footnotes were revised to reflect the above changes and to correct some inconsistencies. Immunogenicity sampling schedules for Treatment Arms A and B were included for ease of reference during the study. 6. The prephase corticosteroid example was increased from 3 days to 5 days in subjects with aggressive NHL. 7. The reporting requirements for SAEs and AEs of special interest after the end of study were revised in alignment with recent global requirements. 8. The needle gauge was revised to include both 25- and 27-gauge needles. 9. The word "MabThera" (trade name) was replaced with the word "rituximab" (generic name) in the PPQ for consistency within the protocol.
02 June 2014	1. It was originally anticipated that the proportion of subjects preferring rituximab SC would be approximately 60%. In order to have a sample size of 720 subjects for analysis of the primary endpoint, the enrollment target was originally 900. However, a preplanned interim analysis revealed that approximately 80% of subjects preferred rituximab SC. After a discussion with the IDMC, the sample size was recalculated, decreasing the required number of subjects from 720 to 560 subjects and the enrollment target to 700 subjects. 2. Although subjects with active hepatitis B or hepatitis C virus were excluded from the study, some hepatitis-related conditions were permitted. 3. As the blastic variant of mantle cell lymphoma is neither DLBCL nor NHL, this was removed as an exclusion criterion from the study. 4. Subjects receiving prior intrathecal methotrexate for central nervous system prophylaxis in DLBCL were not excluded. 5. For study entry, subjects must have had histologically confirmed, previously untreated CD20+ DLBCL or CD20+ follicular NHL Grade 1, 2, or 3a, according to the World Health Organization (WHO) classification system. The patient's diagnosis was to be histologically confirmed prior to randomization. It was clarified that fine-needle aspiration samples were not be used as the sole material for pathological diagnosis. Lymph node excision or adequate core biopsy was required for the diagnosis of diffuse large B cell lymphoma or follicular NHL. 6. For assessment of hematologic function for study eligibility criteria, it was clarified that transfusions were not permitted within 2 weeks prior to the start of study drug administration. 7. The acceptable length of a cycle delay was increased from 10 days to 3 weeks, making it consistent with the 3-week window allowed for the treatment of toxicities and/or AEs.

02 June 2014	8. To allow investigators to decide how best to manage specific hematologic and non-hematologic AEs associated with rituximab-CHOP treatment, the protocol "guidelines" were changed to be considered as "recommendations." Patient management decisions that did not adhere to these recommendations were no longer to be considered as major protocol violations. 9. To comply with doxorubicin's prescribing information, subjects receiving rituximab-CHOP treatment who had a bilirubin value in the range of 20–50 micro mol per liter had their dose of doxorubicin reduced by 50%. 10. Corticosteroids could now be given as part of premedication to reduce the incidence and severity of injection-related reactions. 11. It was clarified that long-term treatment (>1 month) with intermittent corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of autoimmune conditions was permitted. 12. To comply with the guidance given in the current rituximab SC Investigator's Brochure, subjects were now to be observed for at least 15 minutes following rituximab SC administration. A longer period may have been appropriate in subjects with an increased risk of hypersensitivity reactions. 13. To conform to standards of clinical practice, subjects with a high risk of central nervous system involvement could now receive prophylactic intrathecal methotrexate. Intrathecal methotrexate was to be administered according to local standards. 14. To better follow clinical practice, subjects were weighed prior to each treatment so that BSA could be recalculated if necessary. Cyclophosphamide, vincristine, doxorubicin, and bendamustine doses were to be recalculated only if the patient's weight changed by more than ± 10% from baseline. 15. It was clarified that non-investigational medicinal products given as part of the subject's chemotherapy must have been approved for this indication.
02 June 2014	16. Additional chemotherapy regimens of CHOP every 14 days × 8 cycles, CHOP every 28 days × 8 cycles, CVP every 21 days × 6 cycles, and CVP every 28 days × 6 cycles were now permitted. 17. The wording about stability and storage of rituximab SC was updated according to the latest Investigator's Brochure. 18. It was clarified that the end-of-treatment response assessment, including radiology and imaging report, must have been obtained 28 (± 3) days after Day 1 of the last dose of induction treatment. The protocol previously stated that this must have been obtained between 4 and 8 weeks after Day 1 of the last treatment cycle, which was inconsistent with other parts of the protocol describing the final staging assessment. 19. As some study sites were only able to perform an international normalized ratio test, coagulation tests now included at least one of the following tests: international normalized ratio, prothrombin time, and activated partial thromboplastin time. 20. Lactate dehydrogenase (LDH) was previously only required to be tested at screening. However, as normalization of LDH was part of the response assessment according to the International Working Group (Cheson et al. 1999), subjects with an abnormal LDH at screening also had LDH included as part of their interim and final staging assessments. In addition, subjects with abnormal alkaline phosphatase, albumin, blood urea nitrogen, or C reactive protein at screening had these tests repeated as part of their interim and final staging assessments. 21. Neutrophil and lymphocyte counts were added to hematology tests to better monitor safety and to be consistent with other rituximab clinical trial protocols. 22. It was clarified that it was acceptable for subjects to have an MRI if they had a contraindication to CT scans (e.g., subjects with contrast allergy or impaired renal clearance).

02 June 2014	23. It was clarified that CT scans of the pelvis need only be done if clinically indicated. CT scans of the neck, chest, and abdomen continued to be required for all study subjects. 24. To minimize discrepancy between the calculation of follow-up visit dates and CT scan intervals, the wording was modified to allow sites to follow the CT frequency according to local standard of care. 25. The follow-up of subjects after induction treatment occurred every 3 months (± 2 weeks). It was clarified that the visit schedule would be calculated based on Visit 9. 26. The wording around the timing of Visit 5 (interim staging) was clarified. All interim staging and Visit 5 must have occurred prior to Visit 6 (initiation of Cycle 5), regardless of whether the CHOP regimen was given every 14 or 21 days. 27. To reduce redundant sampling, if Visit 5 (interim staging) was within 7 days of Visit 6 (initiation of Cycle 5), there was no need to collect the samples for Visit 6, i.e., only Visit 5 samples were to be collected and labeled as Visit 5. 28. During the post-treatment follow-up (observation) period, laboratory assessments and physical examinations were performed only if clinically indicated. 29. In the definition of disease-free and PFS, it was clarified that in terms of the event (relapse, progression, or death as relevant), these outcomes were to be assessed based on the event that occurred first. 30. The protocol wording was updated to reflect the latest Roche protocol template regarding the following: a) If an adverse event worsened in severity and became serious b) If the electronic data capture system was not available and a pregnancy reporting form needed to be submitted c) Investigators were to document and explain any protocol deviations 31. If new anti-lymphoma treatment had been started, any response to therapy was documented in electronic Case Report Form; however, it was clarified that response assessments were not specifically mandated by this study.
02 June 2014	32. It was clarified that CT scans of the pelvis need only be done if clinically indicated. CT scans of the neck, chest, and abdomen continued to be required for all study subjects. 33. To minimize discrepancy between the calculation of follow-up visit dates and CT scan intervals, the wording was modified to allow sites to follow the CT frequency according to local standard of care. 34. The follow-up of subjects after induction treatment occurred every 3 months (± 2 weeks). It was clarified that the visit schedule would be calculated based on Visit 9. 35. The wording around the timing of Visit 5 (interim staging) was clarified. All interim staging and Visit 5 must have occurred prior to Visit 6 (initiation of Cycle 5), regardless of whether the CHOP regimen was given every 14 or 21 days. 36. To reduce redundant sampling, if Visit 5 (interim staging) was within 7 days of Visit 6 (initiation of Cycle 5), there was no need to collect the samples for Visit 6, i.e., only Visit 5 samples were to be collected and labeled as Visit 5. 37. During the post-treatment follow-up (observation) period, laboratory assessments and physical examinations were performed only if clinically indicated. 38. In the definition of disease-free and PFS, it was clarified that in terms of the event (relapse, progression, or death as relevant), these outcomes were to be assessed based on the event that occurred first. 39. The protocol wording was updated to reflect the latest Roche protocol template regarding the following: a) If an adverse event worsened in severity and became serious b) If the electronic data capture system was not available and a pregnancy reporting form needed to be submitted c) Investigators were to document and explain any protocol deviations 40. If new anti-lymphoma treatment had been started, any response to therapy was documented in electronic Case Report Form; however, it was clarified that response assessments were not specifically mandated by this study.
02 June 2014	41. After study closure initiation, unrelated AEs/SAEs occurring in an off-study patient who had started a new anti-cancer treatment did not need to be reported. 42. Based on current recruitment rates, the study recruitment period was increased from 12 to 18 months, and the study duration was correspondingly adjusted from 3.5 to 4 years. 43. Additional minor changes were made to improve clarity and consistency.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported