Clinical trial results:
A single-arm, multicentre, phase IIIb study to evaluate safety, efficacy and pharmacokinetic (PK) of subcutaneous (SC) rituximab administered during induction phase or maintenance in previously untreated patients with CD20+ diffuse large B cell lymphoma (DLBCL) or follicular lymphoma (FL)

Summary

EudraCT number	2013-000647-12
Trial protocol	IT
Global end of trial date	28 May 2019

Results information

Result version number	v1
This version publication date	14 June 2020
First version publication date	14 June 2020

Trial information

Trial identification

Sponsor protocol code	ML28881

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01889069
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche, Ltd.
Sponsor organisation address	F. Hoffmann-La Roche, Ltd., Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche, Ltd., +41 616878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche, Ltd., +41 616878333, genentech@druginfo.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 May 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 May 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to evaluate the incidence of administration-associated reactions (AARs) following multiple doses of subcutaneous (SC) rituximab during Induction and/or Maintenance therapy in subjects with CD20+ follicular non-Hodgkin's lymphoma (NHL) or CD20+ diffuse large B-cell lymphoma (DLBCL) who had previously received at least one dose of intravenous (IV) rituximab.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 September 2013
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?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 158
Worldwide total number of subjects	158
EEA total number of subjects	158

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)	107
From 65 to 84 years	51

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 37 investigational centers in Italy.

Pre-assignment

Screening details:

Adult participants with CD20+ diffuse large B-cell lymphoma or CD20+ follicular lymphoma.

Total overall participants enrolled in the study was 159, however for the subject disposition and baseline characteristics the enrolled was 158 as one participant discontinued the study prior to treatment.

Period 1

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

Arms

Arm title	Subcutaneous (SC) Rituximab

Arm description:

Participants will receive at least 4 doses of rituximab 1400 mg SC once a month during the Induction period, and at least 6 doses of rituximab 1400 mg SC once every two months during the Maintenance period, in addition to standard chemotherapy. Standard chemotherapy regimen included cyclophosphamide, vincristine, doxorubicin and prednisone (CHOP); or cyclophosphamide, vincristine and prednisone (CVP); or bendamustine as per standard local practice.

Arm type	Experimental
Investigational medicinal product name	MabThera Rituxan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1400 mg of rituximab was injected subcutaneously (SC)

Number of subjects in period 1	Subcutaneous (SC) Rituximab
Started	158
Completed	113
Not completed	45
Consent withdrawn by subject	3
Progression of Disease	14
Death	18
Not Specified	4
Lost to follow-up	6

Baseline characteristics

Reporting groups

Reporting group title	Subcutaneous (SC) Rituximab

Reporting group description:

Participants will receive at least 4 doses of rituximab 1400 mg SC once a month during the Induction period, and at least 6 doses of rituximab 1400 mg SC once every two months during the Maintenance period, in addition to standard chemotherapy. Standard chemotherapy regimen included cyclophosphamide, vincristine, doxorubicin and prednisone (CHOP); or cyclophosphamide, vincristine and prednisone (CVP); or bendamustine as per standard local practice.

Reporting group values	Subcutaneous (SC) Rituximab	Total	
Number of subjects	158	158	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	107	107	
From 65-84 years	51	51	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	58.7		
standard deviation	± 11.28	-	
Sex: Female, Male Units: Participants			
Female	72	72	
Male	86	86	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	9	9	
Not Hispanic or Latino	131	131	
Unknown or Not Reported	18	18	

Subject analysis sets

Subject analysis set title	Diffuse Large B-Cell Lymphoma (DLBCL)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with DLBCL, who had received at least 4 doses of rituximab 1400 mg SC once a month during the treatment phase, up to a maxium of 7 cycles, in addition to standard chemotherapy. Standard chemotherapy regimen included cyclophosphamide, vincristine, doxorubicin and prednisone (CHOP); or cyclophosphamide, vincristine and prednisone (CVP); as per standard local practice.

Subject analysis set title	Follicular Lymphoma (FL)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with CD20+ non-Hodgkin's (FL), who had received at least 4 doses of rituximab 1400 mg SC once a month during the Induction period, and at least 6 doses of rituximab 1400 mg SC once every two months during the Maintenance period, in addition to standard chemotherapy. Standard chemotherapy regimen included cyclophosphamide, vincristine, doxorubicin and prednisone (CHOP); or cyclophosphamide, vincristine and prednisone (CVP); or bendamustine as per standard local practice.

Subject analysis set title	Diffuse Large B-Cell Lymphoma (DLBCL) R-CHOP-14
Subject analysis set type	Sub-group analysis

Subject analysis set description:

DLBCL chemotherapy regimen cyclophosphamide, oncovine (vincristine), doxorubicin, prednisone/prednisolone given every 14 days (R-CHOP-14)

Subject analysis set title	Diffuse Large B-Cell Lymphoma (DLBCL) R-CHOP-21
Subject analysis set type	Sub-group analysis

Subject analysis set description:

DLBCL chemotherapy regimen cyclophosphamide, oncovine (vincristine), doxorubicin, prednisone/prednisolone given every 21 days (R-CHOP-21)

Reporting group values	Diffuse Large B-Cell Lymphoma (DLBCL)	Follicular Lymphoma (FL)	Diffuse Large B-Cell Lymphoma (DLBCL) R-CHOP-14
Number of subjects	72	86	4
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	42	65	
From 65-84 years	30	21	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	59.7	57.8	
standard deviation	± 12.70	± 9.92	±
Sex: Female, Male Units: Participants			
Female	28	44	
Male	44	42	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	4	5	
Not Hispanic or Latino	59	72	
Unknown or Not Reported	9	9	

Reporting group values	Diffuse Large B-Cell Lymphoma (DLBCL) R-CHOP-21		
Number of subjects	31		
Age categorical Units: Subjects			
In utero			

Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: years arithmetic mean standard deviation	±		
Sex: Female, Male Units: Participants			
Female Male			
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Unknown or Not Reported			

End points

End points reporting groups

Reporting group title	Subcutaneous (SC) Rituximab

Reporting group description:

Participants will receive at least 4 doses of rituximab 1400 mg SC once a month during the Induction period, and at least 6 doses of rituximab 1400 mg SC once every two months during the Maintenance period, in addition to standard chemotherapy. Standard chemotherapy regimen included cyclophosphamide, vincristine, doxorubicin and prednisone (CHOP); or cyclophosphamide, vincristine and prednisone (CVP); or bendamustine as per standard local practice.

Subject analysis set title	Diffuse Large B-Cell Lymphoma (DLBCL)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with DLBCL, who had received at least 4 doses of rituximab 1400 mg SC once a month during the treatment phase, up to a maxium of 7 cycles, in addition to standard chemotherapy. Standard chemotherapy regimen included cyclophosphamide, vincristine, doxorubicin and prednisone (CHOP); or cyclophosphamide, vincristine and prednisone (CVP); as per standard local practice.

Subject analysis set title	Follicular Lymphoma (FL)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with CD20+ non-Hodgkin's (FL), who had received at least 4 doses of rituximab 1400 mg SC once a month during the Induction period, and at least 6 doses of rituximab 1400 mg SC once every two months during the Maintenance period, in addition to standard chemotherapy. Standard chemotherapy regimen included cyclophosphamide, vincristine, doxorubicin and prednisone (CHOP); or cyclophosphamide, vincristine and prednisone (CVP); or bendamustine as per standard local practice.

Subject analysis set title	Diffuse Large B-Cell Lymphoma (DLBCL) R-CHOP-14
Subject analysis set type	Sub-group analysis

Subject analysis set description:

DLBCL chemotherapy regimen cyclophosphamide, oncovine (vincristine), doxorubicin, prednisone/prednisolone given every 14 days (R-CHOP-14)

Subject analysis set title	Diffuse Large B-Cell Lymphoma (DLBCL) R-CHOP-21
Subject analysis set type	Sub-group analysis

Subject analysis set description:

DLBCL chemotherapy regimen cyclophosphamide, oncovine (vincristine), doxorubicin, prednisone/prednisolone given every 21 days (R-CHOP-21)

Primary: Percentage of Participants with Administration-Associated Reactions (AAR)

End point title	Percentage of Participants with Administration-Associated Reactions (AAR)[1]

End point description:

AARs were defined as all adverse events (AEs) occurring within 24 hours of rituximab administration and which were considered related to study drug. AARs included infusion/injection-related reactions (IIRRs), injection-site reactions, administration site conditions and all symptoms thereof. Grading was completed according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

End point type	Primary

End point timeframe:

Baseline up to 54 months

Notes:

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

End point values	Subcutaneous (SC) Rituximab	Diffuse Large B-Cell Lymphoma (DLBCL)	Follicular Lymphoma (FL)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	158	72	86	
Units: Percentage of Participants				
number (not applicable)				
At least One AAR	6.3	4.2	8.1	
At Least One AAR Grade ≥3	0	0	0	
Cutaneous and Soft Tissue AARs (Localized)	5.1	1.4	8.1	
Cutaneous and Soft Tissue AARs (Non-Localized)	1.3	2.8	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with At Least One Grade ≥ 3 Treatment-Emergent Adverse Events (TEAEs)

End point title	Percentage of Participants with At Least One Grade ≥ 3 Treatment-Emergent Adverse Events (TEAEs)

End point description:

An AE was any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily have to have a causal relationship with the treatment. An adverse event was therefore any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Pre-existing conditions which worsened during the study were also considered as adverse events. Grading was completed according to the CTCAE, version 4.0.

End point type	Secondary

End point timeframe:

Baseline up to 54 months

End point values	Subcutaneous (SC) Rituximab	Diffuse Large B-Cell Lymphoma (DLBCL)	Follicular Lymphoma (FL)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	158	72	86	
Units: Percentage of Participants				
number (not applicable)	46.8	51.4	43.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with At Least One Grade ≥ 3 Infusion/ Injection Related Reactions (IIRRs)

End point title	Percentage of Participants with At Least One Grade ≥ 3 Infusion/ Injection Related Reactions (IIRRs)

End point description:

Grading of IIRRs was completed according to the CTCAE, version 4.0.

End point type	Secondary

End point timeframe:

Baseline up to 54 months

End point values	Subcutaneous (SC) Rituximab	Diffuse Large B-Cell Lymphoma (DLBCL)	Follicular Lymphoma (FL)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	158	72	86	
Units: Percentage of Participants				
number (not applicable)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with At Least One Treatment-Emergent Serious Adverse Events

End point title	Percentage of Participants with At Least One Treatment-Emergent Serious Adverse Events

End point description:

SAE was defined as any experience that suggested a significant hazard, contraindication, side effect, or precaution, and fulfilled any of the following criteria: fatal (resulted in death), life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/ birth defect, was medically significant or required intervention to prevent any of the other outcomes listed here.

End point type	Secondary

End point timeframe:

Baseline up to 54 months

End point values	Subcutaneous (SC) Rituximab	Diffuse Large B-Cell Lymphoma (DLBCL)	Follicular Lymphoma (FL)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	158	72	86	
Units: Percentage of Participants				
number (not applicable)	31.0	36.1	26.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Event-Free Survival (EFS) According to IWG Response Criteria

End point title	Event-Free Survival (EFS) According to IWG Response Criteria

End point description:

EFS was defined as the time from first dose of rituximab to first occurrence of progression or relapse, according to the International Working Group (IWG) response criteria or other country standards, or initiation of a non–protocol-specified anti-lymphoma therapy or death, whichever occurred first. The value '9999' indicates the median EFS was not estimable due to the low number of patients with events.

End point type	Secondary

End point timeframe:

Day 1 up to first occurrence of progression or relapse, or initiation of a non-protocol-specified anti-lymphoma therapy or death, whichever occurs first (up to maximum 54 months)

End point values	Subcutaneous (SC) Rituximab	Diffuse Large B-Cell Lymphoma (DLBCL)	Follicular Lymphoma (FL)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	158	72	86	
Units: months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)	9999 (9999 to 9999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) According to IWG Response Criteria

End point title	Progression-Free Survival (PFS) According to IWG Response Criteria

End point description:

PFS was defined as the time from first dose of rituximab to the first occurrence of disease progression or relapse, according to the International Working Group (IWG) response criteria or other country standards, or death from any cause, whichever occurred first. The value '9999' indicates the median PFS was not estimable due to the low number of patients with events.

End point type	Secondary

End point timeframe:

Day 1 up to first occurrence of progression or relapse, or death, whichever occurs first (up to maximum 54 months)

End point values	Subcutaneous (SC) Rituximab	Diffuse Large B-Cell Lymphoma (DLBCL)	Follicular Lymphoma (FL)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	158	72	86	
Units: months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)	9999 (9999 to 9999)	

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 first dose of rituximab to death from any cause. The value '9999' indicates median OS was not estimable due to the low number of patients with events (i.e., that died).

End point type	Secondary

End point timeframe:

Day 1 until death (up to maximum 54 months)

End point values	Subcutaneous (SC) Rituximab	Diffuse Large B-Cell Lymphoma (DLBCL)	Follicular Lymphoma (FL)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	158	72	86	
Units: months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)	9999 (9999 to 9999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-Free Survival (DFS) According to IWG Response Criteria

End point title	Disease-Free Survival (DFS) According to IWG Response Criteria

End point description:

DFS assessed in participants achieving complete response (CR) including complete response unconfirmed (Cru) and was defined as the period from 4 to 8 weeks after end of Induction period up to relapse or death from any cause, whichever occured first.

End point type	Secondary

End point timeframe:

From 4 to 8 weeks after end of Induction period up to relapse or death from any cause, whichever occurs first (up to maximum 54 months) (end of Induction period = up to 8 months)

End point values	Subcutaneous (SC) Rituximab	Diffuse Large B-Cell Lymphoma (DLBCL)	Follicular Lymphoma (FL)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	0[2]	72[3]	86[4]	
Units: Months				
arithmetic mean (confidence interval 95%)	(to)	9999 (9999 to 9999)	9999 (9999 to 9999)	

Notes:

[2] - DFS analysis was not performed.

[3] - DFS analysis was not performed.

[4] - DFS analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Complete Response (CR) According to IWG Response Criteria

End point title	Percentage of Participants with Complete Response (CR) According to IWG Response Criteria

End point description:

End point type	Secondary

End point timeframe:

At 4 to 8 weeks after end of Induction period (end of Induction period = up to 8 months)

End point values	Subcutaneous (SC) Rituximab	Diffuse Large B-Cell Lymphoma (DLBCL)	Follicular Lymphoma (FL)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	158	72	86	
Units: Percentage of Participants				
number (confidence interval 95%)	66.4 (57.2 to 74.8)	65.2 (52.4 to 76.5)	67.9 (53.7 to 80.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: FL: Plasma Trough Concentrations of Rituximab

End point title	FL: Plasma Trough Concentrations of Rituximab

End point description:

FL participants could be enrolled during induction or maintenance phase and they should have received at least 1 infusion of rituximab and must have been able to receive at least 4 cycles of rituximab SC if enrolled during induction or 4 cycles of rituximab SC if enrolled during maintenance. Pharmacokinetic (PK) data only collected for participants enrolled during Induction. During the induction phase each Cycle is 21 days.

End point type	Secondary

End point timeframe:

Induction collection: Cycle 2 Predose, Cycle 3 Predose, Cycle 4 Predose, Cycle 5 Predose, Baseline Predose, and Cycle 8 Predose on Day 1

End point values	Follicular Lymphoma (FL)			
Subject group type	Subject analysis set			
Number of subjects analysed	31			
Units: micrograms per millilitre (ug/mL)				
arithmetic mean (standard deviation)				
Cycle 2 Predose (n=10)	55.49 (± 64.275)			
Cycle 3 Predose (n=6)	119.50 (± 139.606)			
Cycle 4 Predose (n=4)	157.25 (± 132.583)			
Cycle 5 Predose (n=1)	7.60 (± 9999999)			
Baseline (n=21)	90.88 (± 107.089)			
Cycle 8 Predose (n=23)	201.56 (± 372.609)			

Statistical analyses

No statistical analyses for this end point

Secondary: FL: Overall Geometric Least Square (LS) Mean Plasma Trough Concentrations of Rituximab

End point title	FL: Overall Geometric Least Square (LS) Mean Plasma Trough Concentrations of Rituximab

End point description:

Measure type reported is geometric least square mean.

FL participants could be enrolled during induction or maintenance phase and they should have received at least 1 infusion of rituximab and must have been able to receive at least 4 cycles of rituximab SC if enrolled during induction or 4 cycles of rituximab SC if enrolled during maintenance. PK data only collected for participants enrolled during Induction. During the induction phase each Cycle is 21 days.

End point type	Secondary

End point timeframe:

Induction collection: Cycle 2 Predose, Cycle 3 Predose, Cycle 4 Predose, Cycle 5 Predose, Baseline Predose, and Cycle 8 Predose on Day 1.

End point values	Follicular Lymphoma (FL)			
Subject group type	Subject analysis set			
Number of subjects analysed	31			
Units: micrograms per millilitre (ug/mL)				
least squares mean (confidence interval 90%)	61.01 (42.49 to 87.61)			

Statistical analyses

No statistical analyses for this end point

Secondary: FL: Plasma Trough Concentrations of Rituximab in Participants with Complete Response/Complete Response Unconfirmed (CR/CRu)

End point title	FL: Plasma Trough Concentrations of Rituximab in Participants with Complete Response/Complete Response Unconfirmed (CR/CRu)

End point description:

FL participants could be enrolled during induction or maintenance phase and they should have received at least 1 infusion of rituximab and must have been able to receive at least 4 cycles of rituximab SC if enrolled during induction or 4 cycles of rituximab SC if enrolled during maintenance. PK data only collected for participants enrolled during Induction. During the induction phase each Cycle is 21 days. The value '9999999' in the results table indicates that the standard deviation could not be calculated using data from a single participant.

End point type	Secondary

End point timeframe:

Induction collection: Cycle 2 Predose, Cycle 3 Predose, Cycle 4 Predose, Cycle 5 Predose, Baseline Predose, and Cycle 8 Predose on Day 1.

End point values	Follicular Lymphoma (FL)			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: micrograms per millilitre (ug/mL)				
arithmetic mean (standard deviation)				
Cycle 2 Predose (n=8)	48.86 (± 57.640)			
Cycle 3 Predose (n=3)	156.33 (± 193.753)			
Cycle 4 Predose (n=3)	200.33 (± 123.411)			
Cycle 5 Predose (n=1)	7.60 (± 9999999)			
Baseline (n=15)	97.90 (± 118.897)			

Cycle 8 Predose (n=12)	284.08 (± 504.113)			

Statistical analyses

No statistical analyses for this end point

Secondary: DLBCL: Plasma Concentrations of Rituximab

End point title	DLBCL: Plasma Concentrations of Rituximab

End point description:

DLBCL participants received at least 1 infusion of rituximab and must have been able to receive at least 4 cycles of rituximab SC; therefore DLBCL participants could be enrolled at Cycle 2, Cycle 3, Cycle 4, or Cycle 5 and as a result the baseline PK sample could be collected at Cycle 2, Cycle 3, Cycle 4, or Cycle 5. Each Cycle is 21 days.

End point type	Secondary

End point timeframe:

Cycle 2 Predose, Cycle 3 Predose, Cycle 4 Predose, Cycle 5 Predose, Baseline Predose, Cycle 7 Predose on Day 1, Cycle 7 Day 7, Cycle 7 Day 14, Cycle 8 Predose on Day 1

End point values	Diffuse Large B-Cell Lymphoma (DLBCL)			
Subject group type	Subject analysis set			
Number of subjects analysed	36			
Units: micrograms per millilitre (ug/mL)				
arithmetic mean (standard deviation)				
Cycle 2 Predose (n=10)	42.53 (± 49.637)			
Cycle 3 Predose (n=9)	88.92 (± 92.790)			
Cycle 4 Predose (n=2)	110.50 (± 101.116)			
Cycle 5 Predose (n=5)	100.20 (± 44.483)			
Baseline (n=30)	92.92 (± 114.466)			
Cycle 7 Predose (n=26)	141.44 (± 122.314)			
Cycle 7 Day 7 (n=20)	348.81 (± 490.785)			
Cycle 7 Day 14 (n=5)	226.40 (± 136.729)			
Cycle 8 Predose (n=28)	117.61 (± 89.394)			

Statistical analyses

No statistical analyses for this end point

Secondary: DLBCL: Plasma Trough Concentrations of Rituximab

End point title	DLBCL: Plasma Trough Concentrations of Rituximab

End point description:

DLBCL participants received at least 1 infusion of rituximab and must have been able to receive at least 4 cycles of rituximab SC; therefore DLBCL participants could be enrolled at Cycle 2, Cycle 3, Cycle 4, or Cycle 5 and as a result the baseline PK sample could be collected at Cycle 2, Cycle 3, Cycle 4, or Cycle 5. Each Cycle is 21 days.

End point type	Secondary

End point timeframe:

Cycle 2 Predose, Cycle 3 Predose, Cycle 4 Predose, Cycle 5 Predose, Baseline Predose, Cycle 7 Predose on Day 1, Cycle 7 Day 7, Cycle 7 Day 14, Cycle 8 pre-dose on Day 1

End point values	Diffuse Large B-Cell Lymphoma (DLBCL)			
Subject group type	Subject analysis set			
Number of subjects analysed	36			
Units: micrograms per millilitre (ug/mL)				
arithmetic mean (standard deviation)				
Cycle 2 Predose (n=10)	42.53 (± 49.637)			
Cycle 3 Predose (n=9)	88.92 (± 92.790)			
Cycle 4 Predose (n=2)	110.50 (± 101.116)			
Cycle 5 Predose (n=5)	100.20 (± 44.483)			
Baseline (n=30)	92.92 (± 114.466)			
Cycle 7 Predose (n=26)	141.44 (± 122.314)			
Cycle 8 Predose (n=21)	117.61 (± 89.394)			

Statistical analyses

No statistical analyses for this end point

Secondary: DLBCL: Area Under the Plasma Concentration-Time Curve (AUC) of Rituximab

End point title	DLBCL: Area Under the Plasma Concentration-Time Curve (AUC) of Rituximab

End point description:

DLBCL participants received at least 1 infusion of rituximab and must have been able to receive at least 4 cycles of rituximab SC; therefore DLBCL participants could be enrolled at Cycle 2, Cycle 3, Cycle 4, or Cycle 5 and as a result the baseline PK sample could be collected at Cycle 2, Cycle 3, Cycle 4, or Cycle 5. Each Cycle is 21 days. The value '9999' indicates AUC was not estimable for available PK concentrations in DLBCL participants.

End point type	Secondary

End point timeframe:

Cycle 2 Predose, Cycle 3 Predose, Cycle 4 Predose, Cycle 5 Predose, Baseline Predose, Cycle 7 Predose on Day 1, Cycle 7 Day 7, Cycle 7 Day 14, Cycle 8 Predose on Day 1

End point values	Diffuse Large B-Cell Lymphoma (DLBCL)			
Subject group type	Subject analysis set			
Number of subjects analysed	36[5]			
Units: micrograms per millilitre (ug/mL)				
arithmetic mean (standard deviation)	9999 (± 9999)			

Notes:

[5] - AUC was not estimable for available PK concentrations in DLBCL participants

Statistical analyses

No statistical analyses for this end point

Secondary: DLBCL: Maximum Plasma Concentration (Cmax) of Rituximab

End point title	DLBCL: Maximum Plasma Concentration (Cmax) of Rituximab

End point description:

DLBCL participants received at least 1 infusion of rituximab and must have been able to receive at least 4 cycles of rituximab SC; therefore DLBCL participants could be enrolled at Cycle 2, Cycle 3, Cycle 4, or Cycle 5 and as a result the baseline PK sample could be collected at Cycle 2, Cycle 3, Cycle 4, or Cycle 5. Each Cycle is 21 days. The value '9999' indicates Cmax was not estimable for available PK concentrations in DLBCL participants.

End point type	Secondary

End point timeframe:

Cycle 2 Predose, Cycle 3 Predose, Cycle 4 Predose, Cycle 5 Predose, Baseline Predose, Cycle 7 Predose on Day 1, Cycle 7 Day 7, Cycle 7 Day 14, Cycle 8 Predose on Day 1

End point values	Diffuse Large B-Cell Lymphoma (DLBCL)			
Subject group type	Subject analysis set			
Number of subjects analysed	36[6]			
Units: micrograms per millilitre (ug/mL)				
arithmetic mean (standard deviation)	9999 (± 9999)			

Notes:

[6] - Cmax was not estimable for available PK concentrations in DLBCL participants.

Statistical analyses

No statistical analyses for this end point

Secondary: DLBCL: Apparent Total Clearance (CL/F) of Rituximab

End point title	DLBCL: Apparent Total Clearance (CL/F) of Rituximab

End point description:

DLBCL participants received at least 1 infusion of rituximab and must have been able to receive at least 4 cycles of rituximab SC; therefore DLBCL participants could be enrolled at Cycle 2, Cycle 3, Cycle 4, or Cycle 5 and as a result the baseline PK sample could be collected at Cycle 2, Cycle 3, Cycle 4, or Cycle 5. Each Cycle is 21 days. The value '9999' indicates that CL/F was not estimable for available PK concentrations in DLBCL participants.

End point type	Secondary

End point timeframe:

Cycle 2 Predose, Cycle 3 Predose, Cycle 4 Predose, Cycle 5 Predose, Baseline Predose, Cycle 7 Predose on Day 1, Cycle 7 Day 7, Cycle 7 Day 14, Cycle 8 Predose on Day 1

End point values	Diffuse Large B-Cell Lymphoma (DLBCL)			
Subject group type	Subject analysis set			
Number of subjects analysed	36[7]			
Units: micrograms per millilitre (ug/mL)				
arithmetic mean (standard deviation)	9999 (± 9999)			

Notes:

[7] - AUC was not estimable for available PK concentrations in DLBCL participants

Statistical analyses

No statistical analyses for this end point

Secondary: DLBCL: Plasma Trough Concentrations of Rituximab in Participants with Complete Response/Complete Response Unconfirmed (CR/CRu)

End point title	DLBCL: Plasma Trough Concentrations of Rituximab in Participants with Complete Response/Complete Response Unconfirmed (CR/CRu)

End point description:

DLBCL participants received at least 1 infusion of rituximab and must have been able to receive at least 4 cycles of rituximab SC; therefore DLBCL participants could be enrolled at Cycle 2, Cycle 3, Cycle 4, or Cycle 5 and as a result the baseline PK sample could be collected at Cycle 2, Cycle 3, Cycle 4, or Cycle 5. Each Cycle is 21 days.

End point type	Secondary

End point timeframe:

Cycle 2 Predose, Cycle 3 Predose, Cycle 4 Predose, Cycle 5 Predose, Baseline Predose, Cycle 7 Predose on Day 1, Cycle 7 Day 7, Cycle 7 Day 14, Cycle 8 Predose on Day 1

End point values	Diffuse Large B-Cell Lymphoma (DLBCL)			
Subject group type	Subject analysis set			
Number of subjects analysed	28			
Units: micrograms per millilitre (ug/mL)				
arithmetic mean (standard deviation)				

Cycle 2 Predose (n=7)	53.97 (± 56.169)			
Cycle 3 Predose (n=7)	101.79 (± 101.223)			
Cycle 4 Predose (n=2)	110.50 (± 101.116)			
Cycle 5 Predose (n=3)	121.67 (± 45.092)			
Baseline (n=23)	109.40 (± 125.603)			
Cycle 7 Predose (n=21)	157.93 (± 131.178)			
Cycle 8 Predose (n=21)	132.57 (± 95.447)			

Statistical analyses

No statistical analyses for this end point

Secondary: DLBCL: Overall Geometric Least Square (LS) Mean Plasma Trough Concentrations of Rituximab

End point title	DLBCL: Overall Geometric Least Square (LS) Mean Plasma Trough Concentrations of Rituximab

End point description:

Measure type reported is geometric least square mean

DDLBCL participants received at least 1 infusion of rituximab and must have been able to receive at least 4 cycles of rituximab SC; therefore DLBCL participants could be enrolled at Cycle 2, Cycle 3, Cycle 4, or Cycle 5 and as a result the baseline PK sample could be collected at Cycle 2, Cycle 3, Cycle 4, or Cycle 5. Each Cycle is 21 days.

End point type	Secondary

End point timeframe:

Cycle 2 Predose, Cycle 3 Predose, Cycle 4 Predose, Cycle 5 Predose, Baseline Predose, Cycle 7 Predose on Day 1, Cycle 7 Day 7, Cycle 7 Day 14, Cycle 8 Predose on Day 1

End point values	Diffuse Large B-Cell Lymphoma (DLBCL)			
Subject group type	Subject analysis set			
Number of subjects analysed	36			
Units: micrograms per millilitre (ug/mL)				
least squares mean (confidence interval 90%)	70.50 (57.60 to 86.28)			

Statistical analyses

No statistical analyses for this end point

Secondary: DLBCL: Plasma Concentrations During Different Scheduling of Rituximab SC R-CHOP-14 or R-CHOP-21

End point title	DLBCL: Plasma Concentrations During Different Scheduling of Rituximab SC R-CHOP-14 or R-CHOP-21

End point description:

Plasma concentrations of rituximab in participants with DLBCL by chemotherapy regimen cyclophosphamide, oncovine (vincristine), doxorubicin, prednisone/prednisolone given every 14 days (R-CHOP-14) or cyclophosphamide, oncovine (vincristine), doxorubicin, prednisone/prednisolone given every 21 days (R-CHOP-21) in the pharmacokinetic (PK) population. The value '99999' in the results table indicates that the standard deviation could not be calculated using data from a single participant. The Value '9999' in the results table indicates data is not reportable as no participants analyzed. DLBCL participants have received at least 1 infusion of rituximab and must be able to receive at least 4 cycles of rituximab SC; therefore DLBCL participants could be enrolled at Cycle 2, Cycle 3, Cycle 4, or Cycle 5 and as a result the baseline pk sample could be collected at Cycle 2, Cycle 3, Cycle 4, or Cycle 5. Each cycle is 21 days.

End point type	Secondary

End point timeframe:

Cycle 2 Predose, Cycle 3 Predose, Cycle 4 Predose, Cycle 5 Predose, Baseline Predose, Cycle 7 Predose on Day 1, Cycle 7 Day 7, Cycle 7 Day 14, Cycle 8 Predose on Day 1

End point values	Diffuse Large B-Cell Lymphoma (DLBCL) R-CHOP-14	Diffuse Large B-Cell Lymphoma (DLBCL) R-CHOP-21		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	31		
Units: micrograms per millilitre (ug/mL)				
arithmetic mean (standard deviation)				
Cycle 2 Predose (n=1,9)	170.00 (± 99999)	28.37 (± 22.695)		
Cycle 3 Predose (n=0,9)	9999 (± 9999)	88.92 (± 92.790)		
Cycle 4 Predose (n=0,2)	9999 (± 9999)	110.50 (± 101.116)		
Cycle 5 Predose (n=1,4)	125.00 (± 99999)	94.00 (± 48.806)		
Baseline (n=4,26)	214.25 (± 233.493)	74.25 (± 77.064)		
Cycle 7 Predose (n=2,23)	93.50 (± 79.903)	150.13 (± 126.221)		
Cycle 7 Day 7 (n=2,17)	71.55 (± 26.092)	398.76 (± 517.974)		
Cycle 7 Day 14 (n=1,4)	42.00 (± 99999)	272.50 (± 103.722)		
Cycle 8 Predose (n=2,25)	78.50 (± 14.849)	123.76 (± 92.606)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rituximab Administration Satisfaction Questionnaire (RASQ) Convenience and Satisfaction Domain Scores

End point title	Rituximab Administration Satisfaction Questionnaire (RASQ) Convenience and Satisfaction Domain Scores

End point description:

Patient-assessed satisfaction was evaluated using RASQ. Participants were asked questions regarding convenience and satisfaction for rituximab SC. Each domain is scored on a scale of 0 to 100, with higher scores indicative of more positive feelings toward therapy. The score for each domain was averaged among all participants. The value '99999' in the results table indicates that the standard deviation could not be calculated using data from a single participant. The value '9999' in the results table indicates DLBCL participants or FL participants did not complete the RASQ at the time point.

End point type	Secondary

End point timeframe:

DLBCL: Cycle (C) 2, C3, C4, C5, C6, End of C8; FL: Induction: C3, C4, C5, C6, C8, Maintenance: C2, C3, C4, C5, C6, C7, C8, C10, C12, End of treatment (4-8 weeks after last dose)

End point values	Diffuse Large B-Cell Lymphoma (DLBCL)	Follicular Lymphoma (FL)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	72	86		
Units: Units on a Scale				
arithmetic mean (standard deviation)				
Convenience domain Cycle 3 Induction (n=0,27)	9999 (± 9999)	81.8 (± 8.66)		
Convenience domain Cycle 4 Induction (n=0,11)	9999 (± 9999)	76.5 (± 6.26)		
Convenience domain Cycle 5 Induction (n=0,9)	9999 (± 9999)	79.6 (± 10.30)		
Convenience domain Cycle 6 Induction (n=0,2)	9999 (± 9999)	95.8 (± 5.89)		
Convenience domain Cycle 8 Induction (n=0,43)	9999 (± 9999)	83.1 (± 9.18)		
Convenience domain Cycle 2 Treatment (n=1,0)	75.0 (± 99999)	9999 (± 9999)		
Convenience domain Cycle 3 Treatment (n=30,0)	81.9 (± 10.28)	9999 (± 9999)		
Convenience domain Cycle 4 Treatment (n=20,0)	82.1 (± 12.17)	9999 (± 9999)		
Convenience domain Cycle 5 Treatment (n=8,0)	83.3 (± 9.96)	9999 (± 9999)		
Convenience domain Cycle 6 Treatment (n=13,0)	80.8 (± 9.85)	9999 (± 9999)		
Convenience domain Cycle 8 Treatment (n=53,0)	83.8 (± 11.60)	9999 (± 9999)		
Convenience domain Cycle 2 Maintenance (n=0,33)	9999 (± 9999)	83.6 (± 8.71)		
Convenience domain Cycle 3 Maintenance (n=0,6)	9999 (± 9999)	87.5 (± 19.54)		
Convenience domain Cycle 4 Maintenance (n=0,2)	9999 (± 9999)	100.0 (± 0.00)		
Convenience domain Cycle 5 Maintenance (n=0,8)	9999 (± 9999)	80.2 (± 12.55)		
Convenience domain Cycle 6 Maintenance (n=0,3)	9999 (± 9999)	83.3 (± 16.67)		
Convenience domain Cycle 7 Maintenance (n=0,39)	9999 (± 9999)	82.7 (± 12.59)		
Convenience domain Cycle 8 Maintenance (n=0,4)	9999 (± 9999)	93.8 (± 12.50)		

Convenience domain Cycle 10 Maintenance (n=0,1)	9999 (± 9999)	91.7 (± 99999)		
Convenience domain Cycle 12 Maintenance (n=0,48)	9999 (± 9999)	86.3 (± 12.69)		
Convenience domain End of Treatment (n=0,3)	9999 (± 9999)	75.0 (± 16.67)		
Satisfaction domain Cycle 3 Induction (n=0,27)	9999 (± 9999)	89.4 (± 10.23)		
Satisfaction domain Cycle 4 Induction (n=0,11)	9999 (± 9999)	84.1 (± 13.80)		
Satisfaction domain Cycle 5 Induction (n=0,9)	9999 (± 9999)	91.7 (± 8.84)		
Satisfaction domain Cycle 6 Induction (n=0,2)	9999 (± 9999)	93.8 (± 8.84)		
Satisfaction domain Cycle 8 Induction (n=0,40)	9999 (± 9999)	91.3 (± 9.47)		
Satisfaction domain Cycle 2 Treatment (n=1,0)	87.5 (± 99999)	9999 (± 9999)		
Satisfaction domain Cycle 3 Treatment (n=30,0)	83.3 (± 11.53)	9999 (± 9999)		
Satisfaction domain Cycle 4 Treatment (n=20,0)	85.6 (± 13.62)	9999 (± 9999)		
Satisfaction domain Cycle 5 Treatment (n=9,0)	83.3 (± 8.84)	9999 (± 9999)		
Satisfaction domain Cycle 6 Treatment (n=13,0)	84.6 (± 14.57)	9999 (± 9999)		
Satisfaction domain Cycle 8 Treatment (n=54,0)	91.2 (± 12.76)	9999 (± 9999)		
Satisfaction domain Cycle 2 Maintenance (n=0,33)	9999 (± 9999)	92.0 (± 9.28)		
Satisfaction domain Cycle 3 Maintenance (n=0,6)	9999 (± 9999)	79.2 (± 20.41)		
Satisfaction domain Cycle 4 Maintenance (n=0,1)	9999 (± 9999)	100.0 (± 99999)		
Satisfaction domain Cycle 5 Maintenance (n=0,8)	9999 (± 9999)	79.7 (± 16.28)		
Satisfaction domain Cycle 6 Maintenance (n=0,2)	9999 (± 9999)	87.5 (± 17.68)		
Satisfaction domain Cycle 7 Maintenance (n=0,39)	9999 (± 9999)	94.2 (± 9.00)		
Satisfaction domain Cycle 8 Maintenance (n=0,4)	9999 (± 9999)	93.8 (± 7.22)		
Satisfaction domain Cycle 10 Maintenance (n=0,1)	9999 (± 9999)	50.0 (± 99999)		
Satisfaction domain Cycle 12 Maintenance (n=0,47)	9999 (± 9999)	91.0 (± 13.21)		
Satisfaction domain End of treatment (n=0,3)	9999 (± 9999)	75.0 (± 21.65)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 54 months

Adverse event reporting additional description:

Post study start AEs (AEs occurring on the day of or after the first administration of study drug and up to 28 days after the last dose) and is defined as treatment-emergent adverse event (TEAE).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Follicular Lymphoma (FL)

Reporting group description:

Participants with CD20+ non-Hodgkin's (FL), who had received at least 4 doses of rituximab 1400 mg SC once a month during the Induction period, and at least 6 doses of rituximab 1400 mg SC once every two months during the Maintenance period, in addition to standard chemotherapy. Standard chemotherapy regimen included cyclophosphamide, vincristine, doxorubicin and prednisone (CHOP); or cyclophosphamide, vincristine and prednisone (CVP); or bendamustine as per standard local practice.

Reporting group title	Diffuse Large B-Cell Lymphoma (DLBCL)

Reporting group description:

Participants with DLBCL, who had received at least 4 doses of rituximab 1400 mg SC once a month during the Induction period, and at least 6 doses of rituximab 1400 mg SC once every two months during the Maintenance period, in addition to standard chemotherapy. Standard chemotherapy regimen included cyclophosphamide, vincristine, doxorubicin and prednisone (CHOP); or cyclophosphamide, vincristine and prednisone (CVP); or bendamustine as per standard local practice.

Serious adverse events	Follicular Lymphoma (FL)	Diffuse Large B-Cell Lymphoma (DLBCL)	
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 86 (26.74%)	26 / 72 (36.11%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostatic Adenoma			
subjects affected / exposed	1 / 86 (1.16%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 86 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	1 / 86 (1.16%)	0 / 72 (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			
Chylothorax			
subjects affected / exposed	0 / 86 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 86 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Failure			
subjects affected / exposed	0 / 86 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Neutrophil Count Decreased			
subjects affected / exposed	1 / 86 (1.16%)	5 / 72 (6.94%)	
occurrences causally related to treatment / all	0 / 1	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
White Blood Cell Count Decreased			
subjects affected / exposed	0 / 86 (0.00%)	2 / 72 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Meniscus Injury			
subjects affected / exposed	1 / 86 (1.16%)	0 / 72 (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	1 / 86 (1.16%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure			
subjects affected / exposed	0 / 86 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus Tachycardia			
subjects affected / exposed	0 / 86 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Monoparesis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 86 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	13 / 86 (15.12%)	15 / 72 (20.83%)	
occurrences causally related to treatment / all	5 / 16	3 / 23	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile Neutropenia			
subjects affected / exposed	2 / 86 (2.33%)	4 / 72 (5.56%)	
occurrences causally related to treatment / all	0 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

Leukopenia			
subjects affected / exposed	1 / 86 (1.16%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphopenia			
subjects affected / exposed	2 / 86 (2.33%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 86 (2.33%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Subileus			
subjects affected / exposed	0 / 86 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis Acute			
subjects affected / exposed	2 / 86 (2.33%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	2 / 86 (2.33%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Bladder Diverticulum			
subjects affected / exposed	1 / 86 (1.16%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	0 / 86 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 86 (0.00%)	2 / 72 (2.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella Infection			
subjects affected / exposed	0 / 86 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Micrococcus Infection			
subjects affected / exposed	0 / 86 (0.00%)	1 / 72 (1.39%)	
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	1 / 86 (1.16%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic Shock			
subjects affected / exposed	0 / 86 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Staphylococcal Infection			
subjects affected / exposed	0 / 86 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes Mellitus			
subjects affected / exposed	1 / 86 (1.16%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			

subjects affected / exposed	0 / 86 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Follicular Lymphoma (FL)	Diffuse Large B-Cell Lymphoma (DLBCL)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 86 (65.12%)	50 / 72 (69.44%)	
Investigations			
Neutrophil Count Decreased			
subjects affected / exposed	1 / 86 (1.16%)	9 / 72 (12.50%)	
occurrences (all)	1	13	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	0 / 86 (0.00%)	5 / 72 (6.94%)	
occurrences (all)	0	6	
Headache			
subjects affected / exposed	7 / 86 (8.14%)	3 / 72 (4.17%)	
occurrences (all)	8	4	
Paraesthesia			
subjects affected / exposed	7 / 86 (8.14%)	9 / 72 (12.50%)	
occurrences (all)	7	11	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	20 / 86 (23.26%)	21 / 72 (29.17%)	
occurrences (all)	46	32	
Anaemia			
subjects affected / exposed	6 / 86 (6.98%)	11 / 72 (15.28%)	
occurrences (all)	10	15	
Leukopenia			
subjects affected / exposed	7 / 86 (8.14%)	2 / 72 (2.78%)	
occurrences (all)	20	3	
Thrombocytopenia			
subjects affected / exposed	3 / 86 (3.49%)	4 / 72 (5.56%)	
occurrences (all)	14	8	

Lymphopenia			
subjects affected / exposed	5 / 86 (5.81%)	1 / 72 (1.39%)	
occurrences (all)	19	1	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	15 / 86 (17.44%)	11 / 72 (15.28%)	
occurrences (all)	23	15	
Asthenia			
subjects affected / exposed	3 / 86 (3.49%)	14 / 72 (19.44%)	
occurrences (all)	3	14	
Influenza Like Illness			
subjects affected / exposed	9 / 86 (10.47%)	2 / 72 (2.78%)	
occurrences (all)	15	2	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 86 (8.14%)	7 / 72 (9.72%)	
occurrences (all)	11	8	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal Pain			
subjects affected / exposed	0 / 86 (0.00%)	5 / 72 (6.94%)	
occurrences (all)	0	5	
Cough			
subjects affected / exposed	15 / 86 (17.44%)	6 / 72 (8.33%)	
occurrences (all)	19	7	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	6 / 86 (6.98%)	0 / 72 (0.00%)	
occurrences (all)	7	0	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	4 / 86 (4.65%)	4 / 72 (5.56%)	
occurrences (all)	4	4	
Infections and infestations			
Bronchitis			
subjects affected / exposed	5 / 86 (5.81%)	1 / 72 (1.39%)	
occurrences (all)	6	1	

Herpes Zoster subjects affected / exposed occurrences (all)	5 / 86 (5.81%) 5	0 / 72 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 March 2014	The first protocol amendment led to protocol version 3, dated 04 Mar 2014, and was implemented for the following reasons: The CT scan timelines were modified from 35 to 45 days prior the first IV administration of rituximab; The meaning of the previous statement on first dosing was clarified;The procedures for enrollment in this study, in particular in the Maintenance period, were clarified; Changes in some inclusion/exclusion criteria were made for better clarity; Guidelines reference for the management of HBV patients was provided; Details for PRO data collection were provided; Details on the actual SAE reporting process were provided; Details on patient discontinuation procedures were given.
05 July 2016	The second protocol amendment led to protocol version 4, dated 05 July 2016, and was implemented for the following reasons: An intermediate analysis was considered necessary to analyse all patients who concluded the Induction phase regarding the safety and PK endpoints (i.e. the analysis performed for the interim Clinical Study Report); Due to inconsistencies between the core text and schedule of assessments, the "Early termination/End of Treatment visit" was added in the Protocol Appendix 11.1 and 11.1.1; Changes in protocol Section 4.3.4 regarding post-study access to Rituximab SC were made in agreement with new requirements.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported