



Clinical trial results:

A Two-Stage Phase III, International, Multi-Center, Randomized, Controlled, Open-Label Study to Investigate the Pharmacokinetics, Efficacy and Safety Of Rituximab SC in Combination With CHOP or CVP Versus Rituximab IV in Combination With CHOP or CVP in Patients With Previously Untreated Follicular Lymphoma Followed by Maintenance Treatment With Either Rituximab SC or Rituximab IV

Summary

EudraCT number	2010-021377-36
Trial protocol	ES GB BE SK IT DK DE FR FI GR BG
Global end of trial date	

Results information

Result version number	v2
This version publication date	07 May 2016
First version publication date	06 August 2015
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	BO22334
-----------------------	---------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01200758
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, CH-4070, Basel, Switzerland,
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	03 February 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 February 2014
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

This is a two-stage, Phase III, international, multicenter, randomized, controlled, open-label study to investigate the pharmacokinetic (PK), efficacy, and safety of rituximab subcutaneous (SC) in combination with cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) or cyclophosphamide, vincristine, prednisolone (CVP) versus rituximab intravenous (IV) in combination with CHOP or CVP in participants with previously untreated follicular lymphoma (FL) followed by maintenance treatment with either rituximab SC or rituximab IV.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 February 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
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	Romania: 9
Country: Number of subjects enrolled	Slovakia: 4
Country: Number of subjects enrolled	Spain: 53
Country: Number of subjects enrolled	United Kingdom: 23
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Bulgaria: 18
Country: Number of subjects enrolled	Denmark: 23
Country: Number of subjects enrolled	Finland: 10
Country: Number of subjects enrolled	France: 38
Country: Number of subjects enrolled	Germany: 21
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Italy: 40
Country: Number of subjects enrolled	Thailand: 9
Country: Number of subjects enrolled	Serbia: 17
Country: Number of subjects enrolled	Russian Federation: 14
Country: Number of subjects enrolled	Colombia: 9
Country: Number of subjects enrolled	Malaysia: 2
Country: Number of subjects enrolled	Australia: 15

Country: Number of subjects enrolled	Peru: 4
Country: Number of subjects enrolled	South Africa: 2
Country: Number of subjects enrolled	Bosnia and Herzegovina: 2
Country: Number of subjects enrolled	Turkey: 8
Country: Number of subjects enrolled	Mexico: 13
Country: Number of subjects enrolled	Canada: 25
Country: Number of subjects enrolled	Brazil: 14
Country: Number of subjects enrolled	Singapore: 7
Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 2
Country: Number of subjects enrolled	Croatia: 8
Country: Number of subjects enrolled	Georgia: 8
Country: Number of subjects enrolled	New Zealand: 9
Worldwide total number of subjects	410
EEA total number of subjects	250

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)	301
From 65 to 84 years	103
85 years and over	6

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening/baseline tests were performed within 28 days before randomization. Randomization was centralized in a 1:1 fashion using the Pocock and Simon dynamic randomization algorithm. All participants irrespective of the treatment period completion will commence follow-up period in both Stage I and II.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Stage I: Rituximab IV + Chemotherapy (CHOP/CVP)

Arm description:

Eight cycles of rituximab IV infusion (375 milligrams per square meter [mg/m^2]; rituximab induction) in combination with up to 8 cycles of CHOP or CVP chemotherapy (as per institutional practice) administered every 3 weeks. Participants achieving at least partial response (PR) during induction, entered rituximab IV maintenance therapy ($375 \text{ mg}/\text{m}^2$) once every 8 weeks for 24 months.

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

Dosage and administration details:

Participants received $375 \text{ mg}/\text{m}^2$ rituximab IV every 3 weeks for 8 cycles (the first cycle of rituximab could have been given on Day 0, Day 1, or Day 2, depending on institutional practice) and then maintenance therapy ($375 \text{ mg}/\text{m}^2$) once every 8 weeks up to 24 months for participants who achieved at least PR.

Arm title	Stage I: Rituximab SC + Chemotherapy (CHOP/CVP)
------------------	---

Arm description:

First cycle of rituximab IV ($375 \text{ mg}/\text{m}^2$) + 7 cycles of rituximab SC (1400 mg; rituximab induction) in combination with up to 8 cycles of CHOP or CVP chemotherapy (as per institutional practice) administered every 3 weeks. Participants achieving at least PR during induction, entered rituximab SC (1400 mg) maintenance therapy once every 8 weeks for 24 months.

Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

Participants received $375 \text{ mg}/\text{m}^2$ rituximab IV for Cycle 1 followed by 1400 mg SC every 3 weeks for 7 cycles and then maintenance therapy (1400 mg SC) once every 8 weeks up to 24 months for participants who achieved at least PR.

Arm title	Stage II: Rituximab IV + Chemotherapy (CHOP/CVP)
------------------	--

Arm description:

Eight cycles of rituximab IV infusion (375 mg/m²; rituximab induction) in combination with up to 8 cycles of CHOP or CVP chemotherapy (as per institutional practice) administered every 3 weeks. Participants achieving at least PR during induction, entered rituximab IV maintenance therapy (375 mg/m²) once every 8 weeks for 24 months.

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

Dosage and administration details:

Participants received 375 mg/m² rituximab IV every 3 weeks for 8 cycles (the first cycle of rituximab could have been given on Day 0, Day 1, or Day 2, depending on institutional practice) and then maintenance therapy (375 mg/m²) once every 8 weeks up to 24 months for participants who achieved at least PR.

Arm title	Stage II: Rituximab SC + Chemotherapy (CHOP/CVP)
------------------	--

Arm description:

First cycle of rituximab IV (375 mg/m²) + 7 cycles of rituximab SC (1400 mg; rituximab induction) in combination with up to 8 cycles of CHOP or CVP chemotherapy (as per institutional practice) administered every 3 weeks. Participants achieving at least PR entered rituximab SC (1400 mg) maintenance therapy once every 8 weeks for 24 months.

Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

Participants received 375 mg/m² rituximab IV for Cycle 1 followed by 1400 mg SC every 3 weeks for 7 cycles and then maintenance therapy (1400 mg SC) once every 8 weeks up to 24 months for participants who achieved at least PR.

Number of subjects in period 1	Stage I: Rituximab IV + Chemotherapy (CHOP/CVP)	Stage I: Rituximab SC + Chemotherapy (CHOP/CVP)	Stage II: Rituximab IV + Chemotherapy (CHOP/CVP)
Started	64	63	141
Completed	17	16	0
Not completed	47	47	141
Consent withdrawn by subject	-	2	2
Investigator's judgement	1	2	4
Disease progression	9	7	8
Adverse event, non-fatal	5	3	3
Protocol violation	-	-	1
Death	-	1	1
Treatment ongoing	30	32	117
Lost to follow-up	-	-	1
Lack of efficacy	2	-	4

Number of subjects in period 1	Stage II: Rituximab SC + Chemotherapy (CHOP/CVP)
Started	142
Completed	0
Not completed	142
Consent withdrawn by subject	1
Investigator's judgement	5
Disease progression	16
Adverse event, non-fatal	2
Protocol violation	4
Death	4
Treatment ongoing	108
Lost to follow-up	-
Lack of efficacy	2

Baseline characteristics

Reporting groups

Reporting group title

Overall trial

Reporting group description:

All participants who randomized into the study irrespective whether they received study drug or not were included.

Reporting group values	Overall trial	Total	
Number of subjects	410	410	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	56.5 ± 12.67	-	
Gender categorical Units: Subjects			
Female	218	218	
Male	192	192	

End points

End points reporting groups

Reporting group title	Stage I: Rituximab IV + Chemotherapy (CHOP/CVP)
Reporting group description: Eight cycles of rituximab IV infusion (375 milligrams per square meter [mg/m ²]; rituximab induction) in combination with up to 8 cycles of CHOP or CVP chemotherapy (as per institutional practice) administered every 3 weeks. Participants achieving at least partial response (PR) during induction, entered rituximab IV maintenance therapy (375 mg/m ²) once every 8 weeks for 24 months.	
Reporting group title	Stage I: Rituximab SC + Chemotherapy (CHOP/CVP)
Reporting group description: First cycle of rituximab IV (375 mg/m ²) + 7 cycles of rituximab SC (1400 mg; rituximab induction) in combination with up to 8 cycles of CHOP or CVP chemotherapy (as per institutional practice) administered every 3 weeks. Participants achieving at least PR during induction, entered rituximab SC (1400 mg) maintenance therapy once every 8 weeks for 24 months.	
Reporting group title	Stage II: Rituximab IV + Chemotherapy (CHOP/CVP)
Reporting group description: Eight cycles of rituximab IV infusion (375 mg/m ² ; rituximab induction) in combination with up to 8 cycles of CHOP or CVP chemotherapy (as per institutional practice) administered every 3 weeks. Participants achieving at least PR during induction, entered rituximab IV maintenance therapy (375 mg/m ²) once every 8 weeks for 24 months.	
Reporting group title	Stage II: Rituximab SC + Chemotherapy (CHOP/CVP)
Reporting group description: First cycle of rituximab IV (375 mg/m ²) + 7 cycles of rituximab SC (1400 mg; rituximab induction) in combination with up to 8 cycles of CHOP or CVP chemotherapy (as per institutional practice) administered every 3 weeks. Participants achieving at least PR entered rituximab SC (1400 mg) maintenance therapy once every 8 weeks for 24 months.	
Subject analysis set title	Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Eight cycles of rituximab IV (375 mg/m ²) in combination with up to 8 cycles of CHOP or CVP chemotherapy administered every 3 weeks. Participants achieving at least PR entered rituximab IV maintenance therapy (375 mg/m ²) once every 8 weeks for 24 months.	
Subject analysis set title	Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP)
Subject analysis set type	Intention-to-treat
Subject analysis set description: First cycle rituximab IV (375 mg/m ²) + 7 cycles of rituximab SC 1400 mg in combination with up to 8 cycles of CHOP or CVP chemotherapy administered every 3 weeks. Participants achieving at least PR entered rituximab SC (1400 mg) maintenance therapy once every 8 weeks for 24 months.	

Primary: Stage I: Trough Serum Concentrations (C_{trough}) of IV and SC Rituximab

End point title	Stage I: Trough Serum Concentrations (C _{trough}) of IV and SC Rituximab ^[1]
End point description: Stage I PK Evaluable Population comprised all participants with data for C _{trough} available at Cycle 7 and/or observed area under the serum concentration-time curve (AUC) available at Cycle 7. Participants were analyzed as per treatment received.	
End point type	Primary
End point timeframe: Stage I: Cycle 7 Day 21 (within 2 hours pre-dose on Cycle 8) of induction treatment	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was intended for Stage I only; hence, only Stage I arms are reported.

End point values	Stage I: Rituximab IV + Chemotherapy (CHOP/CVP)	Stage I: Rituximab SC + Chemotherapy (CHOP/CVP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48 ^[2]	54 ^[3]		
Units: micrograms per milliliter (µg/mL)				
geometric mean (geometric coefficient of variation)	83.1 (± 67.92)	134.6 (± 50.05)		

Notes:

[2] - Number of participants = participants analyzed for this endpoint.

[3] - Number of participants = participants analyzed for this endpoint.

Statistical analyses

Statistical analysis title	Ctrough of IV and SC Rituximab
Statistical analysis description:	
Stage I: Rituximab SC + Chemotherapy (CHOP/CVP) v Stage I: Rituximab IV + Chemotherapy (CHOP/CVP)	
Comparison groups	Stage I: Rituximab SC + Chemotherapy (CHOP/CVP) v Stage I: Rituximab IV + Chemotherapy (CHOP/CVP)
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[4]
Parameter estimate	Geometric mean ratio
Point estimate	1.62
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.36
upper limit	1.94

Notes:

[4] - Non-inferior Ctrough in SC formulation was demonstrated if the lower bound of 90% confidence interval (CI) was above 0.8. Geometric mean ratio adjusted for tumor load at baseline.

Primary: Stage II: Percentage of Participants With Overall Response at the End of Induction Treatment

End point title	Stage II: Percentage of Participants With Overall Response at the End of Induction Treatment ^[5]
End point description:	
Overall Response comprised complete response (CR), CR unconfirmed (CRu), or PR. A participant was defined as a responder if they sustained a CR, CRu or PR at the end of induction treatment. Response assessment was based on clinical examination and computed tomography (CT) scans. Assessment of tumor response was performed according to the International Working Group response criteria for Non-Hodgkin lymphoma (NHL). CR: complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy; CRu: CR along with regression in lymph node mass by more than (>) 75% in the sum of the products of greatest diameters (SPD); PR: Greater than or equal to (≥) 50% decrease in SPD of 6 largest dominant nodes or nodal masses. The 95% CI was estimated using Pearson-Clopper. Intent-to-Treat (ITT) Population = all participants who were randomized into the study irrespective whether they received study drug or not.	
End point type	Primary
End point timeframe:	
Stage II: up to end of induction treatment Cycle 8 (24 weeks)	

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was intended for Stage II only; hence, only Stage II arms are reported.

End point values	Stage II: Rituximab IV + Chemotherapy (CHOP/CVP)	Stage II: Rituximab SC + Chemotherapy (CHOP/CVP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	142		
Units: percentage of participants				
number (confidence interval 95%)	85.1 (78.1 to 90.5)	80.3 (72.8 to 86.5)		

Statistical analyses

Statistical analysis title	Overall Response at the end of Induction Treatment
Statistical analysis description: Stage II: Percentage of Participants With Overall Response at the End of Induction Treatment. The 95% CI for the difference in response rates was estimated using the Hauck-Anderson method.	
Comparison groups	Stage II: Rituximab IV + Chemotherapy (CHOP/CVP) v Stage II: Rituximab SC + Chemotherapy (CHOP/CVP)
Number of subjects included in analysis	283
Analysis specification	Pre-specified
Analysis type	other ^[6]
P-value	= 0.2835
Method	Chi-squared
Parameter estimate	Difference in response rates
Point estimate	-4.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14
upper limit	4.4

Notes:

[6] - Point estimate

Statistical analysis title	Stage II: Overall Response at Induction Treatment
Statistical analysis description: Stage II: Percentage of Participants With Overall Response at the End of Induction Treatment	
Comparison groups	Stage II: Rituximab IV + Chemotherapy (CHOP/CVP) v Stage II: Rituximab SC + Chemotherapy (CHOP/CVP)
Number of subjects included in analysis	283
Analysis specification	Pre-specified
Analysis type	other ^[7]
Parameter estimate	Odds ratio (OR)
Point estimate	0.71

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	1.33

Notes:

[7] - Point estimate

Primary: Stage I and II (Pooled): Percentage of Participants With Overall Response at the End of Induction Treatment

End point title	Stage I and II (Pooled): Percentage of Participants With Overall Response at the End of Induction Treatment
-----------------	---

End point description:

Overall Response comprised of CR, CRu, or PR. A participant was defined as a responder if they sustained a CR, CRu or PR at the end of induction treatment. Response assessment was based on clinical examination and CT scans. Assessment of tumour response was performed according to the International Working Group response criteria for NHL. CR: complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy; CRu: CR along with regression in lymph node mass by >75% in SPD; PR: ≥50% decrease in SPD of 6 largest dominant nodes or nodal masses. The 95% CI for the response rates was estimated for one sample binomial using Pearson-Clopper. ITT Population.

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

End point timeframe:

Stage I and II: Baseline up to end of induction treatment Cycle 8 (24 weeks)

End point values	Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP)	Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	205	205		
Units: percentage of participants				
number (confidence interval 95%)	84.4 (78.7 to 89.1)	83.4 (77.6 to 88.2)		

Statistical analyses

Statistical analysis title	Stage I and II: Overall Response
----------------------------	----------------------------------

Statistical analysis description:

Stage I and II: Overall Response of CR, CRu, or PR at the End of Induction Treatment. The 95% CI for the difference in response rates was estimated using the Hauck-Anderson.

Comparison groups	Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP) v Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP)
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	other ^[8]
P-value	= 0.7881
Method	Chi-squared
Parameter estimate	Difference in response rates
Point estimate	-0.98

Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.4
upper limit	6.4

Notes:

[8] - Point estimate

Statistical analysis title	Stage I and II: Overall Response
-----------------------------------	----------------------------------

Statistical analysis description:

Stage I and II (Pooled): Percentage of Participants With Overall Response at the End of Induction Treatment

Comparison groups	Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP) v Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP)
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	other ^[9]
Parameter estimate	Odds ratio (OR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.58

Notes:

[9] - Point estimate

Secondary: Stage I: Percentage of Participants With Overall Response at the End of Induction Treatment

End point title	Stage I: Percentage of Participants With Overall Response at the End of Induction Treatment ^[10]
-----------------	---

End point description:

Overall Response comprised of CR, CRu, or PR. A participant was defined as a responder if they sustained a CR, CRu or PR at the end of induction treatment. Response assessment was based on clinical examination and CT scans. Assessment of tumour response was performed according to the International Working Group response criteria for NHL. CR: complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy; CRu: CR along with regression in lymph node mass by >75% in SPD; PR: ≥50% decrease in SPD of 6 largest dominant nodes or nodal masses. The 95% CI for the response rates was estimated for one sample binomial using Pearson-Clopper. ITT Population.

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

End point timeframe:

Stage I: up to end of induction treatment Cycle 8 (24 weeks)

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was intended for Stage I only; hence, only Stage I arms are reported.

End point values	Stage I: Rituximab IV + Chemotherapy (CHOP/CVP)	Stage I: Rituximab SC + Chemotherapy (CHOP/CVP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	63		
Units: percentage of participants				
number (confidence interval 95%)	82.8 (71.3 to 91.1)	90.5 (80.4 to 96.4)		

Statistical analyses

Statistical analysis title	Stage I: Overall Response at Induction Treatment
Statistical analysis description: Stage I: Percentage of Participants With Overall Response at the End of Induction Treatment. The 95% CI for the difference in response rates was estimated using the Hauck-Anderson method.	
Comparison groups	Stage I: Rituximab IV + Chemotherapy (CHOP/CVP) v Stage I: Rituximab SC + Chemotherapy (CHOP/CVP)
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	other ^[11]
P-value	= 0.2047
Method	Chi-squared
Parameter estimate	Difference in response rates
Point estimate	7.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	20.3

Notes:

[11] - Point estimate

Statistical analysis title	Stage I: Overall Response at Induction Treatment
Statistical analysis description: Stage I: Percentage of Participants With Overall Response at the End of Induction Treatment	
Comparison groups	Stage I: Rituximab IV + Chemotherapy (CHOP/CVP) v Stage I: Rituximab SC + Chemotherapy (CHOP/CVP)
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	other ^[12]
Parameter estimate	Odds ratio (OR)
Point estimate	1.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	5.71

Notes:

[12] - Point estimate

Secondary: Stage I: Percentage of Participants With Complete Response at the End of Induction Treatment

End point title	Stage I: Percentage of Participants With Complete Response at the End of Induction Treatment ^[13]
-----------------	--

End point description:

Complete Response was comprised CR and CRu. A participant was defined as a responder if they sustained a CR or CRu at the end of induction treatment. Response assessment was based on clinical examination and CT scans. Assessment of tumor response was performed according to the International Working Group response criteria for NHL. CR: complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy; CRu: CR along with regression in lymph node mass by >75% in SPD; PR: ≥50% decrease in SPD of 6 largest dominant nodes or nodal masses. The 95% CI for the response rates was estimated for one sample binomial using Pearson-Clopper. ITT Population.

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

End point timeframe:

Stage I: up to end of induction treatment Cycle 8 (24 weeks)

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was intended for Stage I only; hence, only Stage I arms are reported.

End point values	Stage I: Rituximab IV + Chemotherapy (CHOP/CVP)	Stage I: Rituximab SC + Chemotherapy (CHOP/CVP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	63		
Units: percentage of participants				
number (confidence interval 95%)	25 (15 to 37.1)	42.9 (30.5 to 56)		

Statistical analyses

Statistical analysis title	Stage I: Complete Response
----------------------------	----------------------------

Statistical analysis description:

Stage I: Percentage of Participants With Complete Response at the End of Induction Treatment. The 95 % CI for the difference in response rates was estimated using the Hauck-Anderson method.

Comparison groups	Stage I: Rituximab IV + Chemotherapy (CHOP/CVP) v Stage I: Rituximab SC + Chemotherapy (CHOP/CVP)
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	other ^[14]
P-value	= 0.0335
Method	Chi-squared
Parameter estimate	Difference in response rates
Point estimate	17.86

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	35

Notes:

[14] - Point estimate

Statistical analysis title	Stage I: Complete Response
-----------------------------------	----------------------------

Statistical analysis description:

Stage I: Percentage of Participants With Complete Response at the End of Induction Treatment

Comparison groups	Stage I: Rituximab IV + Chemotherapy (CHOP/CVP) v Stage I: Rituximab SC + Chemotherapy (CHOP/CVP)
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	other ^[15]
Parameter estimate	Odds ratio (OR)
Point estimate	2.25

Confidence interval

level	95 %
sides	2-sided
lower limit	1.06
upper limit	4.78

Notes:

[15] - Point estimate

Secondary: Stage II: Percentage of Participants With Complete Response at the End of Induction Treatment

End point title	Stage II: Percentage of Participants With Complete Response at the End of Induction Treatment ^[16]
-----------------	---

End point description:

Complete Response comprised of CR and CRu. A participant was defined as a responder if they sustained a CR or CRu at the end of induction treatment. Response assessment was based on clinical examination and CT scans. Assessment of tumor response was performed according to the International Working Group response criteria for NHL. CR: complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy; CRu: CR along with regression in lymph node mass by >75% in SPD; PR: ≥50% decrease in SPD of 6 largest dominant nodes or nodal masses. The 95% CI for the response rates was estimated for one sample binomial using Pearson-Clopper. ITT Population.

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

End point timeframe:

Stage II: up to end of induction treatment Cycle 8 (24 weeks)

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was intended for Stage II only; hence, only Stage II arms are reported.

End point values	Stage II: Rituximab IV + Chemotherapy (CHOP/CVP)	Stage II: Rituximab SC + Chemotherapy (CHOP/CVP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	142		
Units: percentage of participants				
number (confidence interval 95%)	34.8 (26.9 to 43.2)	28.2 (20.9 to 36.3)		

Statistical analyses

Statistical analysis title	Stage II: Complete Response
Statistical analysis description:	
Stage II: Percentage of Participants With Complete Response at the End of Induction Treatment. The 95 % CI for the difference in response rates was estimated using the Hauck-Anderson method.	
Comparison groups	Stage II: Rituximab IV + Chemotherapy (CHOP/CVP) v Stage II: Rituximab SC + Chemotherapy (CHOP/CVP)
Number of subjects included in analysis	283
Analysis specification	Pre-specified
Analysis type	other ^[17]
P-value	= 0.2331
Method	Chi-squared
Parameter estimate	Difference in response rates
Point estimate	-6.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.8
upper limit	4.6

Notes:

[17] - Point estimate

Statistical analysis title	Stage II: Complete Response
Statistical analysis description:	
Stage II: Percentage of Participants With Complete Response at the End of Induction Treatment	
Comparison groups	Stage II: Rituximab IV + Chemotherapy (CHOP/CVP) v Stage II: Rituximab SC + Chemotherapy (CHOP/CVP)
Number of subjects included in analysis	283
Analysis specification	Pre-specified
Analysis type	other ^[18]
Parameter estimate	Odds ratio (OR)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	1.22

Notes:

[18] - Point estimate

Secondary: Stage I and II (Pooled): Percentage of Participants With Complete Response at the End of Induction Treatment

End point title	Stage I and II (Pooled): Percentage of Participants With Complete Response at the End of Induction Treatment
-----------------	--

End point description:

Complete Response comprised of CR and CRu. A participant was defined as a responder if they sustained a CR or CRu at the end of induction treatment. Response assessment was based on clinical examination and CT scans. Assessment of tumor response was performed according to the International Working Group response criteria for NHL. CR: complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy; CRu: CR along with regression in lymph node mass by >75% in SPD; PR: ≥50% decrease in SPD of 6 largest dominant nodes or nodal masses. The 95% CI for the response rates was estimated for one sample binomial using Pearson-Clopper. ITT Population.

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

End point timeframe:

Stage I and II: Baseline up to end of induction treatment Cycle 8 (24 weeks)

End point values	Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP)	Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	205	205		
Units: percentage of participants				
number (confidence interval 95%)	31.7 (25.4 to 38.6)	32.7 (26.3 to 39.6)		

Statistical analyses

Statistical analysis title	Stage I and II (Pooled): Complete Response
----------------------------	--

Statistical analysis description:

Stage I and II (Pooled): Percentage of Participants With Complete Response at the End of Induction Treatment. The 95% CI for the difference in response rates was estimated using the Hauck-Anderson method.

Comparison groups	Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP) v Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP)
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	other ^[19]
P-value	= 0.8326
Method	Chi-squared
Parameter estimate	Difference in response rates
Point estimate	0.98

Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.3
upper limit	10.3

Notes:

[19] - Point estimate

Statistical analysis title	Stage I and II (Pooled): Complete Response
-----------------------------------	--

Statistical analysis description:

Stage I and II (Pooled): Percentage of Participants With Complete Response at the End of Induction Treatment

Comparison groups	Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP) v Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP)
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	other ^[20]
Parameter estimate	Odds ratio (OR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.58

Notes:

[20] - Point estimate

Secondary: Stage I and II (Pooled): Percentage of Participants With Complete Response at the End of Maintenance Treatment

End point title	Stage I and II (Pooled): Percentage of Participants With Complete Response at the End of Maintenance Treatment
-----------------	--

End point description:

Complete Response comprised of CR and CRu. A participant was defined as a responder if they sustained a CR or CRu at the end of induction treatment. Response assessment was based on clinical examination and CT scans. Assessment of tumor response was performed according to the International Working Group response criteria for NHL. CR: complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy; CRu: CR along with regression in lymph node mass by >75% in SPD; PR: ≥50% decrease in SPD of 6 largest dominant nodes or nodal masses. ITT population; only participants who completed all 12 cycles of rituximab maintenance or who had withdrawn during the maintenance period were included in the analysis.

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

End point timeframe:

Stage I and II: up to 78 days after last maintenance dose (last maintenance dose: maintenance Cycle 12/Study Cycle 20 [30 months])

End point values	Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP)	Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32 ^[21]	36 ^[22]		
Units: percentage of participants				
number (confidence interval 95%)	25 (11.5 to 43.4)	22.2 (10.1 to 39.2)		

Notes:

[21] - Number of subjects analysed = participants evaluable for the analysis.

[22] - Number of subjects analysed = participants evaluable for the analysis.

Statistical analyses

Statistical analysis title	Stage I and II (Pooled): Complete Response
-----------------------------------	--

Statistical analysis description:

Stage I and II (Pooled): Percentage of Participants With Complete Response at the End of Maintenance Treatment. The 95% CI for the difference in response rates was estimated using the Hauck-Anderson method.

Comparison groups	Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP) v Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other ^[23]
P-value	= 0.7875
Method	Chi-squared
Parameter estimate	Difference in response rates
Point estimate	-2.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.9
upper limit	19.3

Notes:

[23] - Point estimate

Statistical analysis title	Stage I and II (Pooled): Complete Response
-----------------------------------	--

Statistical analysis description:

Stage I and II (Pooled): Percentage of Participants With Complete Response at the End of Maintenance Treatment.

Comparison groups	Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP) v Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other ^[24]
Parameter estimate	Odds ratio (OR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	2.63

Notes:

[24] - Point estimate

Secondary: Stage I and II (Pooled): Percentage of Participants With Overall Response at the End of Maintenance Treatment

End point title	Stage I and II (Pooled): Percentage of Participants With Overall Response at the End of Maintenance Treatment
-----------------	---

End point description:

Overall Response comprised of CR, CRu, or PR. A participant was defined as a responder if they sustained a CR, CRu or PR at the end of induction treatment. Response assessment was based on clinical examination and CT scans. Assessment of tumour response was performed according to the International Working Group response criteria for NHL. CR: complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy; CRu: CR along with regression in lymph node mass by >75% in SPD; PR: $\geq 50\%$ decrease in SPD of 6 largest dominant nodes or nodal masses. The 95% CI for the response rates was estimated for one sample binomial using Pearson-Clopper. ITT population; only participants who completed all 12 cycles of rituximab maintenance or who had withdrawn during the maintenance period were included in the analysis

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

End point timeframe:

Stage I and II: up to 78 days after last maintenance dose (last maintenance dose: maintenance Cycle 12/Study Cycle 20 [30 months])

End point values	Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP)	Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32 ^[25]	36 ^[26]		
Units: percentage of participants				
number (confidence interval 95%)	43.8 (26.4 to 62.3)	44.4 (27.9 to 61.9)		

Notes:

[25] - Number of subjects analysed = participants evaluable for the analysis.

[26] - Number of subjects analysed = participants evaluable for the analysis.

Statistical analyses

Statistical analysis title	Stage I and II: Overall Response
----------------------------	----------------------------------

Statistical analysis description:

Stage I and II (Pooled): Percentage of Participants With Overall Response at the End of Maintenance Treatment. The 95% CI for the difference in response rates was estimated using the Hauck-Anderson method.

Comparison groups	Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP) v Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other ^[27]
P-value	= 0.9541
Method	Chi-squared
Parameter estimate	Difference in response rates
Point estimate	0.69

Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.9
upper limit	26.3

Notes:

[27] - Point estimate

Statistical analysis title	Stage I and II: Overall Response
-----------------------------------	----------------------------------

Statistical analysis description:

Stage I and II (Pooled): Percentage of Participants With Overall Response at the End of Maintenance Treatment

Comparison groups	Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP) v Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other ^[28]
Parameter estimate	Odds ratio (OR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	2.68

Notes:

[28] - Point estimate

Secondary: Stage I and II (Pooled): Progression-Free Survival (PFS)

End point title	Stage I and II (Pooled): Progression-Free Survival (PFS)
-----------------	--

End point description:

PFS was defined as the time from randomization to disease progression/relapse or death due to any cause. If the specified event (disease progression/relapse, death) did not occur, PFS was censored at the last tumor assessment date showing no disease progression, either during treatment or follow-up. Disease progression was defined as progression in the participant's clinical symptoms according to the International Working Group response criteria for NHL. PFS analysis was performed using Kaplan-Meier curves. ITT Population. Data for median and corresponding 95% CI were not reached due to low number (<50%) of participants with event of interest, therefore '9999', '999', and '99999' are reported to reflect not available (NA) data for median and lower and upper range of 95% CI values, respectively.

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

End point timeframe:

Baseline, Day 1 of all cycles (Cycles 1-20), at early withdrawal, at follow-up, every 12 weeks for 96 weeks or until documented disease progression/relapse or death (up to a median of 27 months; up to data cutoff of 31 October 2013)

End point values	Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP)	Stage I and II: Rituximab SC + Chemothera py (CHOP/CVP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	205	205		
Units: days				
median (confidence interval 95%)	9999 (999 to	9999 (999 to		

Statistical analyses

Statistical analysis title	Progression-Free Survival (PFS)
Statistical analysis description:	
Stage 1 and II (Pooled): Progression-Free Survival (PFS)	
Comparison groups	Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP) v Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP)
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	other ^[29]
P-value	= 0.4646
Method	Wald Test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	2.03

Notes:

[29] - Point estimate

Secondary: Percentage of Participants With Disease Progression or Death

End point title	Percentage of Participants With Disease Progression or Death
End point description:	
Disease progression was defined as progression in the participant's clinical symptoms according to the International Working Group response criteria for NHL. ITT Population.	
End point type	Secondary
End point timeframe:	
Baseline, Day 1 of all cycles (Cycles 1-20), at early withdrawal, at follow-up, every 12 weeks for 96 weeks or until documented disease progression/relapse or death (up to a median of 27 months; up to data cutoff of 31 October 2013)	

End point values	Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP)	Stage I and II: Rituximab SC + Chemothera py (CHOP/CVP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	205	205		
Units: percentage of participants				
number (not applicable)	12.7	16.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Stage I and II (Pooled): Event-Free Survival

End point title	Stage I and II (Pooled): Event-Free Survival
-----------------	--

End point description:

Data for event-free survival will be analyzed when pooled data from both stages will be available, therefore '9999', '999', and '99999' are reported to reflect not available data for median and lower and upper range of 95% CI values, respectively. ITT Population.

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

End point timeframe:

Baseline, Day 1 of all cycles (Cycles 1-20), at early withdrawal, at follow-up, every 12 weeks for 96 weeks or until documented disease progression/relapse or death (up to data cutoff of 31 October 2013)

End point values	Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP)	Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	205	205		
Units: days				
median (confidence interval 95%)	9999 (999 to 99999)	9999 (999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Stage I and II (Pooled): Median Time to Overall Survival (OS)

End point title	Stage I and II (Pooled): Median Time to Overall Survival (OS)
-----------------	---

End point description:

OS was defined as the time from randomization to death due to any cause. Participants without event were censored at the time of last follow-up information for survival (i.e., at the last time known to be alive). Data for overall survival will be analyzed when pooled data from both stages of the study will be available, therefore '9999', '999', and '99999' are reported to reflect not available data for median and lower and upper range of 95% CI values, respectively. ITT Population.

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

End point timeframe:

Baseline, Day 1 of all cycles (Cycles 1-20), at early withdrawal, at follow-up, every 12 weeks for 96 weeks or until documented disease progression/relapse or death (up to a median of 27 months; up to data cutoff of 31 October 2013)

End point values	Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP)	Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	205	205		
Units: days				
median (confidence interval 95%)	9999 (999 to 99999)	9999 (999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Stage I: AUC of IV and SC Rituximab at Cycle 7

End point title	Stage I: AUC of IV and SC Rituximab at Cycle 7 ^[30]
-----------------	--

End point description:

AUC is a measure of the serum concentration of the drug over time. It is used to characterize drug absorption. The ratio of observed rituximab serum was determined as AUCSC/AUCIV during Cycle 7 of induction treatment. PK Evaluable Population.

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

End point timeframe:

Stage I (Induction): pre-dose and 24 hours post-dose on Cycle 7 (Days 1, 3, 7, and 15), pre-dose on Cycle 8 Day 1; additionally within 15 minutes after end of infusion on Cycle 7 Day 1 for rituximab IV (up to data cutoff of 11 April 2012)

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was intended for Stage I only; hence, only Stage I arms are reported.

End point values	Stage I: Rituximab IV + Chemotherapy (CHOP/CVP)	Stage I: Rituximab SC + Chemotherapy (CHOP/CVP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58 ^[31]	59 ^[32]		
Units: µg.day/mL				
geometric mean (geometric coefficient of variation)	2734.21 (± 32.51)	3778.93 (± 37.59)		

Notes:

[31] - Number of participants with evaluable PK data contributing to summary statistics were included.

[32] - Number of participants with evaluable PK data contributing to summary statistics were included.

Statistical analyses

Statistical analysis title	AUC of IV and SC Rituximab at Week 7
----------------------------	--------------------------------------

Statistical analysis description:

Geometric mean ratio adjusted for tumor load at baseline.

Comparison groups	Stage I: Rituximab IV + Chemotherapy (CHOP/CVP) v Stage I: Rituximab SC + Chemotherapy (CHOP/CVP)
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	other ^[33]
Parameter estimate	Geometric mean ratio
Point estimate	1.378
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.241
upper limit	1.53

Notes:

[33] - Point estimate

Secondary: Stage I: Maximum Serum Concentrations (Cmax) of IV and SC Rituximab at Cycle 7

End point title	Stage I: Maximum Serum Concentrations (Cmax) of IV and SC Rituximab at Cycle 7 ^[34]
-----------------	--

End point description:

Stage I PK Evaluable Population.

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

End point timeframe:

Stage I (Induction): pre-dose and 24 hours post-dose on Cycle 7 (Days 1, 3, 7, and 15), pre-dose on Cycle 8 Day 1; additionally within 15 minutes after end of infusion on Cycle 7 Day 1 (up to cutoff date of 11 April 2012)

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was intended for Stage I only; hence, only Stage I arms are reported.

End point values	Stage I: Rituximab IV + Chemotherapy (CHOP/CVP)	Stage I: Rituximab SC + Chemotherapy (CHOP/CVP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58 ^[35]	59 ^[36]		
Units: µg/mL				
geometric mean (geometric coefficient of variation)	250.63 (± 19.66)	236.82 (± 31.45)		

Notes:

[35] - Number of participants with evaluable PK data contributing to summary statistics were included.

[36] - Number of participants with evaluable PK data contributing to summary statistics were included.

Statistical analyses

No statistical analyses for this end point

Secondary: Stage I and II (Pooled): Ctrough of Rituximab at Each Induction Treatment Cycle

End point title	Stage I and II (Pooled): Ctrough of Rituximab at Each Induction Treatment Cycle
-----------------	---

End point description:	
ITT Population.	
End point type	Secondary
End point timeframe:	
C-trough values are based upon samples scheduled 21 days after study drug administration (before the next scheduled cycle), except for Cycle 8 which were scheduled 28 days after drug administration (up to data cutoff of 31 October 2013).	

End point values	Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP)	Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	198 ^[37]	193 ^[38]		
Units: µg/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 (n = 198, 193)	14 (± 157.53)	12.88 (± 189.7)		
Cycle 2 (n = 197, 190)	30.13 (± 145.36)	40 (± 124.5)		
Cycle 3 (n = 192, 190)	45.25 (± 110.35)	63.83 (± 101.83)		
Cycle 4 (n = 186, 185)	54.06 (± 108.9)	81.71 (± 92.28)		
Cycle 5 (n = 185, 185)	64.68 (± 89.9)	98 (± 71.91)		
Cycle 6 (n = 187, 180)	71.02 (± 87.6)	109.56 (± 58.74)		
Cycle 7 (n = 183, 172)	78.31 (± 77.76)	120.75 (± 55.6)		
Cycle 8 (n = 52, 54)	77.6 (± 70.53)	131.48 (± 50.2)		

Notes:

[37] - n = number of participants analyzed for the endpoint at the specified timepoint.

[38] - n = number of participants analyzed for the endpoint at the specified timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Stage I and II (Pooled): Ctrough of Rituximab at Each Maintenance Treatment Cycle

End point title	Stage I and II (Pooled): Ctrough of Rituximab at Each Maintenance Treatment Cycle
End point description:	
ITT Population. The data was provided up to data cutoff of 31 October 2013.	
End point type	Secondary
End point timeframe:	
C-trough values are based upon samples scheduled before each maintenance Cycle 9 to 20 (maintenance Cycle 1 to 12). i.e. 'Cycle 8' and 'Cycle 19' are before the first and last maintenance administration at 'Cycle 9' and 'Cycle 20', respectively.	

End point values	Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP)	Stage I and II: Rituximab SC + Chemothera py (CHOP/CVP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	156 ^[39]	158 ^[40]		
Units: µg/mL				
geometric mean (geometric coefficient of variation)				
Cycle 8 (n = 156, 158)	36.54 (± 97.1)	62.08 (± 67)		
Cycle 9 (n = 142, 140)	29.27 (± 73.85)	48.26 (± 83.74)		
Cycle 10 (n = 105, 109)	27.66 (± 78.63)	44.65 (± 78.57)		
Cycle 11 (n = 78, 83)	27.15 (± 71.27)	44.65 (± 66.62)		
Cycle 12 (n = 61, 58)	27.12 (± 59.19)	45.7 (± 67.32)		
Cycle 13 (n = 49, 52)	28.33 (± 52.03)	45.52 (± 67.02)		
Cycle 14 (n = 47, 52)	28.18 (± 44.8)	45.54 (± 65.44)		
Cycle 15 (n = 43, 49)	28.45 (± 35.36)	45.16 (± 69.99)		
Cycle 16 (n = 45, 51)	29.36 (± 44)	44.09 (± 65.08)		
Cycle 17 (n = 42, 46)	31.5 (± 43.97)	42.96 (± 63.89)		
Cycle 18 (n = 29, 26)	31.29 (± 39.15)	49.11 (± 56.03)		
Cycle 19 (n = 17, 16)	31.1 (± 36.91)	44.99 (± 61.55)		

Notes:

[39] - n = number of participants analyzed for the endpoint at the specified timepoint.

[40] - n = number of participants analyzed for the endpoint at the specified timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Stage I and II (Pooled): Rituximab Levels 12 Weeks, 24 Weeks, and 36 Weeks After the Last Rituximab Administration

End point title	Stage I and II (Pooled): Rituximab Levels 12 Weeks, 24 Weeks, and 36 Weeks After the Last Rituximab Administration
-----------------	--

End point description:

Safety Analysis Population included all participants who received at least one dose of rituximab, either IV or SC. Participants were analyzed as treated. Here "n"= participants who were evaluable for each category, for respective arm groups.

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

End point timeframe:

12 weeks, 24 weeks, and 36 weeks after the last rituximab administration (median treatment duration: 383.5 days for IV dose and 406 days for SC dose; up to data cutoff of 31 October 2013)

End point values	Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP)	Stage I and II: Rituximab SC + Chemothera py (CHOP/CVP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5 ^[41]	6 ^[42]		
Units: µg/mL				
median (full range (min-max))				
Week 12: Follow-up Visit 1 (n = 5, 6)	21 (4.76 to 80.4)	29.35 (24.1 to 50.5)		
Week 24: Follow-up Visit 2 (n = 2, 5)	5.03 (1.25 to 8.81)	10.4 (3.31 to 62.1)		
Week 36: Follow-up Visit 3 (n = 2, 1)	26.22 (1.03 to 51.4)	8.93 (8.93 to 8.93)		

Notes:

[41] - n = number of participants analyzed for the endpoint at the specified timepoint.

[42] - n = number of participants analyzed for the endpoint at the specified timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With B-Cell Depletion by Cycle for Induction Phase

End point title	Percentage of Participants With B-Cell Depletion by Cycle for Induction Phase
-----------------	---

End point description:

Depletion is defined as a CD19 value < 80 cells/mm³, percentages are based upon the number of participants with non-missing values. ITT Population. The data was presented up to data cutoff of 31 October 2013.

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

End point timeframe:

Stage I and II (induction): for rituximab IV - Day 1 of Cycle 1 to 8; for rituximab SC - Day 1 of Cycle 1 and Cycle 3 to 8, Day 0 of Cycle 2, thereafter at follow-up visits every 12 weeks after the last rituximab administration until 72 weeks

End point values	Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP)	Stage I and II: Rituximab SC + Chemothera py (CHOP/CVP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	188 ^[43]	168 ^[44]		
Units: percentage of participants				
number (not applicable)				
Cycle 1 Day 1 - Baseline (n=188, 168)	51.6	54.8		
Cycle 2 Day 0/1 (n=183, 180)	95.1	95		
Cycle 3 Day 1 (n=175, 175)	99.4	99.4		
Cycle 4 Day 1 (n=178, 179)	99.4	100		
Cycle 5 Day 1 (n=179, 176)	100	100		
Cycle 6 Day 1 (n=173, 175)	100	100		

Cycle 7 Day 1 (n=178, 173)	100	100		
Cycle 8 Day 1 (n=175, 174)	100	100		
Cycle 8 Day 19 Final Assessment (n=151, 145)	100	100		
Week 12: Follow-up Visit 1 (n=20, 17)	90	100		
Week 24: Follow-up Visit 2 (n=10, 10)	100	100		
Week 36: Follow-up Visit 3 (n=3, 3)	100	100		
Week 48: Follow-up Visit 4 (n=3, 1)	66.7	100		
Week 60: Follow-up Visit 5 (n=1, 0)	100	0		
Week 72: Follow-up Visit 6 (n=1, 0)	100	0		

Notes:

[43] - n = number of participants analyzed for the endpoint at the specified timepoint.

[44] - n = number of participants analyzed for the endpoint at the specified timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With B-Cell Depletion by Cycle for Maintenance Phase

End point title	Percentage of Participants With B-Cell Depletion by Cycle for Maintenance Phase
-----------------	---

End point description:

Depletion is defined as a CD19 value < 80 cells/mm³, percentages are based upon the number of participants with non-missing values. Here "n" = participants who were evaluable for each category, for respective arm groups. ITT Population.

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

End point timeframe:

Stage I and II (maintenance): Day 1 of Cycle 9 to 20 (up to data cutoff of 31 October 2013)

End point values	Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP)	Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	169 ^[45]	160 ^[46]		
Units: percentage of participants				
number (not applicable)				
Cycle 9 Day 1 (n=169, 160)	99.4	100		
Cycle 10 Day 1 (n=158, 159)	99.4	100		
Cycle 11 Day 1 (n=130, 139)	99.2	100		
Cycle 12 Day 1 (n=106, 110)	100	100		
Cycle 13 Day 1 (n=79, 81)	100	100		
Cycle 14 Day 1 (n=62, 62)	100	100		
Cycle 15 Day 1 (n=47, 48)	100	100		
Cycle 16 Day 1 (n=45, 49)	100	100		
Cycle 17 Day 1 (n=45, 50)	100	100		
Cycle 18 Day 1 (n=43, 49)	100	100		
Cycle 19 Day 1 (n=45, 43)	100	100		
Cycle 20 Day 1 (n=31, 35)	100	100		

Notes:

[45] - n = number of participants analyzed for the endpoint at the specified timepoint.

[46] - n = number of participants analyzed for the endpoint at the specified timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Stage I and II (Pooled): Percentage of Participants Positive for Human Anti-Chimeric Antibodies (HACAs)

End point title	Stage I and II (Pooled): Percentage of Participants Positive for Human Anti-Chimeric Antibodies (HACAs)
-----------------	---

End point description:

Levels of HACA in serum were collected at day of each cycle up to Cycle 8 and at follow-up visit. Here "n"= participants who were evaluable for each category, for respective arm groups. Safety Analysis Population.

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

End point timeframe:

Baseline, Post-Baseline (Cycle 1 Day 1 [induction] up to follow-up) (a median of 27 months; up to data cutoff of 31 October 2013)

End point values	Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP)	Stage I and II: Rituximab SC + Chemothera py (CHOP/CVP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	207 ^[47]	197 ^[48]		
Units: percentage of participants				
number (not applicable)				
Baseline (n=207, 189)	6	3		
Post-Baseline (n=206, 197)	1	2		

Notes:

[47] - n = number of participants analyzed for the endpoint at the specified timepoint.

[48] - n = number of participants analyzed for the endpoint at the specified timepoint.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Other adverse event (AE): up to 28 days after last treatment (up to 31 months)

Treatment-emergent serious AEs (SAEs): up to 1 year after last treatment of study drug (up to 42 months)

Treatment-related SAEs: up to the end of the study (up to 91 months).

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

Dictionary used

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

Dictionary version	16.1
--------------------	------

Reporting groups

Reporting group title	Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP)
-----------------------	--

Reporting group description:

First cycle rituximab IV (375 mg/m²) + 7 cycles of rituximab SC 1400 mg in combination with up to 8 cycles of CHOP or CVP chemotherapy administered every 3 weeks. Participants achieving at least PR entered rituximab SC (1400 mg) maintenance therapy once every 8 weeks for 24 months.

Reporting group title	Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP)
-----------------------	--

Reporting group description:

Eight cycles of rituximab IV (375 mg/m²) in combination with up to 8 cycles of CHOP or CVP chemotherapy administered every 3 weeks. Participants achieving at least PR entered rituximab IV maintenance therapy (375 mg/m²) once every 8 weeks for 24 months.

Serious adverse events	Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP)	Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP)	
Total subjects affected by serious adverse events			
subjects affected / exposed	57 / 197 (28.93%)	55 / 210 (26.19%)	
number of deaths (all causes)	8	5	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Rectal adenocarcinoma			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 197 (0.51%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			

subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid cancer			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial occlusive disease			
subjects affected / exposed	1 / 197 (0.51%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 197 (0.51%)	0 / 210 (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			

Malaise			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	6 / 197 (3.05%)	5 / 210 (2.38%)	
occurrences causally related to treatment / all	1 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Reproductive system and breast disorders			
Pelvic cyst			
subjects affected / exposed	1 / 197 (0.51%)	0 / 210 (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 / 197 (0.51%)	4 / 210 (1.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 197 (0.51%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hydropneumothorax			

subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 197 (1.02%)	3 / 210 (1.43%)	
occurrences causally related to treatment / all	2 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Major depression			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Eastern Cooperative Oncology Group performance status worsened			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	1 / 197 (0.51%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress fracture			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site pain			

subjects affected / exposed	1 / 197 (0.51%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foreign body			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple injuries			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fracture			
subjects affected / exposed	1 / 197 (0.51%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 197 (0.51%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 197 (1.02%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			

subjects affected / exposed	1 / 197 (0.51%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 197 (0.51%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Myocardial ischaemia			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
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 / 197 (0.51%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Nervous system disorder			
subjects affected / exposed	1 / 197 (0.51%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	1 / 197 (0.51%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			

subjects affected / exposed	1 / 197 (0.51%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma hepatic			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	11 / 197 (5.58%)	9 / 210 (4.29%)	
occurrences causally related to treatment / all	6 / 13	5 / 12	
deaths causally related to treatment / all	1 / 2	0 / 0	
Anaemia			
subjects affected / exposed	2 / 197 (1.02%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	3 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	5 / 197 (2.54%)	4 / 210 (1.90%)	
occurrences causally related to treatment / all	6 / 7	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 197 (0.51%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	2 / 197 (1.02%)	2 / 210 (0.95%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 197 (0.00%)	3 / 210 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral lichen planus			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	1 / 197 (0.51%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal			

subjects affected / exposed	1 / 197 (0.51%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 197 (0.51%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 197 (0.51%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctocolitis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth ulceration			
subjects affected / exposed	1 / 197 (0.51%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	1 / 197 (0.51%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			

subjects affected / exposed	1 / 197 (0.51%)	0 / 210 (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			
Skin ulcer			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperhidrosis			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lichen planus			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	2 / 197 (1.02%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
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			
Arthralgia			
subjects affected / exposed	1 / 197 (0.51%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Back pain			
subjects affected / exposed	2 / 197 (1.02%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 197 (0.00%)	2 / 210 (0.95%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 197 (0.51%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	1 / 197 (0.51%)	0 / 210 (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			
Cystitis			
subjects affected / exposed	2 / 197 (1.02%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	7 / 197 (3.55%)	4 / 210 (1.90%)	
occurrences causally related to treatment / all	0 / 8	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neutropenic sepsis			
subjects affected / exposed	1 / 197 (0.51%)	4 / 210 (1.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			

subjects affected / exposed	1 / 197 (0.51%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 197 (0.00%)	2 / 210 (0.95%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 197 (0.51%)	1 / 210 (0.48%)	
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	1 / 197 (0.51%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 197 (0.00%)	2 / 210 (0.95%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	2 / 197 (1.02%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial prostatitis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Creutzfeldt-Jakob disease			
subjects affected / exposed	1 / 197 (0.51%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Giardiasis			

subjects affected / exposed	1 / 197 (0.51%)	0 / 210 (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	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia mycoplasmal			
subjects affected / exposed	1 / 197 (0.51%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	1 / 197 (0.51%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis externa			
subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
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 / 197 (0.51%)	0 / 210 (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	1 / 197 (0.51%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	1 / 197 (0.51%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 197 (0.51%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	2 / 197 (1.02%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	1 / 197 (0.51%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	1 / 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	Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP)	Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	169 / 197 (85.79%)	171 / 210 (81.43%)	
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	20 / 197 (10.15%)	30 / 210 (14.29%)	
occurrences (all)	31	36	
Headache			
subjects affected / exposed	23 / 197 (11.68%)	12 / 210 (5.71%)	
occurrences (all)	31	21	
Dizziness			

subjects affected / exposed	11 / 197 (5.58%)	13 / 210 (6.19%)	
occurrences (all)	42	15	
Paraesthesia			
subjects affected / exposed	28 / 197 (14.21%)	25 / 210 (11.90%)	
occurrences (all)	41	29	
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	26 / 197 (13.20%)	0 / 210 (0.00%)	
occurrences (all)	104	0	
Chills			
subjects affected / exposed	13 / 197 (6.60%)	17 / 210 (8.10%)	
occurrences (all)	13	20	
Fatigue			
subjects affected / exposed	36 / 197 (18.27%)	32 / 210 (15.24%)	
occurrences (all)	51	40	
Pyrexia			
subjects affected / exposed	26 / 197 (13.20%)	24 / 210 (11.43%)	
occurrences (all)	35	33	
Chest pain			
subjects affected / exposed	13 / 197 (6.60%)	6 / 210 (2.86%)	
occurrences (all)	14	8	
Injection site pain			
subjects affected / exposed	14 / 197 (7.11%)	0 / 210 (0.00%)	
occurrences (all)	14	0	
Asthenia			
subjects affected / exposed	29 / 197 (14.72%)	22 / 210 (10.48%)	
occurrences (all)	43	37	
Mucosal inflammation			
subjects affected / exposed	10 / 197 (5.08%)	14 / 210 (6.67%)	
occurrences (all)	15	16	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	60 / 197 (30.46%)	53 / 210 (25.24%)	
occurrences (all)	151	135	
Anaemia			

subjects affected / exposed occurrences (all)	28 / 197 (14.21%) 59	24 / 210 (11.43%) 30	
Leukopenia subjects affected / exposed occurrences (all)	12 / 197 (6.09%) 20	22 / 210 (10.48%) 41	
Gastrointestinal disorders			
Constipation subjects affected / exposed occurrences (all)	46 / 197 (23.35%) 58	52 / 210 (24.76%) 78	
Diarrhoea subjects affected / exposed occurrences (all)	29 / 197 (14.72%) 40	28 / 210 (13.33%) 41	
Nausea subjects affected / exposed occurrences (all)	59 / 197 (29.95%) 99	45 / 210 (21.43%) 85	
Abdominal pain subjects affected / exposed occurrences (all)	24 / 197 (12.18%) 35	19 / 210 (9.05%) 25	
Dyspepsia subjects affected / exposed occurrences (all)	16 / 197 (8.12%) 19	10 / 210 (4.76%) 15	
Vomiting subjects affected / exposed occurrences (all)	26 / 197 (13.20%) 46	25 / 210 (11.90%) 28	
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	35 / 197 (17.77%) 44	21 / 210 (10.00%) 28	
Oropharyngeal pain subjects affected / exposed occurrences (all)	16 / 197 (8.12%) 25	10 / 210 (4.76%) 11	
Dyspnoea subjects affected / exposed occurrences (all)	19 / 197 (9.64%) 22	12 / 210 (5.71%) 12	
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	16 / 197 (8.12%)	11 / 210 (5.24%)	
occurrences (all)	24	13	
Pruritus			
subjects affected / exposed	19 / 197 (9.64%)	19 / 210 (9.05%)	
occurrences (all)	20	20	
Erythema			
subjects affected / exposed	16 / 197 (8.12%)	11 / 210 (5.24%)	
occurrences (all)	32	12	
Alopecia			
subjects affected / exposed	28 / 197 (14.21%)	22 / 210 (10.48%)	
occurrences (all)	29	23	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	18 / 197 (9.14%)	15 / 210 (7.14%)	
occurrences (all)	21	17	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	10 / 197 (5.08%)	4 / 210 (1.90%)	
occurrences (all)	14	4	
Pain in extremity			
subjects affected / exposed	16 / 197 (8.12%)	8 / 210 (3.81%)	
occurrences (all)	19	8	
Arthralgia			
subjects affected / exposed	13 / 197 (6.60%)	14 / 210 (6.67%)	
occurrences (all)	14	18	
Back pain			
subjects affected / exposed	15 / 197 (7.61%)	18 / 210 (8.57%)	
occurrences (all)	16	20	
Myalgia			
subjects affected / exposed	12 / 197 (6.09%)	9 / 210 (4.29%)	
occurrences (all)	16	17	
Bone pain			
subjects affected / exposed	19 / 197 (9.64%)	16 / 210 (7.62%)	
occurrences (all)	24	21	
Infections and infestations			

Urinary tract infection			
subjects affected / exposed	11 / 197 (5.58%)	18 / 210 (8.57%)	
occurrences (all)	13	31	
Upper respiratory tract infection			
subjects affected / exposed	18 / 197 (9.14%)	13 / 210 (6.19%)	
occurrences (all)	27	20	
Nasopharyngitis			
subjects affected / exposed	15 / 197 (7.61%)	14 / 210 (6.67%)	
occurrences (all)	19	14	
Bronchitis			
subjects affected / exposed	10 / 197 (5.08%)	11 / 210 (5.24%)	
occurrences (all)	12	14	
Sinusitis			
subjects affected / exposed	10 / 197 (5.08%)	6 / 210 (2.86%)	
occurrences (all)	11	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 March 2012	<ul style="list-style-type: none">- Added additional flexibility in the protocol for the number of cycles of CHOP chemotherapy to reflect institutional practice based on the PRIMA study.-- Added guidance to clarify acceptable timeframe for dose delays during maintenance treatment.-- Provided clarification on acceptable malignancy types and remission time periods that render a participant eligible.- Removed past hepatitis C virus (HCV) exposure from the exclusion criteria because only anecdotal reports in the literature of HCV reactivation and no clear links established that rituximab is involved in HCV reactivation in previously infected HCV participant. Thus, exclusion of participants with a history of HCV infection was, on balance, not considered necessary.-- Removed bone marrow aspirate and biopsy at unscheduled visit for ethical reasons.-- Added that following drug administration, any participant experiencing a severe or serious adverse event, which is considered immunogenic and possibly related to rituximab administration, serum samples for rituximab PK, anti-rituximab, (and following Cycle 2 for participants randomized in the SC arm anti-rHuPH20) were to be collected within 7 days of the event becoming known to the investigator to ensure participant safety was monitored thoroughly.-- Clarified that anti-rHuPH20 sampling should only be performed in participants receiving rituximab SC formulation, as only this formulation includes rHuPH20 excipient.
15 October 2012	Added possibility of performing safety snapshot(s) during the study to address potential health authority or regulatory questions.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
21 October 2011	Temporary stop on recruitment occurred between Stage 1 and Stage 2 whilst PK non-inferiority was confirmed by the 1400 mg Stage 1 dose.	16 July 2012

Notes:

Limitations and caveats

None reported