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	31 October 2017

Results information

Result version number	v4 (current)
This version publication date	14 November 2018
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, Basel, Switzerland, CH-4070
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	Final
Date of interim/final analysis	31 October 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was 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	15 February 2011
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. The study was conducted in 2 stages: Stage I & II. All participants irrespective of the treatment period completion commenced 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?	Yes
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 mg/m^2) once every 8 weeks for 24 months.

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

Dosage and administration details:

Participants received 375 mg/m^2 rituximab IV every 3 weeks for 8 cycles (the first cycle of rituximab was given on Day 0, Day 1, or Day 2, depending on institutional practice) and then maintenance therapy (375 mg/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 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.

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

Dosage and administration details:

Participants received 375 mg/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/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.

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

Dosage and administration details:

Participants received 375 mg/m^2 rituximab IV every 3 weeks for 8 cycles (the first cycle of rituximab was given on Day 0, Day 1, or Day 2, depending on institutional practice) and then maintenance therapy (375 mg/m^2) 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/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.

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

Dosage and administration details:

Participants received 375 mg/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.

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	46	46	100
Not completed	18	17	41
Consent withdrawn by subject	1	2	4
Physician decision	1	1	5
Disease progression	9	7	16
Adverse event, non-fatal	5	5	5
Death	-	1	3
Lost to follow-up	-	-	3
Lack of efficacy	2	1	4
Protocol deviation	-	-	1

Number of subjects in period 1	Stage II: Rituximab SC + Chemotherapy (CHOP/CVP)
Started	142

Completed	92
Not completed	50
Consent withdrawn by subject	1
Physician decision	7
Disease progression	21
Adverse event, non-fatal	9
Death	5
Lost to follow-up	1
Lack of efficacy	2
Protocol deviation	4

Baseline characteristics

Reporting groups

Reporting group title	Overall trial (overall period)

Reporting group description: -

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	410	410	
Age categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	 56.5 ± 12.67	 -	
Gender, Male/Female Units: Subjects			
Female	219	219	
Male	191	191	

Subject analysis sets

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 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.

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 infusion (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.

Subject analysis set title	All Participants
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP): First cycle rituximab IV infusion (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. Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP): 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 values	Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP)	Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP)	All Participants
Number of subjects	205	205	410

Age categorical Units: Subjects			

Age Continuous Units: years			
arithmetic mean	56.9	56.1	56.5
standard deviation	± 12.69	± 12.66	± 12.67
Gender, Male/Female Units: Subjects			
Female	99	120	219
Male	106	85	191

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 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.

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 infusion (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.

Subject analysis set title	All Participants
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Stage I and II: Rituximab SC + Chemotherapy (CHOP/CVP): First cycle rituximab IV infusion (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. Stage I and II: Rituximab IV + Chemotherapy (CHOP/CVP): 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.

Primary: Stage I: Trough Serum Concentrations (Ctrough) of IV and SC Rituximab

End point title	Stage I: Trough Serum Concentrations (Ctrough) of IV and SC Rituximab[1]

End point description:

Stage I PK Evaluable Population comprised all participants with data for Ctrough 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. Number of participants analyzed = participants analyzed for this outcome measure.

End point type	Primary

End point timeframe:

Stage I: Cycle (Cy) 7 Day (D) 21 (within 2 hours predose on Cy8) of induction treatment (1 Cy=3 weeks)

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: Data for this endpoint was provided only for those arms which were planned to be 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	54		
Units: micrograms per milliliter (mcg/mL)				
geometric mean (geometric coefficient of variation)	83.1 (± 36.7)	134.6 (± 43.2)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stage I: Rituximab SC + Chemotherapy (CHOP/CVP) vs Stage I: Rituximab IV + Chemotherapy (CHOP/CVP)

Comparison groups	Stage I: Rituximab IV + Chemotherapy (CHOP/CVP) v Stage I: Rituximab SC + Chemotherapy (CHOP/CVP)
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
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:

[2] - Non-inferior Ctrough in SC formulation was demonstrated, if the lower bound of 90% confidence interval (CI) was above 0.8.

Primary: Stage II: Percentage of Participants With Overall Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for Non-Hodgkin lymphoma (NHL)

End point title	Stage II: Percentage of Participants With Overall Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for Non-Hodgkin lymphoma (NHL)[3]

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 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 for one sample binomial using Pearson-Clopper. Stage II ITT population included all participants who were randomized in Stage II irrespective whether they received study drug or not.

End point type	Primary

End point timeframe:

Stage II: Baseline up to end of induction treatment Cy8 (24 weeks) (1 Cy=3 weeks)

Notes:

[3] - 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: Data for this endpoint was provided only for those arms which were planned to be 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	Statistical Analysis 1

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
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

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

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

Using International Working Group Response Criteria for NHL

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
Parameter estimate	Odds ratio (OR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	1.33

Secondary: Stage I: Percentage of Participants With Overall Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL

End point title	Stage I: Percentage of Participants With Overall Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL[4]

End point description:

Overall Response comprised 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 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 the SPD; PR: ≥50% decrease in SPD of 6 largest dominant nodes or nodal masses. The 95% CI was estimated for one sample binomial using Pearson-Clopper. Stage I ITT Population included all participants who were randomized in Stage I irrespective whether they received study drug or not.

End point type	Secondary

End point timeframe:

Stage I: Baseline up to end of induction treatment Cy8 (24 weeks) (1 Cy=3 weeks)

Notes:

[4] - 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: Data for this endpoint was provided only for those arms which were planned to be 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	Statistical Analysis 1

Statistical analysis description:

Stage I: Percentage of Participants With Overall Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL. 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
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

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Stage I: Percentage of Participants With Overall Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL

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
Parameter estimate	Odds ratio (OR)
Point estimate	1.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	5.71

Secondary: Stage I and II (Pooled): Percentage of Participants With Overall Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL

End point title	Stage I and II (Pooled): Percentage of Participants With Overall Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL

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 and II: Baseline up to end of induction treatment Cy8 (24 weeks) (1 Cy=3 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%)	84.9 (79.2 to 89.5)	84.4 (78.7 to 89.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stage I and II: Overall Response of CR, CRu, or PR at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL. 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
P-value	= 0.8911
Method	Chi-squared
Parameter estimate	Difference in response rates
Point estimate	-0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.7
upper limit	6.8

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Stage I and II (Pooled): Percentage of Participants With Overall Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL

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
Parameter estimate	Odds ratio (OR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.65

Secondary: Stage I: Percentage of Participants With Complete Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL

End point title	Stage I: Percentage of Participants With Complete Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL[5]

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. The 95% CI was estimated for one sample binomial using Pearson-Clopper. Stage I ITT population.

End point type	Secondary

End point timeframe:

Stage I: Baseline up to end of induction treatment Cy8 (24 weeks) (1 Cy=3 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: Data for this endpoint was provided only for those arms which were planned to be 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%)	25.0 (15.0 to 37.4)	42.9 (30.5 to 56.0)		

Statistical analyses

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Stage I: Percentage of Participants With Complete Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL

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
Parameter estimate	Odds ratio (OR)
Point estimate	2.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.06
upper limit	4.78

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stage I: Percentage of Participants With Complete Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL. 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
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

Secondary: Stage II: Percentage of Participants With Complete Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL

End point title	Stage II: Percentage of Participants With Complete Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL[6]

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. The 95% CI for the response rates was estimated for one sample binomial using Pearson-Clopper. Stage II ITT population.

End point type	Secondary

End point timeframe:

Stage II: Baseline up to end of induction treatment Cy8 (24 weeks) (1 Cy=3 weeks)

Notes:

[6] - 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: Data for this endpoint was provided only for those arms which were planned to be 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	Statistical Analysis 1

Statistical analysis description:

Stage II: Percentage of Participants With Complete Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL. 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
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

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Stage II: Percentage of Participants With Complete Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL

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
Parameter estimate	Odds ratio (OR)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	1.22

Secondary: Stage I and II (Pooled): Percentage of Participants With Complete Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL

End point title	Stage I and II (Pooled): Percentage of Participants With Complete Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL

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. 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 Cy8 (24 weeks) (1 Cy=3 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)	32.2 (25.9 to 39.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Stage I and II (Pooled): Percentage of Participants With Complete Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL

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
Parameter estimate	Odds ratio (OR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.51

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stage I and II (Pooled): Percentage of Participants With Complete Response at the End of Induction Treatment Assessed Using International Working Group Response Criteria for NHL. 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	410
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9157
Method	Chi-squared
Parameter estimate	Difference in response rates
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.8
upper limit	9.8

Secondary: Stage I and II (Pooled): Percentage of Participants With Complete Response at the End of Maintenance Treatment Assessed Using International Working Group Response Criteria for NHL

End point title	Stage I and II (Pooled): Percentage of Participants With Complete Response at the End of Maintenance Treatment Assessed Using International Working Group Response Criteria for NHL

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. ITT population; only participants who entered the maintenance phase and received at least 1 cycle of rituximab maintenance treatment from Cycle 9 to Cycle 20 were included in the analysis.

End point type	Secondary

End point timeframe:

Stage I and II: Baseline up to 57 days after last maintenance dose (last maintenance dose: maintenance Cy12/Study Cy20 [30 months]) (up to data cutoff of 31 Oct 2017 [up to 6 years]) (1 Cy=8

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	178	172		
Units: percentage of participants				
number (confidence interval 95%)	57.9 (50.4 to 65.2)	50.6 (42.9 to 58.3)		

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Stage I and II (Pooled): Percentage of Participants With Complete Response at the End of Maintenance Treatment Assessed Using International Working Group Response Criteria for NHL.	
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	350
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Odds ratio (OR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.22

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Stage I and II (Pooled): Percentage of Participants With Complete Response at the End of Maintenance Treatment Assessed Using International Working Group Response Criteria for NHL. 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	350
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1715
Method	Chi-squared
Parameter estimate	Difference in response rates
Point estimate	-7.28

Confidence interval	
level	95 %
sides	2-sided
lower limit	-18
upper limit	3.5

Secondary: Stage I and II (Pooled): Percentage of Participants With Overall Response at the End of Maintenance Treatment Assessed Using International Working Group Response Criteria for NHL

End point title	Stage I and II (Pooled): Percentage of Participants With Overall Response at the End of Maintenance Treatment Assessed Using International Working Group Response Criteria for NHL

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; only participants who entered the maintenance phase and received at least 1 cycle of rituximab maintenance treatment from Cycle 9 to Cycle 20 were included in the analysis.

End point type	Secondary

End point timeframe:

Stage I and II: Baseline up to 57 days after last maintenance dose (last maintenance dose: maintenance Cy12/Study Cy20 [30 months]) (1 Cy=8 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	178	172		
Units: percentage of participants				
number (confidence interval 95%)	78.1 (71.3 to 83.9)	77.9 (71.0 to 83.9)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stage I and II (Pooled): Percentage of Participants With Overall Response at the End of Maintenance Treatment Assessed Using International Working Group Response Criteria for NHL. 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	350
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9671
Method	Chi-squared
Parameter estimate	Difference in response rates
Point estimate	-0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.2
upper limit	8.8

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Stage I and II (Pooled): Percentage of Participants With Overall Response at the End of Maintenance Treatment Assessed Using International Working Group Response Criteria for NHL	
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	350
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Odds ratio (OR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.64

Secondary: Stage I and II (Pooled): Progression-Free Survival (PFS) Assessed Using International Working Group Response Criteria for NHL

End point title	Stage I and II (Pooled): Progression-Free Survival (PFS) Assessed Using International Working Group Response Criteria for NHL

End point description:

PFS: time from randomization to PD/relapse or death due to any cause, analyzed using Kaplan-Meier curves. If the specified event (PD/relapse, death) did not occur, PFS was censored at the last tumor assessment date showing no PD, either during treatment or follow-up. Disease progression: Disease progression: ≥50% increase from nadir in the SPD of any previously identified abnormal node or appearance of any new lesion during or at the end of therapy or ≥50% increase in the greatest diameter of any previously identified node >1 cm in its short axis or in the SPD of more than one node. Data for median and corresponding 95% CI were not reached due to <50% of participants with event of interest, therefore '99999' are reported. Baseline, D1 of Cy 1-20 (1 Cy=3 weeks for Cy1-8 & 8 weeks for Cy9-20), at early withdrawal, at follow-up, every 12 weeks for 96 weeks or until documented PD/relapse or death (up to median of 27 months; up to data cutoff of 31 Oct 2017 [up to 6 years])

End point type	Secondary

End point timeframe:

Baseline up to disease progression or death up to data cutoff of 31 Oct 2017 (up to 6 years) (See detailed timeframe in Outcome Measure description)

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%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Progression-Free Survival (PFS)
Statistical analysis description:	
Stage 1 and II (Pooled): Progression-Free Survival (PFS) Assessed Using International Working Group Response Criteria for NHL	
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
P-value	= 0.5526
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.26

Secondary: Stage I and II (Pooled): Percentage of Participants With Disease Progression/Relapse or Death Assessed Using International Working Group Response Criteria for NHL

End point title	Stage I and II (Pooled): Percentage of Participants With Disease Progression/Relapse or Death Assessed Using International Working Group Response Criteria for NHL

End point description:

Disease progression: ≥50% increase from nadir in the SPD of any previously identified abnormal node or appearance of any new lesion during or at the end of therapy or ≥50% increase in the greatest diameter of any previously identified node >1 cm in its short axis or in the SPD of more than one node. Here, number of participants analyzed = participants who were evaluable for this outcome measure. ITT population. Baseline, D1 of all cycles (Cy 1-20) (1 Cy=3 weeks for Cy1-8 & 8 weeks for Cy9-20), at early withdrawal, at follow-up, every 12 weeks for 96 weeks or until documented disease progression/relapse or death (up to median of 27 months; up to data cutoff of 31 Oct 2017 [up to 6 years])

End point type	Secondary

End point timeframe:

Baseline up to disease progression or death up to data cutoff of 31 Oct 2017 (up to 6 years) (See detailed timeframe in Outcome Measure description)

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 (not applicable)	34.6	31.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Stage I and II (Pooled): Event-Free Survival Assessed Using International Working Group Response Criteria for NHL

End point title	Stage I and II (Pooled): Event-Free Survival Assessed Using International Working Group Response Criteria for NHL

End point description:

Event-free survival was defined as the time from randomization to disease progression/relapse, death or initiation of new NHL therapy treatment. If the specified event (progression/relapse, death or new NHL treatment) did not occur, event-free survival was censored at the last tumor assessment date either during treatment or follow up. Event-free survival analysis was performed using Kaplan-Meier curves. ITT population. Data for median and upper limit of 95% CI were not reached due to low number (<50%) of participants with event of interest, therefore '99999' are reported to reflect not available (NA) data for median and upper range of 95% CI values. Baseline, D1 of all cycles (Cy 1-20) (1 Cy=3 weeks for Cy1-8 & 8 weeks for Cy9-20), 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 Oct 2017 [up to 6 years])

End point type	Secondary

End point timeframe:

Baseline up to disease progression or death up to data cutoff of 31 Oct 2017 (up to 6 years) (See detailed timeframe in Outcome Measure description)

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%)	99999 (2126 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Stage I and II (Pooled): Event-Free Survival
Statistical analysis description:	
Stage I and II (Pooled): Event-Free Survival Assessed Using International Working Group Response Criteria for NHL	
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
P-value	= 0.9115
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.36

Secondary: Stage I and II (Pooled): Percentage of Participants With Disease Progression/Relapse, New Anti-Lymphoma Treatment or Death Assessed Using International Working Group Response Criteria for NHL

End point title	Stage I and II (Pooled): Percentage of Participants With Disease Progression/Relapse, New Anti-Lymphoma Treatment or Death Assessed Using International Working Group Response Criteria for NHL
End point description:	
Disease progression: ≥50% increase from nadir in the SPD of any previously identified abnormal node or appearance of any new lesion during or at the end of therapy or ≥50% increase in the greatest diameter of any previously identified node >1 cm in its short axis or in the SPD of more than one node. Here, number of participants analyzed = participants who were evaluable for this outcome measure. ITT population. Baseline, D1 of all cycles (Cy 1-20) (1 Cy=3 weeks for Cy1-8 & 8 weeks for Cy9-20), 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 Oct 2017 [up to 6 years])	
End point type	Secondary
End point timeframe:	
Baseline up to disease progression or death up to data cutoff of 31 Oct 2017 (up to 6 years) (See detailed timeframe in Outcome Measure description)	

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 (not applicable)	36.1	35.1		

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 due to any cause. Participants without event were censored at the time of last follow-up information for survival, ie, at the last time known to be alive. ITT population. Data for median and corresponding 95% CI were not reached due to low number (<10%) of participants with event of interest, therefore '99999' are reported to reflect not available (NA) data for median and corresponding 95% CI values.

End point type	Secondary

End point timeframe:

Baseline up to death (up to data cutoff of 31 Oct 2017 [up to 6 years])

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%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Stage 1: Observed Area Under the Serum Concentration-Time Curve (AUC) of Rituximab

End point title	Stage 1: Observed Area Under the Serum Concentration-Time Curve (AUC) of Rituximab[7]

End point description:

AUC is a measure of the serum concentration of the drug over time. It is used to characterize drug absorption. PK evaluable population. Here, number of participants analyzed = participants evaluable for this outcome measure. Predose (within 2 hr) and 24 hrs postdose on Cy 7 (D1,3,7,15), predose (within

2 hr) on Cy 8 D1 (1 Cy=3 weeks); additionally within 15 minutes after end of infusion (infusion duration=30 minutes) on Cy 7 D1 for rituximab IV (up to data cutoff of 11 Apr 2012 [up to 26 months])

End point type	Secondary

End point timeframe:

Stage I (Induction): Predose (within 2hr) up to data cutoff of 11 Apr 2012 [up to 26 months]) (See detailed timeframe in Outcome Measure description)

Notes:

[7] - 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: Data for this endpoint was provided only for those arms which were planned to be 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	55		
Units: mcg*day/mL				
geometric mean (geometric coefficient of variation)	2734.21 (± 32.51)	3778.93 (± 37.59)		

Statistical analyses

Statistical analysis title	Stage 1: AUC of Rituximab

Statistical analysis description:

The ratio of observed rituximab serum was determined as AUC SC/AUC IV during Cycle 7 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	113
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric mean ratio
Point estimate	1.38
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.24
upper limit	1.53

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

End point title	Stage I: Maximum Serum Concentrations (Cmax) of IV and SC Rituximab[8]

End point description:

Predose (within 2 hr) and 24 hrs postdose on Cy 7 (D1,3,7,15), predose (within 2 hr) on Cy 8 D1 (1 Cy=3 weeks); additionally within 15 minutes after end of infusion (infusion duration=30 minutes) on Cy 7 D1 for rituximab IV (up to data cutoff of 11 Apr 2012 [up to 26 months])

End point type	Secondary

End point timeframe:

Stage I (Induction): Predose (within 2hr) up to data cutoff of 11 Apr 2012 [up to 26 months]) (See

detailed timeframe in Outcome Measure description)

Notes:

[8] - 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: Data for this endpoint was provided only for those arms which were planned to be 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	59		
Units: mcg/mL				
geometric mean (geometric coefficient of variation)	250.63 (± 19.66)	236.82 (± 31.45)		

Statistical analyses

Statistical analysis title	Stage I: Cmax of IV and SC Rituximab
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
Parameter estimate	Geometric mean ratio
Point estimate	0.941
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.872
upper limit	1.015

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:

Stage I and II (Induction): Rituximab IV: Predose (within 2 hr) on D1 of Cy1-8 (1 Cy=3 weeks & 4 weeks for Cy8); Rituximab SC: Predose (within 2 hr) on D1 of Cy1 & Cy3-8 (1 Cy=3 weeks and 4 weeks for Cy8), predose (within 2 hr) on D0 of Cy2 (up to data cutoff of 31 Oct 2013 [up to 32 months])

End point type	Secondary

End point timeframe:

Stage I and II (induction): Predose (within 2hr) up to data cutoff of 31 Oct 2013 [up to 32 months]) (See detailed timeframe in Outcome Measure description)

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	155	154		
Units: mcg/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 (n = 198, 193)	14.00 (± 157.53)	12.88 (± 189.70)		
Cycle 2 (n = 197, 190)	30.13 (± 145.36)	40.00 (± 124.50)		
Cycle 3 (n = 192, 190)	45.25 (± 110.35)	63.83 (± 101.83)		
Cycle 4 (n = 186, 185)	54.06 (± 108.90)	81.71 (± 92.28)		
Cycle 5 (n = 185, 185)	64.68 (± 89.90)	98.00 (± 71.91)		
Cycle 6 (n = 187, 180)	71.02 (± 87.60)	109.56 (± 58.74)		
Cycle 7 (n = 183, 172)	80.7 (± 40.7)	122.2 (± 43.8)		
Cycle 8 (n = 52, 54)	77.60 (± 70.53)	131.48 (± 50.20)		

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:

Stage I and II (maintenance): D29 of Cy8 (induction; 1 Cy=4 weeks), predose (within 2 hr) on D1 of Cy 9 to 19 (maintenance Cycle 1 to 12 [1 Cy=8 weeks]; up to data cutoff of 11 Jan 2016 [up to 6 years]). ITT Population. Here, number of participants analyzed = participants evaluable for the outcome measure. Here "n" = number of participants evaluable for this outcome measure at specified timepoint.

End point type	Secondary

End point timeframe:

Stage I and II (maintenance): Predose (within 2hr) up to data cutoff of 11 Jan 2016 [up to 6 years]) (See detailed timeframe in Outcome Measure description)

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	174	170		
Units: mcg/mL				
geometric mean (geometric coefficient				

of variation)				
Cycle 8 (n = 174, 170)	37.69 (± 94.30)	61.31 (± 65.52)		
Cycle 9 (n = 171, 168)	30.35 (± 75.03)	49.47 (± 81.23)		
Cycle 10 (n = 164, 160)	28.44 (± 84.64)	47.27 (± 73.03)		
Cycle 11 (n = 164, 157)	28.77 (± 65.28)	46.70 (± 66.80)		
Cycle 12 (n = 160, 150)	28.80 (± 56.97)	44.72 (± 68.74)		
Cycle 13 (n = 157, 150)	28.84 (± 54.04)	44.32 (± 67.67)		
Cycle 14 (n = 153, 147)	28.09 (± 55.61)	43.32 (± 67.97)		
Cycle 15 (n = 148, 143)	28.19 (± 52.69)	44.11 (± 67.92)		
Cycle 16 (n = 150, 145)	28.05 (± 57.19)	42.96 (± 64.32)		
Cycle 17 (n = 149, 143)	28.24 (± 57.51)	42.82 (± 65.67)		
Cycle 18 (n = 143, 132)	28.59 (± 62.06)	44.79 (± 68.56)		
Cycle 19 (n = 138, 131)	27.75 (± 78.26)	43.69 (± 69.02)		

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, number of participants analyzed = participants evaluable for the outcome measure. 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 (up to data cutoff of 11 Jan 2016 [up to 6 years])

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	117	118		
Units: mcg/mL				
median (full range (min-max))				

Week 12: Follow-up Visit 1 (n = 117, 118)	15.60 (0.70 to 80.40)	22.35 (0.65 to 107.00)		
Week 24: Follow-up Visit 2 (n = 88, 96)	2.89 (0.58 to 17.40)	5.19 (0.69 to 62.10)		
Week 36: Follow-up Visit 3 (n = 38, 53)	1.08 (0.52 to 51.40)	2.02 (0.53 to 33.90)		

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 cluster of differentiation (CD) 19 value <80 cells per cubic millimeter (cells/mm^3). ITT Population. Here, number of participants analyzed = participants evaluable for the outcome measure. Here "n" = number of participants evaluable for this outcome measure at specified timepoint.

End point type	Secondary

End point timeframe:

Time Frame: Stage I and II (induction): for rituximab IV - D1 of Cy 1 to 8 (1 Cy=3 weeks); for rituximab SC - D1 of Cy 1 and Cy 3 to 8, D0 of Cy2

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	188	180		
Units: percentage of participants				
number (not applicable)				
Cycle 1 Day 1 - Baseline (n=188, 168)	51.6	54.8		
Cycle 2 Day 0 (n=183, 180)	95.1	95.0		
Cycle 3 Day 1 (n=175, 175)	99.4	99.4		
Cycle 4 Day 1 (n=178, 180)	99.4	100.0		
Cycle 5 Day 1 (n=179, 176)	100.0	100.0		
Cycle 6 Day 1 (n=173, 175)	100.0	100.0		
Cycle 7 Day 1 (n=178, 173)	100.0	100.0		
Cycle 8 Day 1 (n=175, 174)	100.0	100.0		

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/mm^3. ITT Population. Here, number of participants analyzed = participants evaluable for the outcome measure. Here "n" = number of participants evaluable for this outcome measure at specified timepoint.

End point type	Secondary

End point timeframe:

Stage I and II (maintenance): D1 of Cy 9 to 20 (1 Cy=8 weeks) (up to data cutoff of 11 Jan 2016 [up to 6 years])

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	170	164		
Units: percentage of participants				
number (not applicable)				
Cycle 9 Day 1 (n=170, 161)	99.4	100.0		
Cycle 10 Day 1 (n=165, 164)	99.4	100.0		
Cycle 11 Day 1 (n=158, 158)	99.4	100.0		
Cycle 12 Day 1 (n=151, 146)	100.0	100.0		
Cycle 13 Day 1 (n=149, 141)	100.0	100.0		
Cycle 14 Day 1 (n=152, 143)	100.0	100.0		
Cycle 15 Day 1 (n=149, 140)	100.0	100.0		
Cycle 16 Day 1 (n=142, 141)	100.0	100.0		
Cycle 17 Day 1 (n=145, 142)	100.0	100.0		
Cycle 18 Day 1 (n=141, 140)	100.0	100.0		
Cycle 19 Day 1 (n=140, 138)	100.0	100.0		
Cycle 20 Day 1 (n=139, 134)	100.0	100.0		

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) to Rituximab

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

End point description:

Levels of HACA in serum were detected at Day 1 of each cycle up to Cycle 8 and at follow-up visit. Safety Analysis Population: included 6 participants who were randomized under Rituximab SC arm but withdrew after Cy1 and then analyzed under Rituximab IV arm. Here, number of participants analyzed = participants evaluable for the outcome measure. Here "n" = number of participants evaluable for this outcome measure at specified timepoint. Stage I and II: Baseline: pre-dose (72 hours prior) D1 of Cy1, Cy 3-20, D0 of Cy2 (1 Cy=3 weeks for Cy1-8 & 8 weeks for Cy9-20), post-baseline: every 12 weeks after last rituximab administration until 96 weeks (a median of 27 months; up to data cutoff of 11 Jan 2016 [up to 6 years])

End point type	Secondary

End point timeframe:

Stage I and II: Baseline, post-baseline (See detailed timeframe in Outcome Measure description)

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	208	197		
Units: percentage of participants				
number (not applicable)				
Baseline (n=208, 191)	5.8	2.6		
Post-Baseline (n=206, 197)	1.5	2.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Stage I and II (Pooled): Percentage of Participants Positive for Human Anti-Human Antibodies (HAHAs) to Rituximab

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

End point description:

Levels of HAHA in serum were detected at Day 1 of each cycle up to Cycle 8 and at follow-up visit. Safety Analysis Population. Here, number of participants analyzed = participants evaluable for the outcome measure. Here "n" = number of participants evaluable for this outcome measure at specified timepoint. Stage I and II: Baseline: pre-dose (72 hours prior) D1 of Cy1, Cy 3-20, D0 of Cy2 (1 Cy=3 weeks for Cy1-8 & 8 weeks for Cy9-20), post-baseline: every 12 weeks after last rituximab administration until 96 weeks (a median of 27 months; up to data cutoff of 11 Jan 2016 [up to 6 years])

End point type	Secondary

End point timeframe:

Stage I and II: Baseline, post-baseline (See detailed timeframe in Outcome Measure description)

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	68	197		
Units: percentage of participants				
number (not applicable)				
Baseline (n=68, 188)	10.3	11.2		
Post-Baseline (n=66, 197)	7.6	13.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Stage I and II (Pooled): Percentage of Responses Showing Time Saved of Staff as Per Physician/Nurse Opinions With Each Administration of Rituximab SC as Compared to Rituximab IV at the End of Cy 8, 15 and 20

End point title	Stage I and II (Pooled): Percentage of Responses Showing Time Saved of Staff as Per Physician/Nurse Opinions With Each Administration of Rituximab SC as Compared to Rituximab IV at the End of Cy 8, 15 and 20

End point description:

All investigator physicians and nurses involved in this study were asked to provide the staff time that could be saved with each administration of rituximab SC as compared with rituximab IV to participants in routine practice afetr Cy 8, 15, 20 and categorized as less than (<) 1 hr, at least 1 hr but <2 hrs, at least 2 hrs but <3 hrs, at least 3 hrs but <4 hrs, >/=4 hrs. Staff were asked not to consider the time needed for the first IV administration. ITT Population. Here, number of participants analyzed = participants evaluable for the outcome measure. Here "n" = number of participants evaluable for this outcome measure at specified timepoint. Analysis was done in all participants to show a comparison on the time saved by staffs when administered via SC and IV.

End point type	Secondary

End point timeframe:

After Cycle 8 of induction treatment (24 weeks) and during the maintenance part of the study after 12 months (i.e., Cycle 15), and after the end of the maintenance treatment, (i.e., Cycle 20) (1 Cycle=4 weeks for Cycle 8 and 8 weeks for Cycles 15 and 20)

End point values	All Participants			
Subject group type	Subject analysis set			
Number of subjects analysed	166			
Units: percentage of responses				
Cycle 8: <1 hour (n=166)	11			
Cycle 8: ≥1 to <2 hours (n=166)	20			
Cycle 8: ≥2 to <3 hours (n=166)	35			
Cycle 8: ≥3 to <4 hours (n=166)	18			
Cycle 8: ≥4 hours (n=166)	16			
Cycle 15: <1 hour (n=130)	13			
Cycle 15: ≥1 to <2 hours (n=130)	17			
Cycle 15: ≥2 to <3 hours (n=130)	34			
Cycle 15: ≥3 to <4 hours (n=130)	14			
Cycle 15: ≥4 hours (n=130)	22			
Cycle 20: <1 hour (n=126)	14			
Cycle 20: ≥1 to <2 hours (n=126)	32			
Cycle 20: ≥2 to <3 hours (n=126)	21			
Cycle 20: ≥3 to <4 hours (n=126)	13			
Cycle 20: ≥4 hours (n=126)	19			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Responses Who Showed Rituximab SC Formulation Convenient as Compared to Rituximab IV Formulation as Assessed by Physician/Nurse Opinion

End point title	Percentage of Responses Who Showed Rituximab SC Formulation Convenient as Compared to Rituximab IV Formulation as Assessed by Physician/Nurse Opinion

End point description:

All investigator physicians and nurses involved in this study were asked to complete question i.e. "Which formulation of rituximab (SC or IV) do you think is more convenient?" based on their experience with the rituximab SC and IV formulations across all participants and presented as rituximab SC is much more convenient; rituximab SC is a little more convenient; both formulations are equally convenient; rituximab IV is a little more convenient; and rituximab IV is much more convenient. ITT Population. Here, number of participants analyzed = participants evaluable for the outcome measure. Here "n" = number of participants evaluable for this outcome measure at specified timepoint.

End point type	Secondary

End point timeframe:

After Cycle 8 of induction treatment (24 weeks) and during the maintenance part of the study after 12 months (i.e., Cycle 15), and after the end of the maintenance treatment, (i.e., Cycle 20) (1 Cycle=4 weeks for Cycle 8 and 8 weeks for Cycles 15 and 20)

End point values	All Participants			
Subject group type	Subject analysis set			
Number of subjects analysed	166			
Units: percentage of responses				
Cy8: Rituximab SC much more convenient (n=166)	81			
Cy8: Rituximab SC little more convenient (n=166)	13			
Cy8: Both formulations equally convenient (n=166)	2			
Cy8: Rituximab IV little more convenient (n=166)	4			
Cy8: Rituximab IV much more convenient (n=166)	0			
Cy15: Rituximab SC much more convenient (n=130)	88			
Cy15: Rituximab SC little more convenient (n=130)	7			
Cy15: Both formulations equally convenient (n=130)	5			
Cy15: Rituximab IV little more convenient (n=130)	0			
Cy15: Rituximab IV much more convenient (n=130)	0			

Cy20: Rituximab SC much more convenient (n=126)	88			
Cy20: Rituximab SC little more convenient (n=126)	9			
Cy20: Both formulations equally convenient (n=126)	2			
Cy20: Rituximab IV little more convenient (n=126)	1			
Cy20: Rituximab IV much more convenient (n=126)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Died

End point title	Percentage of Participants Who Died
End point description: ITT population.	
End point type	Secondary
End point timeframe: Baseline up to death (up to data cutoff of 31 Oct 2017 [up to 6 years])	

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 (not applicable)	12.7	8.8		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to data cutoff date of 31 Oct 2017 (up to 6 years)

Adverse event reporting additional description:

Safety Analysis Population included all participants who received at least one dose of rituximab, either IV or SC. Safety Analysis Population included 6 participants who were randomized under Rituximab SC arm but withdrew after Cy1 and then analyzed under Rituximab IV arm.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

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

Reporting group description:

First cycle of rituximab IV infusion (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.

Reporting group title	Stage I and 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.

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	74 / 197 (37.56%)	76 / 210 (36.19%)	
number of deaths (all causes)	16	28	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
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	
Prostate cancer			
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	

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 of lung			
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	
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	
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 197 (0.51%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix carcinoma stage 0			
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	
Adenocarcinoma of colon			
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	
Colon cancer			
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	
Kaposi’s sarcoma			
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	
Renal 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	
Lung neoplasm malignant			
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	
Uterine leiomyoma			
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	
Myelodysplastic syndrome			
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	
Adenocarcinom			
alternative dictionary used: MedDRA 20.1			
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	
Plasma cell myeloma			
alternative dictionary used: MedDRA 20.1			
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	
Breast cancer			
alternative dictionary used: MedDRA 20.1			
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	
Squamous cell carcinoma			
alternative dictionary used: MedDRA 20.1			

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	
Vascular disorders			
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	
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	
Hypertensive crisis			
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	
Subclavian artery occlusion			
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	
Surgical and medical procedures			
Bladder calculus removal			
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	
Hysterectomy			
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			
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	
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	
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	
Death			
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 / 2	
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	
Ovarian 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	
Uterovaginal prolapse			
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	
Uterine polyp			
alternative dictionary used: MedDRA 20.1			

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			
Dyspnoea			
subjects affected / exposed	2 / 197 (1.02%)	3 / 210 (1.43%)	
occurrences causally related to treatment / all	1 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
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	1 / 197 (0.51%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	1 / 1	
Pneumothorax			
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	
Bronchitis chronic			
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	
Psychiatric disorders			
Major depression			
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	

Bipolar disorder			
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	
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			
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	
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	
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	
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	
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	
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	
Lumbar vertebral 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	
Fall			
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	
Traumatic intracranial haemorrhage			
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	
Procedural 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	
Wrist 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	
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	
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	
Cardiac failure congestive			
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	
Bradycardia			
alternative dictionary used: MedDRA 20.1			
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	
Nervous system disorders			
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	

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	
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	
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	
Cognitive disorder			
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	
Hypoglycaemic coma			
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	
Transient ischaemic attack			
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	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	12 / 197 (6.09%)	10 / 210 (4.76%)	
occurrences causally related to treatment / all	7 / 14	5 / 13	
deaths causally related to treatment / all	1 / 2	0 / 0	
Neutropenia			

subjects affected / exposed	6 / 197 (3.05%)	4 / 210 (1.90%)	
occurrences causally related to treatment / all	8 / 9	2 / 5	
deaths causally related to treatment / all	0 / 0	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	
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	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	
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	
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	
Pancreatitis			

subjects affected / exposed	0 / 197 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
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	
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	
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	
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	
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	
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	
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	
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	
Mesenteric vein thrombosis			
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	
Colitis			
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	
Abdominal wall haematoma			
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	
Large intestine polyp			
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			
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	
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	
Jaundice			
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			

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	
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	
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	
Calculus bladder			
alternative dictionary used: MedDRA 20.1			
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			
Back pain			

subjects affected / exposed	2 / 197 (1.02%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
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	
Arthralgia			
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	
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	
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	
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	
Arthritis			
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			
Pneumonia			
subjects affected / exposed	11 / 197 (5.58%)	7 / 210 (3.33%)	
occurrences causally related to treatment / all	1 / 13	2 / 8	
deaths causally related to treatment / all	0 / 0	1 / 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	
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	
Lower respiratory tract infection			
subjects affected / exposed	2 / 197 (1.02%)	2 / 210 (0.95%)	
occurrences causally related to treatment / all	2 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary tract infection			
subjects affected / exposed	2 / 197 (1.02%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchitis			
subjects affected / exposed	1 / 197 (0.51%)	2 / 210 (0.95%)	
occurrences causally related to treatment / all	2 / 2	0 / 3	
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	3 / 197 (1.52%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
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	
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	
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	
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	
Meningitis			
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	
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	
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	
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	
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	
Respiratory tract infection			

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	
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	
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	
Appendicitis			
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	
Urosepsis			
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	
Cellulitis			
subjects affected / exposed	1 / 197 (0.51%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess			
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	
Chronic hepatitis B			
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	
Bacteraemia			

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	
Hepatitis viral			
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	
Erysipelas			
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	
Intestinal sepsis			
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	
Pulmonary tuberculosis			
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	
Respiratory tract infection fungal			
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	
Pyelonephritis			
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	
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	
Cellulitis gangrenous			
alternative dictionary used: MedDRA 20.1			

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	
Metabolism and nutrition disorders			
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	
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	

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	186 / 197 (94.42%)	187 / 210 (89.05%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	12 / 197 (6.09%)	13 / 210 (6.19%)	
occurrences (all)	15	13	
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	30 / 197 (15.23%)	27 / 210 (12.86%)	
occurrences (all)	43	32	
Dizziness			
subjects affected / exposed	16 / 197 (8.12%)	15 / 210 (7.14%)	
occurrences (all)	47	17	
Neuropathy peripheral			
subjects affected / exposed	24 / 197 (12.18%)	30 / 210 (14.29%)	
occurrences (all)	34	39	
Headache			

subjects affected / exposed	27 / 197 (13.71%)	20 / 210 (9.52%)	
occurrences (all)	35	31	
Hypoaesthesia			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	10 / 197 (5.08%)	7 / 210 (3.33%)	
occurrences (all)	13	8	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	42 / 197 (21.32%)	38 / 210 (18.10%)	
occurrences (all)	58	48	
Injection site erythema			
subjects affected / exposed	27 / 197 (13.71%)	0 / 210 (0.00%)	
occurrences (all)	125	0	
Pyrexia			
subjects affected / exposed	29 / 197 (14.72%)	29 / 210 (13.81%)	
occurrences (all)	38	41	
Asthenia			
subjects affected / exposed	35 / 197 (17.77%)	27 / 210 (12.86%)	
occurrences (all)	53	44	
Chills			
subjects affected / exposed	16 / 197 (8.12%)	18 / 210 (8.57%)	
occurrences (all)	17	21	
Mucosal inflammation			
subjects affected / exposed	9 / 197 (4.57%)	12 / 210 (5.71%)	
occurrences (all)	14	14	
Injection site pain			
subjects affected / exposed	16 / 197 (8.12%)	0 / 210 (0.00%)	
occurrences (all)	16	0	
Chest pain			
subjects affected / exposed	14 / 197 (7.11%)	7 / 210 (3.33%)	
occurrences (all)	16	9	
Oedema peripheral			
subjects affected / exposed	10 / 197 (5.08%)	13 / 210 (6.19%)	
occurrences (all)	13	17	
Influenza like illness			

subjects affected / exposed	5 / 197 (2.54%)	12 / 210 (5.71%)	
occurrences (all)	6	15	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	65 / 197 (32.99%)	57 / 210 (27.14%)	
occurrences (all)	165	159	
Anaemia			
subjects affected / exposed	30 / 197 (15.23%)	26 / 210 (12.38%)	
occurrences (all)	66	34	
Leukopenia			
subjects affected / exposed	13 / 197 (6.60%)	23 / 210 (10.95%)	
occurrences (all)	21	44	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	65 / 197 (32.99%)	47 / 210 (22.38%)	
occurrences (all)	113	89	
Vomiting			
subjects affected / exposed	29 / 197 (14.72%)	27 / 210 (12.86%)	
occurrences (all)	52	31	
Diarrhoea			
subjects affected / exposed	34 / 197 (17.26%)	35 / 210 (16.67%)	
occurrences (all)	47	49	
Constipation			
subjects affected / exposed	50 / 197 (25.38%)	55 / 210 (26.19%)	
occurrences (all)	66	87	
Abdominal pain			
subjects affected / exposed	29 / 197 (14.72%)	25 / 210 (11.90%)	
occurrences (all)	43	32	
Dyspepsia			
subjects affected / exposed	16 / 197 (8.12%)	14 / 210 (6.67%)	
occurrences (all)	19	22	
Abdominal pain upper			
subjects affected / exposed	11 / 197 (5.58%)	11 / 210 (5.24%)	
occurrences (all)	14	16	
Stomatitis			

subjects affected / exposed	12 / 197 (6.09%)	11 / 210 (5.24%)	
occurrences (all)	15	13	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	49 / 197 (24.87%)	32 / 210 (15.24%)	
occurrences (all)	60	47	
Oropharyngeal pain			
subjects affected / exposed	17 / 197 (8.63%)	17 / 210 (8.10%)	
occurrences (all)	29	18	
Dyspnoea			
subjects affected / exposed	21 / 197 (10.66%)	13 / 210 (6.19%)	
occurrences (all)	24	16	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	20 / 197 (10.15%)	25 / 210 (11.90%)	
occurrences (all)	22	26	
Erythema			
subjects affected / exposed	19 / 197 (9.64%)	11 / 210 (5.24%)	
occurrences (all)	34	13	
Alopecia			
subjects affected / exposed	28 / 197 (14.21%)	23 / 210 (10.95%)	
occurrences (all)	29	25	
Rash			
subjects affected / exposed	20 / 197 (10.15%)	14 / 210 (6.67%)	
occurrences (all)	28	18	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	19 / 197 (9.64%)	19 / 210 (9.05%)	
occurrences (all)	22	21	
Anxiety			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	11 / 197 (5.58%)	7 / 210 (3.33%)	
occurrences (all)	13	8	
Musculoskeletal and connective tissue disorders			

Bone pain			
subjects affected / exposed	20 / 197 (10.15%)	16 / 210 (7.62%)	
occurrences (all)	26	22	
Back pain			
subjects affected / exposed	18 / 197 (9.14%)	25 / 210 (11.90%)	
occurrences (all)	19	29	
Myalgia			
subjects affected / exposed	16 / 197 (8.12%)	10 / 210 (4.76%)	
occurrences (all)	20	17	
Muscle spasms			
subjects affected / exposed	17 / 197 (8.63%)	7 / 210 (3.33%)	
occurrences (all)	21	7	
Pain in extremity			
subjects affected / exposed	22 / 197 (11.17%)	11 / 210 (5.24%)	
occurrences (all)	25	13	
Arthralgia			
subjects affected / exposed	26 / 197 (13.20%)	22 / 210 (10.48%)	
occurrences (all)	27	35	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	30 / 197 (15.23%)	26 / 210 (12.38%)	
occurrences (all)	51	39	
Urinary tract infection			
subjects affected / exposed	16 / 197 (8.12%)	28 / 210 (13.33%)	
occurrences (all)	23	49	
Nasopharyngitis			
subjects affected / exposed	22 / 197 (11.17%)	25 / 210 (11.90%)	
occurrences (all)	29	31	
Bronchitis			
subjects affected / exposed	15 / 197 (7.61%)	15 / 210 (7.14%)	
occurrences (all)	18	23	
Sinusitis			
subjects affected / exposed	14 / 197 (7.11%)	10 / 210 (4.76%)	
occurrences (all)	16	15	
Conjunctivitis			

subjects affected / exposed	9 / 197 (4.57%)	12 / 210 (5.71%)	
occurrences (all)	10	15	
Pneumonia			
subjects affected / exposed	12 / 197 (6.09%)	4 / 210 (1.90%)	
occurrences (all)	12	5	
Influenza			
subjects affected / exposed	9 / 197 (4.57%)	14 / 210 (6.67%)	
occurrences (all)	10	16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 March 2012	- 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