Clinical trial results:
Open-Label, Single-arm, Phase IIIb Clinical Trial to Evaluate the Safety of Switching from Intravenous Rituximab to Subcutaneous Rituximab During First-Line Treatment for CD20+ Non-Hodgkin's Follicular Lymphoma and Diffuse Large B-cell Lymphoma

Summary

EudraCT number	2013-001118-14
Trial protocol	ES
Global end of trial date	11 April 2017

Results information

Result version number	v1 (current)
This version publication date	20 April 2018
First version publication date	20 April 2018

Trial information

Trial identification

Sponsor protocol code	ML28943

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01987505
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	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, + 41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 April 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 April 2017
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 November 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	Spain: 140
Worldwide total number of subjects	140
EEA total number of subjects	140

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)	80
From 65 to 84 years	60

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 140 subjects were enrolled across 39 sites in Spain.

Pre-assignment

Screening details:

This study included adult subjects with CD20+ diffuse large B-cell lymphoma or CD20+ follicular lymphoma, who had already received at least one complete dose of rituximab IV during induction or maintenance.

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 Rituximab

Arm description:

Subjects with CD20+ non-Hodgkin's follicular lymphoma (FL) or diffuse large B-cell lymphoma (DLBCL), who had already received at least one full dose of intravenous (IV) rituximab were treated with subcutaneous (SC) rituximab during first-line treatment. Subjects with FL were administered 1400 mg rituximab during induction therapy (once monthly for 4-7 cycles) and maintenance therapy (once every 2 months for 6-12 cycles). Subjects with DLBCL were administered 1400 mg SC of rituximab once monthly for 4-7 cycles. Treatment duration was expected to last up to 7 months for subjects with DLBCL and up to 32 months for subjects with FL.

Arm type	Experimental
Investigational medicinal product name	Rituximab SC
Investigational medicinal product code	
Other name	MabThera Rituxan
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 Rituximab
Started	140
Completed	106
Not completed	34
Consent withdrawn by subject	2
Death	4
Unknown	9
Other Reason	2
Investigator Decision	2
Lost to follow-up	15

Baseline characteristics

Reporting groups

Reporting group title	Subcutaneous Rituximab

Reporting group description:

Subjects with CD20+ non-Hodgkin's follicular lymphoma (FL) or diffuse large B-cell lymphoma (DLBCL), who had already received at least one full dose of intravenous (IV) rituximab were treated with subcutaneous (SC) rituximab during first-line treatment. Subjects with FL were administered 1400 mg rituximab during induction therapy (once monthly for 4-7 cycles) and maintenance therapy (once every 2 months for 6-12 cycles). Subjects with DLBCL were administered 1400 mg SC of rituximab once monthly for 4-7 cycles. Treatment duration was expected to last up to 7 months for subjects with DLBCL and up to 32 months for subjects with FL.

Reporting group values	Subcutaneous Rituximab	Total	
Number of subjects	140	140	
Age categorical Units: Subjects			
Adults (18-64 years)	80	80	
From 65-84 years	60	60	
Age Continuous Units: years			
arithmetic mean	60.2		
standard deviation	± 12.4	-	
Sex: Female, Male Units: Subjects			
Female	65	65	
Male	75	75	
Race/Ethnicity, Customized Units: Subjects			
Black	1	1	
Caucasian	139	139	

Subject analysis sets

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

Subject analysis set description:

Subjects with diffuse large B-cell lymphoma (DLBCL), who had already received at least one full dose of intravenous (IV) rituximab were treated with subcutaneous (SC) rituximab. Subjects with DLBCL were administered 1400 mg SC of rituximab once monthly for 4-7 cycles. Treatment duration was expected to last up to 7 months for subjects with DLBCL.

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

Subject analysis set description:

Subjects with CD20+ non-Hodgkin's follicular lymphoma (FL), who had already received at least one full dose of intravenous (IV) rituximab were treated with subcutaneous (SC) rituximab. Subjects with FL were administered 1400 mg rituximab during induction therapy (once monthly for 4-7 cycles) and maintenance therapy (once every 2 months for 6-12 cycles). Treatment duration was expected to last to 32 months for subjects with FL.

Reporting group values	Diffuse Large B-Cell Lymphoma (DLBCL)	Follicular Lymphoma (FL)	
Number of subjects	29	111	
Age categorical Units: Subjects			
Adults (18-64 years)	14	66	
From 65-84 years	15	45	
Age Continuous Units: years			
arithmetic mean	62.5	59.6	
standard deviation	± 12.0	± 12.5	
Sex: Female, Male Units: Subjects			
Female	12	53	
Male	17	58	
Race/Ethnicity, Customized Units: Subjects			
Black	0	1	
Caucasian	29	110	

End points

End points reporting groups

Reporting group title	Subcutaneous Rituximab

Reporting group description:

Subjects with CD20+ non-Hodgkin's follicular lymphoma (FL) or diffuse large B-cell lymphoma (DLBCL), who had already received at least one full dose of intravenous (IV) rituximab were treated with subcutaneous (SC) rituximab during first-line treatment. Subjects with FL were administered 1400 mg rituximab during induction therapy (once monthly for 4-7 cycles) and maintenance therapy (once every 2 months for 6-12 cycles). Subjects with DLBCL were administered 1400 mg SC of rituximab once monthly for 4-7 cycles. Treatment duration was expected to last up to 7 months for subjects with DLBCL and up to 32 months for subjects with FL.

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

Subject analysis set description:

Subjects with diffuse large B-cell lymphoma (DLBCL), who had already received at least one full dose of intravenous (IV) rituximab were treated with subcutaneous (SC) rituximab. Subjects with DLBCL were administered 1400 mg SC of rituximab once monthly for 4-7 cycles. Treatment duration was expected to last up to 7 months for subjects with DLBCL.

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

Subject analysis set description:

Subjects with CD20+ non-Hodgkin's follicular lymphoma (FL), who had already received at least one full dose of intravenous (IV) rituximab were treated with subcutaneous (SC) rituximab. Subjects with FL were administered 1400 mg rituximab during induction therapy (once monthly for 4-7 cycles) and maintenance therapy (once every 2 months for 6-12 cycles). Treatment duration was expected to last to 32 months for subjects with FL.

Primary: Percentage of Subjects with Administration-Associated Reactions (AARs)

End point title	Percentage of Subjects with Administration-Associated Reactions (AARs)[1]

End point description:

AARs were defined as all adverse events (AEs) occurring within 24 hours of rituximab SC 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. Safety Population included all enrolled subjects who received at least one dose of study medication.

End point type	Primary

End point timeframe:

Up to 32 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: Only descriptive analysis was planned to be reported for the Primary Endpoint. Therefore, no statistical analysis is provided.

End point values	Subcutaneous 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	140	29	111	
Units: percentage of subjects				
number (not applicable)				
At Least One AAR	48.6	34.5	52.3	
At Least One AAR Grade ≥ 3	2.1	0	2.7	

At Least One Serious AARs	1.4	0	1.8	
Generalised or Remote from the Injection Site AARs	15.1	57.9	11.1	
Localised at the injection site AARs	84.9	42.1	88.9	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with At Least One Grade >/= 3 Adverse Event (AE)

End point title	Percentage of Subjects with At Least One Grade >/= 3 Adverse Event (AE)

End point description:

An adverse event was any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can, therefore, be any unfavorable 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 worsen during a study are also considered as adverse events. Grading was completed according to the CTCAE, version 4.0. Safety Population included all enrolled subjects who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Up to 32 months

End point values	Subcutaneous 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	140	29	111	
Units: percentage of subjects				
number (not applicable)	38.6	48.3	36.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with At Least One Grade >/= 3 Infusion/ Injection Related Reaction (IIRR)

End point title	Percentage of Subjects with At Least One Grade >/= 3 Infusion/ Injection Related Reaction (IIRR)

End point description:

Grading of IIRRs was completed according to the CTCAE, version 4.0. Safety Population included all enrolled subjects who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Up to 32 months

End point values	Subcutaneous 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	140	29	111	
Units: percentage of subjects				
number (not applicable)	2.1	0.0	2.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with At Least One Serious Adverse Event (SAE)

End point title	Percentage of Subjects with At Least One Serious Adverse Event (SAE)

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. Safety Population included all enrolled subjects who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Up to 32 months

End point values	Subcutaneous 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	140	29	111	
Units: percentage of subjects				
number (not applicable)	30.0	37.9	27.9	

Statistical analyses

No statistical analyses for this end point

Secondary: Event-Free Survival (EFS)

End point title	Event-Free Survival (EFS)

End point description:

EFS was defined as the time from first dose of rituximab IV to first occurrence of progressive disease (PD) or relapse, according to the International Working Group (IWG) response criteria or initiation of a non–protocol-specified anti-lymphoma therapy or death, whichever occurs first. PD: >/= 50% increase lymph nodes and nodal mass size, any new lesion, enlarged liver/spleen, reappearance bone marrow abnormalities. Intent-to-Treat (ITT) population included all enrolled subjects.

End point type	Secondary

End point timeframe:

Up to 32 months

End point values	Subcutaneous 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	140	29	111	
Units: months				
arithmetic mean (confidence interval 95%)	52.314 (49.162 to 55.466)	25.79 (20.800 to 30.776)	54.39 (51.416 to 57.362)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)

End point description:

PFS was defined as the time from first dose of rituximab IV to the first occurrence of progressive disease (PD) or relapse, according to the International Working Group (IWG) response criteria or death from any cause. PD: >/= 50% increase lymph nodes and nodal mass size, any new lesion, enlarged liver/spleen, reappearance bone marrow abnormalities. The ITT population included all enrolled subjects.

End point type	Secondary

End point timeframe:

Up to 32 months

End point values	Subcutaneous 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	140	29	111	
Units: months				
arithmetic mean (confidence interval 95%)	53.118 (50.108 to 56.127)	27.952 (23.443 to 32.460)	54.389 (51.416 to 57.362)	

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 IV to death from any cause. The ITT population included all enrolled subjects.

End point type	Secondary

End point timeframe:

Up to 32 months

End point values	Subcutaneous 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	140	29	111	
Units: months				
arithmetic mean (confidence interval 95%)	59.516 (57.999 to 61.033)	37.42 (33.354 to 41.485)	60.61 (59.692 to 61.535)	

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-Free Survival (DFS)

End point title	Disease-Free Survival (DFS)

End point description:

DFS was assessed in subjects achieving complete response (CR) including complete response unconfirmed (Cru) and was defined as the period from the date of the initial CR/CRu until the date of relapse or death from any cause. CR: 1) disappearance of all evidence/symptoms of disease, 2) lymph nodes and nodal masses normal size, 3) enlarged spleen must have regressed in size, 4) normal bone marrow; CRu: see 1) and 3) of CR plus > 75% decrease in residual lymph node mass, indeterminate bone marrow. The ITT population included all enrolled subjects. Here, 99999 signifies that there were no events in this arm, therefore mean and 95% Confidence Interval could not be calculated.

End point type	Secondary

End point timeframe:

Up to 32 months

End point values	Subcutaneous 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	140	29	111	
Units: months				
arithmetic mean (confidence interval 95%)	33.044 (31.489 to 34.600)	26.062 (23.510 to 28.613)	99999 (99999 to 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment Response Rate

End point title	Treatment Response Rate

End point description:

Treatment response rate was classified according to the International Working Group (IWG) response criteria: CR/Cru, partial response (PR), stable disease (SD) and PD. CR: 1) disappearance of all evidence/symptoms of disease, 2) lymph nodes and nodal masses normal size, 3) enlarged spleen must have regressed in size, 4) normal bone marrow; CRu: see 1) and 3) of CR plus > 75% decrease in residual lymph node mass, indeterminate bone marrow; PR: >/= 50% decrease lymph nodes and nodal mass size; decrease in liver/spleen size, no new sites; SD: less than a PR, but is not PD; PD: >/= 50% increase lymph nodes and nodal mass size, any new lesion, enlarged liver/spleen, reappearance bone marrow abnormalities. ITT population included all enrolled subjects.

End point type	Secondary

End point timeframe:

4-6 weeks after the last dose of Induction (Up to approximately 8 months)

End point values	Subcutaneous 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	140	29	111	
Units: percentage of subjects				
number (not applicable)				
Complete Response (CR)	64.3	62.1	66.7	
Complete Response Unconfirmed (CRu)	5.4	3.4	7.4	
Partial Response (PR)	7.1	3.4	11.1	
Stable Disease (SD)|	1.8	0.0	3.7	
Progressive disease (PD)	12.5	17.2	7.4	
Unable to Assess (UA)	3.6	6.9	0.0	
Not Evaluable	5.4	6.9	3.7	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 32 months

Adverse event reporting additional description:

An adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. Safety Population included all enrolled subjects who received at least one dose of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Subcutaneous Rituximab

Reporting group description:

Subjects with CD20+ non-Hodgkin's follicular lymphoma (FL) or diffuse large B-cell lymphoma (DLBCL), who had already received at least one full dose of intravenous (IV) rituximab were treated with subcutaneous (SC) rituximab during first-line treatment. Subjects with FL were administered 1400 mg rituximab during induction therapy (once monthly for 4-7 cycles) and maintenance therapy (once every 2 months for 6-12 cycles). Subjects with DLBCL were administered 1400 mg SC of rituximab once monthly for 4-7 cycles. Treatment duration was expected to last up to 7 months for subjects with DLBCL and up to 32 months for subjects with FL.

Serious adverse events	Subcutaneous Rituximab		
Total subjects affected by serious adverse events			
subjects affected / exposed	42 / 140 (30.00%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain neoplasm			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastric neoplasm			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant melanoma			

subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostate cancer			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Venous thrombosis			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary mass			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Toxicity to various agents			

subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Presyncope			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	12 / 140 (8.57%)		
occurrences causally related to treatment / all	5 / 15		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	10 / 140 (7.14%)		
occurrences causally related to treatment / all	8 / 13		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			

subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 140 (1.43%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enteritis			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorder			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Intestinal obstruction			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Paraesthesia oral			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Umbilical hernia			

subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Enterobacter bacteraemia			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia bacteraemia			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	3 / 140 (2.14%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Pneumonia			
subjects affected / exposed	4 / 140 (2.86%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Pneumonia pneumococcal			
subjects affected / exposed	2 / 140 (1.43%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	4 / 140 (2.86%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Urinary tract infection			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	2 / 140 (1.43%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypomagnesaemia			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malnutrition			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Subcutaneous Rituximab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	117 / 140 (83.57%)		
Nervous system disorders			
Dizziness			
subjects affected / exposed	7 / 140 (5.00%)		
occurrences (all)	8		
Headache			
subjects affected / exposed	11 / 140 (7.86%)		
occurrences (all)	15		
Paraesthesia			
subjects affected / exposed	14 / 140 (10.00%)		
occurrences (all)	14		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	13 / 140 (9.29%)		
occurrences (all)	23		
Neutropenia			
subjects affected / exposed	24 / 140 (17.14%)		
occurrences (all)	39		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	31 / 140 (22.14%)		
occurrences (all)	41		
Injection site erythema			
subjects affected / exposed	12 / 140 (8.57%)		
occurrences (all)	29		
Pain			
subjects affected / exposed	9 / 140 (6.43%)		
occurrences (all)	10		
Pyrexia			
subjects affected / exposed	14 / 140 (10.00%)		
occurrences (all)	17		
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	13 / 140 (9.29%)		
occurrences (all)	13		
Diarrhoea			
subjects affected / exposed	22 / 140 (15.71%)		
occurrences (all)	34		
Dyspepsia			
subjects affected / exposed	8 / 140 (5.71%)		
occurrences (all)	8		
Nausea			
subjects affected / exposed	12 / 140 (8.57%)		
occurrences (all)	14		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	14 / 140 (10.00%)		
occurrences (all)	20		
Productive cough			
subjects affected / exposed	9 / 140 (6.43%)		
occurrences (all)	9		
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	36 / 140 (25.71%)		
occurrences (all)	97		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	13 / 140 (9.29%)		
occurrences (all)	16		
Back pain			
subjects affected / exposed	15 / 140 (10.71%)		
occurrences (all)	15		
Infections and infestations			
Respiratory tract infection			
subjects affected / exposed	23 / 140 (16.43%)		
occurrences (all)	32		
Upper respiratory tract infection			

subjects affected / exposed	12 / 140 (8.57%)		
occurrences (all)	19		
Urinary tract infection			
subjects affected / exposed	11 / 140 (7.86%)		
occurrences (all)	13		
Viral upper respiratory tract infection			
subjects affected / exposed	21 / 140 (15.00%)		
occurrences (all)	29		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported