Clinical trial results:
A randomized phase III trial evaluating two strategies of rituximab administration for the treatment of first line/low tumor burden follicular lymphoma (Follicular Lymphoma IV/SC Rituximab Therapy)

Summary

EudraCT number	2014-000128-22
Trial protocol	FR
Global end of trial date	29 June 2021

Results information

Result version number	v1 (current)
This version publication date	30 June 2022
First version publication date	30 June 2022

Trial information

Trial identification

Sponsor protocol code	FLIRT

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02303119
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	LYSARC
Sponsor organisation address	CH Lyon Sud - Batiment 2D, Pierre-Bénite, France,
Public contact	Stéphanie Doyen, LYSARC, +33 4 72 66 93 33, stephanie.doyen@lysarc.org
Scientific contact	Pr Guillaume Cartron, LYSA, +33 4 67 33 83 62,

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	29 June 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to compare the efficacy of two therapeutic strategies (rituximab SC vs rituximab IV), based on the progression free survival (PFS) assessed according to response criteria for malignant lymphoma 1999 (Cheson 1999), in patients with previously untreated low tumor burden follicular lymphoma.

Protection of trial subjects:

Premedication consisting of acetaminophen and an antihistamine should be administered before each rituximab infusion

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 January 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 223
Worldwide total number of subjects	223
EEA total number of subjects	223

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)	160
From 65 to 84 years	62
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The recruitment was performed from 02-February-2015 to 29-June-2018 in France

Pre-assignment

Screening details:

The subject’s eligibility is evaluated during the baseline period prior to the first administration of the study drug. The assessments were : Tumor biopsy, Ann Arbor Staging, Evaluation of FLIPI 1 and 2, Clinical examination, hematology and Biochemistry tests, serology.
263 patients screened, 223 patients included with 202 randomized

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard

Arm description:

Rituximab IV

Arm type	Active comparator
Investigational medicinal product name	rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

4 cycles of rituximab IV (375 mg/m²) at D1, D8, D15 and D22.

Arm title	Experimental

Arm description:

Rituximab SC after 1 rituximab IV

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

Dosage and administration details:

Patients randomized in experimental arm B will receive 8 cycles of rituximab: Rituximab IV (375 mg/m²) at the first cycle and then, in absence of grade 3-4 infusion related reaction (IRR) during cycle 1, rituximab SC (1400mg) at D8, D15, D22, M3, M5, M7 and M9

Number of subjects in period 1[1]	Standard	Experimental
Started	102	100
Completed	95	89
Not completed	7	11
Physician decision	-	1
Adverse event, non-fatal	-	3
Death	-	1
Progression	5	1
Concurrent illness	1	-
Protocol deviation	1	4
Lack of efficacy	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: In this study, we do not have 2 real periods but 2 distinct cohorts that we represent in these 2 periods. Period 1 is the principal cohort on which the main objective is analyzed

Period 2

Period 2 title	overall additional trial
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	rituximab SC as of C1 cohort

Arm description:

only rituximab SC

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

Dosage and administration details:

Patients 1 to 4:
In cycle 1, the administration will be split to 200mg at D1 and the second part of the split dose (1200mg) will be given on the following day, at least 12 hours after the first administration in absence of Rituximab related grade 3-4 AE
Patients 5 to 20:
Patients will receive 8 cycles of the full dose of Rituximab SC (1400mg) at D1, D8, D15, D22, M3, M5, M7 and M9

Number of subjects in period 2[2]	rituximab SC as of C1 cohort
Started	21
Completed	19
Not completed	2
Adverse event, non-fatal	1
Lack of efficacy	1

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Period 2 is a separate cohort with additional patients independent of period 1

Baseline characteristics

Reporting groups	
Reporting group title	Standard
Reporting group description:	
Rituximab IV	
Reporting group title	Experimental
Reporting group description:	
Rituximab SC after 1 rituximab IV	

Reporting group values	Standard	Experimental	Total
Number of subjects	102	100	202
Age categorical			
Units: Subjects			
Adults (18-64 years)	71	72	143
From 65-84 years	31	27	58
85 years and over	0	1	1
Age continuous			
Units: years			
median	59.5	59	
full range (min-max)	33 to 80	32 to 85	-
Gender categorical			
Units: Subjects			
Female	57	44	101
Male	45	56	101

Subject analysis sets	
Subject analysis set title	Intent-to-Treat Set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT set includes all patients randomized regardless of study drug being received or not. Patients will be analyzed based on the assigned treatment group at the time of randomization.	
Subject analysis set title	Efficacy Set
Subject analysis set type	Full analysis
Subject analysis set description:	
The Efficacy set includes all patients included in the ITT set with histopathologically confirmed follicular lymphoma by central review having: - received at least one dose of rituximab o For patients randomized in the arm B, only patients who correctly switched to rituximab SC after one IV cycle will be included in this set - baseline tumor assessments - at least one post baseline tumor assessment	
Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety set includes all patients who took at least one dose of study drug. Patients will be analyzed according to the actual treatment received ("as treated")	

Reporting group values	Intent-to-Treat Set	Efficacy Set	Safety Set
Number of subjects	202	175	200
Age categorical Units: Subjects			
Adults (18-64 years)	143	123	141
From 65-84 years	58	51	58
85 years and over	1	1	1
Age continuous Units: years			
median	59	60	59
full range (min-max)	32 to 85	32 to 85	32 to 85
Gender categorical Units: Subjects			
Female	101	86	99
Male	101	89	101

End points

End points reporting groups

Reporting group title	Standard
Reporting group description:	
Rituximab IV	
Reporting group title	Experimental
Reporting group description:	
Rituximab SC after 1 rituximab IV	
Reporting group title	rituximab SC as of C1 cohort
Reporting group description:	
only rituximab SC	
Subject analysis set title	Intent-to-Treat Set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT set includes all patients randomized regardless of study drug being received or not. Patients will be analyzed based on the assigned treatment group at the time of randomization.	
Subject analysis set title	Efficacy Set
Subject analysis set type	Full analysis
Subject analysis set description:	
The Efficacy set includes all patients included in the ITT set with histopathologically confirmed follicular lymphoma by central review having: - received at least one dose of rituximab o For patients randomized in the arm B, only patients who correctly switched to rituximab SC after one IV cycle will be included in this set - baseline tumor assessments - at least one post baseline tumor assessment	
Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety set includes all patients who took at least one dose of study drug. Patients will be analyzed according to the actual treatment received ("as treated")	

Primary: PFS

End point title	PFS
End point description:	
FLIRT SC: The Median-PFS was not reached at the end of study.	
End point type	Primary
End point timeframe:	
6 years PFS	

End point values	Standard	Experimental	rituximab SC as of C1 cohort	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	100	21	
Units: percent				
number (not applicable)	36.1	73.8	0	

Attachments (see zip file)	PFS by randomization arm - ITT set/pfs.jpg PFS since inclusion – Rituximab SC as of C1 cohort/pfs sc.jpg

Statistical analyses

Statistical analysis title	PFS by randomization arm - Stratified analysis

Statistical analysis description:

Model is performed on 202 patients (101 events and 101 censoring)
For Likelihood Ratio Chi-Square=7.07 DF=1 and Pr > Chi-Square=0.008.
HR and 95% CI are from Cox regression model stratified on FLIPI at randomization

Comparison groups	Standard v Experimental
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	equivalence[1]
P-value	= 0.0076 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.585
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.393
upper limit	0.871

Notes:

[1] - A two-sided log-rank test will be used for testing the difference in PFS between the two treatment arms.
The significance level for the primary analysis will be 0.05.
The hypothesis will be: H0: PFS (rituximab SC) = PFS (rituximab IV) vs HA: PFS (rituximab SC) ≠ PFS (rituximab IV)

[2] - To provide 90% power to detect Hazard Ratio (HR) of 0.52 (hazard of rituximab SC versus rituximab IV) with two-sided alpha (type I error) of 0.05, a total of 102 events from both arms were required. HR of 0.52 corresponds to an increase of the median

Secondary: OS

End point title	OS

End point description:

FLIRT-RANDO: The Median-OS was not reached for the both arms at the end of study.
FLIRT-SC: no death were recorded.

End point type	Secondary

End point timeframe:

6 years OS

End point values	Standard	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	100		
Units: percent				
number (not applicable)	0	0		

Attachments (see zip file)	OS by randomization arm - ITT set/os.jpg

Statistical analyses

Statistical analysis title	OS by randomization arm - Stratified analysis
Comparison groups	Standard v Experimental
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.3354
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.551
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.161
upper limit	1.885

Secondary: TTNLT

End point title	TTNLT

End point description:

The Median-TTNLT was not reached for the Experimental Arm at the end of study.

End point type	Secondary

End point timeframe:

6 years

End point values	Standard	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	100		
Units: percent				
number (not applicable)	60.6	0		

Attachments (see zip file)	TTNLT by randomization arm - ITT set/ttnlt.jpg

Statistical analyses

Statistical analysis title	TTNLT by randomization arm - Stratified analysis

Statistical analysis description:

Model is performed on 202 patients (85 events and 117 censoring).
For Likelihood Ratio Chi-Square=0.98 DF=1 and Pr > Chi-Square=0.322.
HR and 95% CI are from Cox regression model stratified on FLIPI at randomization.

Comparison groups	Standard v Experimental
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.3218
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.806
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.526
upper limit	1.236

Secondary: ORR at M3

End point title	ORR at M3

End point description:

Response according to Cheson 1999 criteria.
Patients without response assessment (due to whatever reason) are considered as non-responders.

End point type	Secondary

End point timeframe:

M3 or treatment discontinuation

End point values	Standard	Experimental	rituximab SC as of C1 cohort	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	100	21	
Units: percent				
number (confidence interval 95%)	83.3 (74.7 to 90)	80 (70.8 to 87.3)	85.7 (63.7 to 97)	

Statistical analyses

Statistical analysis title	ORR at M3 - Chi2
Comparison groups	Experimental v Standard

Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.54
Method	Chi-squared

Secondary: CRR at M3

End point title	CRR at M3

End point description:

Response according to Cheson 1999 criteria.
Patients without response assessment (due to whatever reason) are considered as non-responders.

End point type	Secondary

End point timeframe:

M3 or treatment discontinuation

End point values	Standard	Experimental	rituximab SC as of C1 cohort	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	100	21	
Units: percent				
number (confidence interval 95%)	38.2 (28.8 to 48.4)	29 (20.4 to 38.9)	33.3 (14.6 to 57)	

Statistical analyses

Statistical analysis title	CRR at M3 - Chi2
Comparison groups	Experimental v Standard
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.165
Method	Chi-squared

Secondary: ORR at EoT

End point title	ORR at EoT

End point description:

Response according to Cheson 1999.
Patients without response assessment (due to whatever reason) are considered as non-responders.

End point type	Secondary

End point timeframe:

End of treatment or treatment discontinuation

End point values	Standard	Experimental	rituximab SC as of C1 cohort	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	100	21	
Units: percent				
number (confidence interval 95%)	69.6 (59.7 to 78.3)	80 (70.8 to 87.3)	85.7 (63.7 to 97)	

Statistical analyses

Statistical analysis title	ORR at EoT - Chi2
Comparison groups	Standard v Experimental
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.089
Method	Chi-squared

Secondary: CRR at EoT

End point title	CRR at EoT

End point description:

Response according to Cheson 1999.
Patients without response assessment (due to whatever reason) are considered as non-responders.

End point type	Secondary

End point timeframe:

End of treatment or treatment discontinuation

End point values	Standard	Experimental	rituximab SC as of C1 cohort	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	100	21	
Units: percent				
number (confidence interval 95%)	46.1 (36.2 to 56.2)	55 (44.7 to 65)	57.1 (34 to 78.2)	

Statistical analyses

Statistical analysis title	CRR at EoT - Chi2
Comparison groups	Standard v Experimental

Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.205
Method	Chi-squared

Secondary: OMR at EoT

End point title	OMR at EoT

End point description:

Response according to Lugano 2014.
Patients without response assessment (due to whatever reason) are considered as non-responders.

End point type	Secondary

End point timeframe:

End of treatment or treatment discontinuation

End point values	Standard	Experimental	rituximab SC as of C1 cohort	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	100	21	
Units: percent				
number (confidence interval 95%)	52 (41.8 to 62)	73 (63.2 to 81.4)	66.7 (43 to 85.4)	

Statistical analyses

Statistical analysis title	OMR at EoT - Chi2
Comparison groups	Standard v Experimental
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.002
Method	Chi-squared

Secondary: CMR at EoT

End point title	CMR at EoT

End point description:

Response according to Lugano 2014.
Patients without response assessment (due to whatever reason) are considered as non-responders.

End point type	Secondary

End point timeframe:

End of treatment or treatment discontinuation

End point values	Standard	Experimental	rituximab SC as of C1 cohort	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	100	21	
Units: percent				
number (confidence interval 95%)	36.3 (27 to 46.4)	59 (48.7 to 68.7)	52.4 (29.8 to 74.3)	

Statistical analyses

Statistical analysis title	CMR at EoT - Chi2
Comparison groups	Standard v Experimental
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.001
Method	Chi-squared

Adverse events

Adverse events information

Timeframe for reporting adverse events:

infections and neurological toxicities of grade 2-5 + other toxicities of grade 3-5 regardless of their relationship to investigational product occurring from the date of informed consent signature and up to 30 days after last drug administration

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Standard
Reporting group description: -	
Reporting group title	Experimental
Reporting group description: -	
Reporting group title	rituximab SC as of C1 cohort
Reporting group description: -	

Serious adverse events	Standard	Experimental	rituximab SC as of C1 cohort
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 103 (3.88%)	12 / 97 (12.37%)	1 / 21 (4.76%)
number of deaths (all causes)	3	1	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin cancer			
subjects affected / exposed	0 / 103 (0.00%)	3 / 97 (3.09%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign neoplasm			
subjects affected / exposed	0 / 103 (0.00%)	1 / 97 (1.03%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid cancer			
subjects affected / exposed	0 / 103 (0.00%)	1 / 97 (1.03%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			

Administration related reaction			
subjects affected / exposed	0 / 103 (0.00%)	0 / 97 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 103 (0.97%)	0 / 97 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 103 (0.00%)	1 / 97 (1.03%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Nervous system disorders			
Migraine			
subjects affected / exposed	0 / 103 (0.00%)	1 / 97 (1.03%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuralgic amyotrophy			
subjects affected / exposed	0 / 103 (0.00%)	1 / 97 (1.03%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy peripheral			
subjects affected / exposed	0 / 103 (0.00%)	1 / 97 (1.03%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Injection site hypersensitivity			
subjects affected / exposed	1 / 103 (0.97%)	2 / 97 (2.06%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ULCER GASTRODUODENAL			

subjects affected / exposed	1 / 103 (0.97%)	1 / 97 (1.03%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	0 / 103 (0.00%)	1 / 97 (1.03%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Pyoderma gangrenosum			
subjects affected / exposed	1 / 103 (0.97%)	0 / 97 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal cyst			
subjects affected / exposed	0 / 103 (0.00%)	1 / 97 (1.03%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal injury			
subjects affected / exposed	0 / 103 (0.00%)	1 / 97 (1.03%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal infection			
subjects affected / exposed	1 / 103 (0.97%)	0 / 97 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 103 (0.00%)	1 / 97 (1.03%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Standard	Experimental	rituximab SC as of C1 cohort
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 103 (15.53%)	30 / 97 (30.93%)	13 / 21 (61.90%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin cancer			
subjects affected / exposed	0 / 103 (0.00%)	3 / 97 (3.09%)	0 / 21 (0.00%)
occurrences (all)	0	3	0
Benign neoplasm			
subjects affected / exposed	0 / 103 (0.00%)	1 / 97 (1.03%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Thyroid cancer			
subjects affected / exposed	0 / 103 (0.00%)	1 / 97 (1.03%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 103 (0.97%)	0 / 97 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	2 / 103 (1.94%)	0 / 97 (0.00%)	1 / 21 (4.76%)
occurrences (all)	3	0	1
Asthenia			
subjects affected / exposed	0 / 103 (0.00%)	0 / 97 (0.00%)	3 / 21 (14.29%)
occurrences (all)	0	0	3
Induration			
subjects affected / exposed	0 / 103 (0.00%)	0 / 97 (0.00%)	3 / 21 (14.29%)
occurrences (all)	0	0	3
Injection site pain			
subjects affected / exposed	0 / 103 (0.00%)	0 / 97 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Injection site rash			
subjects affected / exposed	0 / 103 (0.00%)	0 / 97 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Inflammation			
subjects affected / exposed	0 / 103 (0.00%)	1 / 97 (1.03%)	0 / 21 (0.00%)
occurrences (all)	0	1	0

Influenza like illness			
subjects affected / exposed	0 / 103 (0.00%)	1 / 97 (1.03%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Injection site discomfort			
subjects affected / exposed	0 / 103 (0.00%)	1 / 97 (1.03%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Injection site hypersensitivity			
subjects affected / exposed	2 / 103 (1.94%)	2 / 97 (2.06%)	0 / 21 (0.00%)
occurrences (all)	2	2	0
Respiratory, thoracic and mediastinal disorders			
Bronchopneumopathy			
subjects affected / exposed	0 / 103 (0.00%)	1 / 97 (1.03%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Rhinitis allergic			
subjects affected / exposed	0 / 103 (0.00%)	0 / 97 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Psychiatric disorders			
Mixed anxiety and depressive disorder			
subjects affected / exposed	0 / 103 (0.00%)	0 / 97 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Wound			
subjects affected / exposed	0 / 103 (0.00%)	1 / 97 (1.03%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Administration related reaction			
subjects affected / exposed	0 / 103 (0.00%)	0 / 97 (0.00%)	4 / 21 (19.05%)
occurrences (all)	0	0	5
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 103 (0.97%)	0 / 97 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Myocardial ischaemia			
subjects affected / exposed	0 / 103 (0.00%)	1 / 97 (1.03%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Syncope			

subjects affected / exposed	0 / 103 (0.00%)	1 / 97 (1.03%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Migraine			
subjects affected / exposed	0 / 103 (0.00%)	1 / 97 (1.03%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Neuralgic amyotrophy			
subjects affected / exposed	0 / 103 (0.00%)	1 / 97 (1.03%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Neuropathy peripheral			
subjects affected / exposed	0 / 103 (0.00%)	1 / 97 (1.03%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	3 / 103 (2.91%)	2 / 97 (2.06%)	0 / 21 (0.00%)
occurrences (all)	3	2	0
Gastrointestinal disorders			
ULCER GASTRODUODENAL			
subjects affected / exposed	1 / 103 (0.97%)	1 / 97 (1.03%)	0 / 21 (0.00%)
occurrences (all)	1	1	0
Large intestine polyp			
subjects affected / exposed	0 / 103 (0.00%)	1 / 97 (1.03%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Inguinal hernia			
subjects affected / exposed	0 / 103 (0.00%)	0 / 97 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 103 (0.00%)	0 / 97 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 103 (0.00%)	1 / 97 (1.03%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 103 (0.00%)	1 / 97 (1.03%)	3 / 21 (14.29%)
occurrences (all)	0	1	3

Rash			
subjects affected / exposed	0 / 103 (0.00%)	0 / 97 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Rash maculo-papular			
subjects affected / exposed	0 / 103 (0.00%)	0 / 97 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Pyoderma gangrenosum			
subjects affected / exposed	1 / 103 (0.97%)	0 / 97 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Renal cyst			
subjects affected / exposed	0 / 103 (0.00%)	1 / 97 (1.03%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Renal injury			
subjects affected / exposed	0 / 103 (0.00%)	1 / 97 (1.03%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Respiratory tract infection			
subjects affected / exposed	3 / 103 (2.91%)	10 / 97 (10.31%)	0 / 21 (0.00%)
occurrences (all)	3	16	0
Gastrointestinal infection			
subjects affected / exposed	1 / 103 (0.97%)	1 / 97 (1.03%)	0 / 21 (0.00%)
occurrences (all)	1	1	0
Viral infection			
subjects affected / exposed	0 / 103 (0.00%)	2 / 97 (2.06%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Abdominal infection			
subjects affected / exposed	1 / 103 (0.97%)	0 / 97 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Genital infection			
subjects affected / exposed	1 / 103 (0.97%)	0 / 97 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Lymphadenitis bacterial			
subjects affected / exposed	1 / 103 (0.97%)	0 / 97 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			

subjects affected / exposed	0 / 103 (0.00%)	1 / 97 (1.03%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Acarodermatitis			
subjects affected / exposed	0 / 103 (0.00%)	0 / 97 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	0 / 103 (0.00%)	0 / 97 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Rhinitis			
subjects affected / exposed	0 / 103 (0.00%)	0 / 97 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Tinea cruris			
subjects affected / exposed	0 / 103 (0.00%)	0 / 97 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hypophosphataemia			
subjects affected / exposed	0 / 103 (0.00%)	0 / 97 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Hypercalcaemia			
subjects affected / exposed	0 / 103 (0.00%)	1 / 97 (1.03%)	0 / 21 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 June 2018	Addition of a new cohort receiving exclusively subcutaneous rituximab, i.e. from the first injection, unlike the patients randomized in the experimental arm receiving intravenous on D1 followed by subcutaneous

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

none

Notes: