Clinical trial results:
A randomised double blind placebo controlled clinical trial of anti B-cell therapy in patients with primary Sjögren's syndrome.

Summary

EudraCT number	2010-021430-64
Trial protocol	GB
Global end of trial date	16 January 2015

Results information

Result version number	v1 (current)
This version publication date	25 March 2018
First version publication date	25 March 2018

Trial information

Trial identification

Sponsor protocol code	RR10/9389

Additional study identifiers

ISRCTN number	ISRCTN65360827
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Leeds
Sponsor organisation address	Hyde Terrace, Leeds, United Kingdom, LS2 9LN
Public contact	QA Manager, QA Department, Leeds Institute of Clinical Trials Research, ctruq@leeds.ac.uk
Scientific contact	QA Manager, QA Department, Leeds Institute of Clinical Trials Research, ctruq@leeds.ac.uk

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	10 March 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 January 2015
Global end of trial reached?	Yes
Global end of trial date	16 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the extent to which rituximab improves symptoms of fatigue and oral dryness in patients with primary Sjögren's syndrome.

Protection of trial subjects:

Patients were monitored closely throughout the trial and were asked to attend regular outpatient appointments and trial treatment visits.

Patients received two doses of trial treatment (Rituximab/placebo) delivered at 2 week intervals. This was repeated 6 months later. During the trial treatment visits, Rituximab/placebo was administered in an environment where full resuscitation facilities were available and under close supervision of an experienced physician. The frequency of the outpatient appointments between the trial treatment visits were more than standard care to monitor disease symptoms and conduct a safety evaluation.

CTRU prepared annual safety reports containing annonymised data to the MHRA, main REC, Sponsor. The Data Monitoring and Ethics Committee reviewed un-blinded periodic safety data to determine patterns and trends of events or to identify safety issues which would not be apparent on an individual case basis.

Trial data was collected on paper CRFs and was sent to the CTRU where it was entered onto a trial database application - MACRO. The database is stored on a private network protected by a firewall. Access is restricted to trials staff by login and password. The trial data was then filed in locked filling cabinets.

CTRU will comply with all aspects of Data Protection Act 1998. All information collected during the trial will be kept strictly confidential. Patient names were collected on the consent form however, for all other data collection forms that were transferred to or from CTRU, the data was coded with a trial number, the patient's initials and date of birth.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 July 2011
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	United Kingdom: 133
Worldwide total number of subjects	133
EEA total number of subjects	133

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)	103
From 65 to 84 years	30
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from hospital research centres within the United Kingdom.   From July 2011 to January 2014 a total of 133 patients were enrolled into the TRACTISS trial.

Pre-assignment

Screening details:

The patients registered on the Medical Research Council funded UK Primary Sjogren's Syndrome Registry (UKPSSR) were sent an invitation letter. Also, patients were approached during standard clinic visits and provided with verbal plus written details about the trial. The patients were given at least 24 hours to consider participation.

Pre-assignment period milestones

Number of subjects started	172[1]
Number of subjects completed	133

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Ineligible: 23
Reason: Number of subjects	Other Reason: 4
Reason: Number of subjects	Consent withdrawn by subject: 12

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same. Justification: 172 participants gave consent to non-standard trial-specific tests to confirm eligibility, conducted during the pre-assignment period. Following this, 133 patients were confirmed to be eligible and had not withdrawn consent. Thus: 133 participants were randomised to receive rituximab or placebo, and these participants form the basis of the reporting.

Period 1

Period 1 title	Baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

The placebo infusion bags were identical in appearance to the Rituximab infusion bags. The Investigator and team were blinded to the treatment allocations however, the pharmacist preparing the infusion bags were un-blinded.

 Interim reports provided un-blinded to DMEC by the Trial Statistician. Only the Statisticians have access to these reports and they were stored securely with password protection.

Arms

Are arms mutually exclusive?	Yes
Arm title	Rituximab

Arm description:

Active treatment arm

Arm type	Experimental
Investigational medicinal product name	Rituximab (MabThera)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received two doses of rituximab (1000 mg) by intravenous infusion given with IV methylprednisolone (100 mg) at 2 week intervals at T=0 (Day 1) and T=2 (Day 15). This was repeated at T=24 weeks (Day 168) and T=26 weeks (Day 182).

Arm title	Placebo
Arm description:	
Control arm. Saline IV.	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Patients received two doses of placebo by intravenous infusion given with IV methylprednisolone (100 mg) at 2 week intervals at T=0 (Day 1) and T=2 (Day 15). This was repeated at T=24 weeks (Day 168) and T=26 weeks (Day 182).

Number of subjects in period 1	Rituximab	Placebo
Started	67	66
Completed	63	58
Not completed	4	8
Consent withdrawn by subject	3	7
Lost to follow-up	1	1

Baseline characteristics

Reporting groups

Reporting group title	Rituximab
Reporting group description:	
Active treatment arm	
Reporting group title	Placebo
Reporting group description:	
Control arm. Saline IV.	

Reporting group values	Rituximab	Placebo	Total
Number of subjects	67	66	133
Age categorical			
Units: Subjects			
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	52	51	103
From 65-84 years	15	15	30
85 years and over	0	0	0
Age continuous			
Units: years			
median	55	53.5	
full range (min-max)	34 to 80	28 to 76	-
Gender categorical			
Units: Subjects			
Female	63	61	124
Male	4	5	9
Years since diagnosis			
Units: Years			
median	3.8	4.8	
full range (min-max)	0 to 20	0 to 22	-
Unstimulated Salivary Flow			
Units: mL/15 mins			
median	0.8	0.74	
full range (min-max)	0 to 6.6	0 to 11.8	-
Total Schirmers			
Lachrymal Flow, defined as the total of Schirmer test results from Left and Right eyes.			
Units: mm/5 min			
median	6	8	
full range (min-max)	0 to 80	0 to 95	-
Fatigue - Visual Analogue Scale (VAS)			
Patient response to Visual Analogue Scale question "Mark on the line to represent the level of fatigue (tiredness) that you have experienced on average over the past 2 weeks." Range: 0=No Fatigue, 100=Severe Fatigue. Two participants (1 RTX, 1PLC) did not complete the VAS at baseline. Hence data is on 65 placebo participants, and 66 rituximab participants.			
Units: mm			
median	74	76	
full range (min-max)	29 to 99	35 to 100	-
Oral Dryness Visual Analogue Scale (VAS)			

Patient response to Visual Analogue Scale question "Mark on the line to represent the level of oral dryness that you have experienced on average over the past 2 weeks." Range: 0=No oral dryness, 100=Severe oral dryness. Two participants (1 RTX, 1PLC) did not complete the VAS at baseline. Hence data is on 65 placebo participants, and 66 rituximab participants.			
Units: mm			
median	75	82	
full range (min-max)	38 to 100	15 to 100	-
Ocular Dryness Visual Analogue Scale (VAS)			
Patient response to the visual analogue scale question "Mark on the line to represent the level of ocular dryness that you have experienced on average over the past 2 weeks." Range: 0=No ocular dryness, 100=Severe oral dryness. Three participants (1 RTX, 2 PLC) did not complete the VAS at baseline. Hence data is on 64 placebo participants, and 66 rituximab participants.			
Units: mm			
median	72	74.5	
full range (min-max)	2 to 100	15 to 100	-

Subject analysis sets

Subject analysis set title	Intention-To-Treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intention-to-treat analysis dataset comprised all participants randomised into the trial, included in the group to which they had been assigned, regardless of treatment adherence or attending follow-up.

For the primary endpoint analysis, multiple imputation was used to ensure that any patients with incomplete data could be included in the final analysis

Reporting group values	Intention-To-Treat		
Number of subjects	133		
Age categorical			
Units: Subjects			
Adolescents (12-17 years)	0		
Adults (18-64 years)	103		
From 65-84 years	30		
85 years and over	0		
Age continuous			
Units: years			
median	54		
full range (min-max)	28 to 80		
Gender categorical			
Units: Subjects			
Female	124		
Male	9		
Years since diagnosis			
Units: Years			
median			
full range (min-max)			
Unstimulated Salivary Flow			
Units: mL/15 mins			
median	0.76		
full range (min-max)	0 to 11.8		
Total Schirmers			

Lachrymal Flow, defined as the total of Schirmer test results from Left and Right eyes.			
Units: mm/5 min			
median	8		
full range (min-max)	0 to 95		
Fatigue - Visual Analogue Scale (VAS)			
Patient response to Visual Analogue Scale question "Mark on the line to represent the level of fatigue (tiredness) that you have experienced on average over the past 2 weeks." Range: 0=No Fatigue, 100=Severe Fatigue. Two participants (1 RTX, 1PLC) did not complete the VAS at baseline. Hence data is on 65 placebo participants, and 66 rituximab participants.			
Units: mm			
median	74		
full range (min-max)	29 to 100		
Oral Dryness Visual Analogue Scale (VAS)			
Patient response to Visual Analogue Scale question "Mark on the line to represent the level of oral dryness that you have experienced on average over the past 2 weeks." Range: 0=No oral dryness, 100=Severe oral dryness. Two participants (1 RTX, 1PLC) did not complete the VAS at baseline. Hence data is on 65 placebo participants, and 66 rituximab participants.			
Units: mm			
median	78		
full range (min-max)	15 to 100		
Ocular Dryness Visual Analogue Scale (VAS)			
Patient response to the visual analogue scale question "Mark on the line to represent the level of ocular dryness that you have experienced on average over the past 2 weeks." Range: 0=No ocular dryness, 100=Severe oral dryness. Three participants (1 RTX, 2 PLC) did not complete the VAS at baseline. Hence data is on 64 placebo participants, and 66 rituximab participants.			
Units: mm			
median	73.5		
full range (min-max)	2 to 100		

End points

End points reporting groups

Reporting group title	Rituximab
Reporting group description:	
Active treatment arm	
Reporting group title	Placebo
Reporting group description:	
Control arm. Saline IV.	
Subject analysis set title	Intention-To-Treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intention-to-treat analysis dataset comprised all participants randomised into the trial, included in the group to which they had been assigned, regardless of treatment adherence or attending follow-up.

For the primary endpoint analysis, multiple imputation was used to ensure that any patients with incomplete data could be included in the final analysis

Primary: Treatment response

End point title	Treatment response

End point description:

Treatment response: a patient has responded to treatment if, at Week 48, the patient has reported either:
* a relative 30% reduction from baseline in fatigue (VAS); or
* a relative 30% reduction from baseline in oral dryness (VAS).

For example: a patient whose fatigue changes from 90 at baseline to 62 at week 48 has achieved 31.1% reduction in fatigue, and so has achieved treatment response, regardless of change in oral dryness over the same period. A patient whose fatigue and oral dryness change from 80 to 57 and from 70 to 50 has achieved reductions of 28.8% and 28.6% respectively, and so has not achieved treatment response.

End point type	Primary

End point timeframe:

Randomisation to 48 weeks

End point values	Rituximab	Placebo	Intention-To-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	61[1]	56[2]	117[3]	
Units: Patients				
Responded	24	21	45	
No response	37	35	72	

Notes:

[1] - Prior to imputation, 61 patients had complete data to derive the primary endpoint.

[2] - Prior to imputation, 56 patients had complete data to derive the primary endpoint.

[3] - Prior to imputation, 117 patients had complete data to derive the primary endpoint.

Statistical analyses

Statistical analysis title	Primary endpoint analysis

Statistical analysis description:

Missing data: missing fatigue and oral dryness VAS scores imputed using Fully Conditional Specification. 16 fully-imputed datasets analysed individually, and resulting parameter estimates combined. All 133

participants included in this analysis.

Adjusted analysis: adjusted for age category (18-64, 65-80), years since diagnosis (0-9, 10+), consent for ultrasound substudy (Yes, No) consent for biopsy substudy (Yes, No) all as fixed effects, and randomising centre as a random effect.

Comparison groups	Rituximab v Placebo
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.76
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	2.55

Notes:

[4] - The primary endpoint analysis was performed on the full trial population of 133 patients, after multiple imputation was used to impute missing fatigue and oral dryness data at baseline and Week 48.

Secondary: Fatigue VAS score

End point title	Fatigue VAS score

End point description:

Patient response to VAS question "Mark on the line to represent the level of fatigue (tiredness) that you have experienced on average over the past 2 weeks." 0=No fatigue, 100=Severe fatigue.

End point type	Secondary

End point timeframe:

VAS Score - Range 0 - 100 mm evaluated at baseline and weeks 16, 24, 36 and 48.

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67[5]	66[6]		
Units: mm				
least squares mean (confidence interval 95%)	67.9 (61.3 to 74.4)	65.8 (59.3 to 72.2)		

Notes:

[5] - All participants were included in the mixed model, even if data was not fully complete at all visits

[6] - All participants were included in the mixed model, even if data was not fully complete at all visits

Statistical analyses

Statistical analysis title	Fatigue VAS at Week 48

Statistical analysis description:

Differences in Least-Squares Means of baseline-adjusted Fatigue VAS at Week 48. Result of covariance-pattern type mixed effects model. Fixed effects: baseline fatigue, randomised treatment, timepoint, treat-by-time interaction, age category, disease duration, consent to two substudies. Random effects: patient and patient-by-timepoint. Unstructured covariance pattern used.

Comparison groups	Rituximab v Placebo

Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6053
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.9
upper limit	10.1

Secondary: Oral Dryness VAS Score

End point title	Oral Dryness VAS Score

End point description:

Patient response to VAS question "Mark on the line to represent the level of oral dryness that you have experienced on average over the past 2 weeks." 0=No oral dryness, 100=Severe oral dryness.

End point type	Secondary

End point timeframe:

VAS Score range 0 - 100 mm evaluated at baseline and weeks 16, 24, 36 and 48.

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67[7]	66[8]		
Units: mm				
least squares mean (confidence interval 95%)	66.4 (59.2 to 73.7)	70.5 (64.5 to 76.4)		

Notes:

[7] - All participants were included in the mixed model, even if data was not fully complete at all visits

[8] - All participants were included in the mixed model, even if data was not fully complete at all visits

Statistical analyses

Statistical analysis title	Oral Dryness VAS at Week 48

Statistical analysis description:

Differences in Least-Squares Means of baseline-adjusted Oral Dryness VAS at Week 48. Result of covariance pattern type mixed effects model. Fixed effects: baseline oral dryness, randomised treatment, timepoint, treat-by-time interaction, age category, disease duration, consent to two substudies. Random effects: patient and patient-by-timepoint. Unstructured covariance pattern used.

Comparison groups	Rituximab v Placebo
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3157
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-4.06

Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.01
upper limit	3.89

Secondary: Ocular Dryness VAS Score

End point title	Ocular Dryness VAS Score
End point description:	

Patient response to VAS question "Mark on the line to represent the level of ocular dryness that you have experienced on average over the past 2 weeks." 0=No ocular dryness, 100=Severe ocular dryness.

End point type	Secondary
End point timeframe:	

VAS Score - Range 0 - 100 mm evaluated at baseline and weeks 16, 24, 36 and 48.

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67[9]	66[10]		
Units: mm				
least squares mean (confidence interval 95%)	61.5 (54.2 to 68.8)	66.1 (59.1 to 73)		

Notes:

[9] - All participants were included in the mixed model, even if data was not fully complete at all visits

[10] - All participants were included in the mixed model, even if data was not fully complete at all visits

Statistical analyses

Statistical analysis title	Ocular dryness VAS at Week 48
Statistical analysis description:	

Differences in Least-Squares Means of baseline-adjusted Ocular dryness VAS at Week 48. Result of covariance pattern type mixed effects model. Fixed effects: baseline ocular dryness, randomised treatment, timepoint, treat-by-time interaction, age category, disease duration, consent to two substudies. Random effects: patient and patient-by-timepoint. Unstructured covariance pattern used.

Comparison groups	Rituximab v Placebo
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2963
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.1
upper limit	4

Secondary: Patient global assessment VAS Score

End point title	Patient global assessment VAS Score

End point description:

Patient response to VAS question "Taking everything into account (pain, fatigue and surface dryness) please mark on the line the level of disease activity that you have experienced on average over the past 2 weeks.." 0=SS inactive, 100=SS very active.

End point type	Secondary

End point timeframe:

VAS Score - Range 0 - 100 mm evaluated at baseline and weeks 16, 24, 36 and 48.

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67[11]	66[12]		
Units: mm				
least squares mean (confidence interval 95%)	64.9 (58.1 to 71.7)	64.1 (57.7 to 70.5)		

Notes:

[11] - All participants were included in the mixed model, even if data was not fully complete at all visits

[12] - All participants were included in the mixed model, even if data was not fully complete at all visits

Statistical analyses

Statistical analysis title	Patient Global Assessment VAS at Week 48

Statistical analysis description:

Differences in Least-Squares Means of baseline-adjusted pt global assessment VAS at Week 48. Result of covariance pattern type mixed effects model. Fixed effects: baseline global assessment, randomised treatment, timepoint, treat-by-time interaction, age category, disease duration, consent to two substudies. Random effects: patient and patient-by-timepoint. Unstructured covariance pattern used.

Comparison groups	Rituximab v Placebo
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8475
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.2
upper limit	8.7

Secondary: Physician global assessment: disease activity

End point title	Physician global assessment: disease activity

End point description:

Physician response to the question
Please indicate, according to your clinical experience, the level of disease activity over the past two weeks in this patient. (Range 0=Inactive disease, 10=Very highly active disease

End point type	Secondary

End point timeframe:

Disease activity assessment evaluated at baseline and weeks 16, 24, 36 and 48.

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59[13]	57[14]		
Units: mm				
median (full range (min-max))	2 (0 to 8)	3 (0 to 7)		

Notes:

[13] - 59 participants attended the Week 48 visit for this question to be answered.

[14] - 57 patients attended the Week 48 visit for this question to be answered.

Statistical analyses

No statistical analyses for this end point

Secondary: Salivary Flow - unstimulated

End point title	Salivary Flow - unstimulated

End point description:

Total Salivary flow over 15minutes. Values were transformed by $y=\log[2](x+0.1)$ for analysis, and the estimates back-transformed for reporting. Accordingly arithmetic means of log-values become geometric means, and differences in log values become ratios.

End point type	Secondary

End point timeframe:

Performed at screening, 16, 24, 36 and 48 weeks.

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67[15]	66[16]		
Units: mL				
least squares mean (confidence interval 95%)	1 (0.8 to 1.3)	0.6 (0.4 to 0.8)		

Notes:

[15] - All participants were included in the mixed model, even if data was not fully complete at all visits

[16] - All participants were included in the mixed model, even if data was not fully complete at all visits

Statistical analyses

Statistical analysis title	Unstimulated Salivary Flow at Week 48

Statistical analysis description:

(Back-transformed) Differences in Least-Squares Means of baseline-adjusted log-USF at Week 48. Result of covariance pattern type mixed effects model. Fixed effects: baseline log-USF, randomised treatment, timepoint, treat-by-time interaction, age category, disease duration, consent to two

substudies. Random effects: patient and patient-by-timepoint. Unstructured covariance pattern used.

Comparison groups	Rituximab v Placebo
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0015
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	2.4

Secondary: Salivary flow - stimulated

End point title	Salivary flow - stimulated

End point description:

Total salivary flow (stimulated by citric acid) over 5 minutes. Prior to analysis, data was logarithm transformed by $y=\log[2](x+0.1)$ to produce a more normal distribution. Results have been back-transformed, so that arithmetic means of logged variables become geometric means, and differences in means of logged variables become ratios.

End point type	Secondary

End point timeframe:

Performed at baseline, 16, 24, 36 and 48 weeks.

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67[17]	66[18]		
Units: mL				
least squares mean (confidence interval 95%)	2.5 (1.9 to 3.1)	2.1 (1.6 to 2.6)		

Notes:

[17] - All participants were included in the mixed model, even if data was not fully complete at all visits

[18] - All participants were included in the mixed model, even if data was not fully complete at all visits

Statistical analyses

Statistical analysis title	Stimulated Salivary Flow at Week 48

Statistical analysis description:

(Back-transformed) Differences in Least-Squares Means of baseline-adjusted log-Stimulated Salivary Flow at Week 48. Result of covariance pattern type mixed effects model. Fixed effects: baseline log(SSF), randomised treatment, timepoint, treat-by-time interaction, age category, disease duration, consent to two substudies. Random effects: patient and patient-by-timepoint. Unstructured covariance pattern used.

Comparison groups	Rituximab v Placebo

Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2487
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.6

Secondary: Lachrymal Flow

End point title	Lachrymal Flow

End point description:

Mean Lachrymal flow from both left and right eyes over 5minutes. Values were transformed by $y=\log_2(x+1)$ for analysis, and the
estimates back-transformed for reporting. Accordingly arithmetic means of log-values become geometric means, and differences in log values become ratios.

End point type	Secondary

End point timeframe:

Schirmers I test of ocular function performed at baseline, 16, 24, 36 and 48 weeks.

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67[19]	66[20]		
Units: mm				
least squares mean (confidence interval 95%)	4.5 (3.5 to 5.9)	3.9 (3 to 5.1)		

Notes:

[19] - All participants were included in the mixed model, even if data was not fully complete at all visits

[20] - All participants were included in the mixed model, even if data was not fully complete at all visits

Statistical analyses

Statistical analysis title	Mean Lachrymal Flow at Week 48

Statistical analysis description:

(Back-transformed) Differences in Least-Squares Means of baseline-adjusted log-mean-lachrymal-flow at Week 48. Result of covariance pattern type mixed effects model. Fixed effects: baseline log-mean-lachrymal-flow, randomised treatment, timepoint, treat-by-time interaction, age category, disease duration, consent to two substudies. Random effects: patient and patient-by-timepoint. Unstructured covariance pattern used.

Comparison groups	Rituximab v Placebo

Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3698
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.6

Secondary: ESSPRI - EULAR Sjogren's Syndrome Patient Reported Index

End point title	ESSPRI - EULAR Sjogren's Syndrome Patient Reported Index

End point description:

Patient-completed ESSPRI questionnaire.

End point type	Secondary

End point timeframe:

Quality of Life evaluated at baseline and weeks 16, 24, 36 and 48.

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	66		
Units: point				
least squares mean (confidence interval 95%)	6.3 (5.7 to 6.9)	5.7 (5.2 to 6.2)		

Statistical analyses

Statistical analysis title	ESSPRI at Week 48

Statistical analysis description:

Differences in Least-Squares Means of baseline-adjusted ESSPRI at Week 48. Result of covariance pattern type mixed effects model. Fixed effects: baseline ESSPRI, randomised treatment, timepoint, treat-by-time interaction, age category, disease duration, consent to two substudies. Random effects: patient and patient-by-timepoint. Unstructured covariance pattern used.

Comparison groups	Rituximab v Placebo
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1087
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.54

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	1.2

Secondary: ESSDAI - EULAR Sjogren's Syndrome Disease Activity Index

End point title	ESSDAI - EULAR Sjogren's Syndrome Disease Activity Index

End point description:

Prior to analysis, data was logarithm transformed by $y=\log[2](x+1)$ to produce a more normal distribution. Results have been back transformed, so that arithmetic means of logged variables become geometric means, and differences in means of logged variables become ratios.

End point type	Secondary

End point timeframe:

Evaluated at baseline and weeks 16, 24, 36 and 48.

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	66		
Units: point				
least squares mean (confidence interval 95%)	3.4 (2.7 to 4.3)	4.5 (3.5 to 5.8)		

Statistical analyses

Statistical analysis title	ESSDAI at Week 48

Statistical analysis description:

(Back-transformed) Differences in Least-Squares Means of baseline-adjusted log-ESSDAI at Week 48. Result of covariance pattern type mixed effects model. Fixed effects: baseline log(ESSDAI), randomised treatment, timepoint, treat-by-time interaction, age category, disease duration, consent to two substudies. Random effects: patient and patient-by-timepoint. Unstructured covariance pattern used.

Comparison groups	Rituximab v Placebo
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0721
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.03

Secondary: SF-36 - Physical Component Summary

End point title	SF-36 - Physical Component Summary
End point description:	
SF36 v2 (UK version). Range 0=Greatest disability, 100=Least disability.	
End point type	Secondary
End point timeframe:	
Evaluated at baseline and weeks 24 and 48.	

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	66		
Units: point				
least squares mean (confidence interval 95%)	37.1 (34.9 to 39.3)	37.9 (35.8 to 40)		

Statistical analyses

Statistical analysis title	SF36 Physical Component Summary Score at Week 48
Statistical analysis description:	
Differences in Least-Squares Means of baseline-adjusted SF36 PCS at Week 48. Result of covariance pattern type mixed effects model. Fixed effects: baseline SF36-PCS, randomised treatment, timepoint, treat-by-time interaction, age category, disease duration, consent to two substudies. Random effects: patient and patient-by-timepoint. Unstructured covariance pattern used.	
Comparison groups	Placebo v Rituximab
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5246
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	1.7

Secondary: SF36 - Mental Component Summary

End point title	SF36 - Mental Component Summary
End point description:	

End point type	Secondary

End point timeframe:

Evaluated at baseline and weeks 24 and 48.

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	66		
Units: point				
least squares mean (confidence interval 95%)	41.1 (38.1 to 44.1)	41 (37.8 to 44.2)		

Statistical analyses

Statistical analysis title	SF36-Mental Component Summary at Week 48

Statistical analysis description:

Differences in Least-Squares Means of baseline-adjusted SF36-MCS at Week 48. Result of covariance pattern type mixed effects model. Fixed effects: baseline SF36-MCS, randomised treatment, timepoint, treat-by-time interaction, age category, disease duration, consent to two substudies. Random effects: patient and patient-by-timepoint. Unstructured covariance pattern used.

Comparison groups	Rituximab v Placebo
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9495
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6
upper limit	3.8

Secondary: Physician global assessment: disease damage

End point title	Physician global assessment: disease damage

End point description:

Grading the possible disease-related damage in the present patient from 0 (completely absent) to 10 (maximum of possible damage), please score the level of damage/inability by using the scale below.

End point type	Secondary

End point timeframe:

Disease damage assessment evaluated at baseline and weeks 24 and 48.

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60[21]	57[22]		
Units: Point				
median (full range (min-max))	2 (0 to 7)	2 (0 to 8)		

Notes:

[21] - 60 patients attended Week 48 and had complete data for this endpoint

[22] - 57 patients attended Week 48 and had complete data for this endpoint

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:	
Randomisation to 30 days following the last administration of rituximab/placebo.	
Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

All participants randomised to receive placebo. All such participants received at least one placebo infusion.

Reporting group title	Rituximab

Reporting group description:

Among all participants randomised to receive rituximab, 2 withdrew from treatment prior to first infusion, but are counted here as exposed. One of these two experienced an SAE, which is reported here.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Leeds Clinical Trials Research is an academic trials unit where full MedDRA coding of non-serious adverse
events is not the standard. It has therefore not been possible for adverse event data to be accurately entered into the full data view within EudraCT as all mandatory categories cannot be completed.

Serious adverse events	Placebo	Rituximab	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 66 (13.64%)	9 / 67 (13.43%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events		0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic carcinoma			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anaphylactic reaction			
subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			

subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders

Myocardial infarction

subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders

Diarrhoea

subjects affected / exposed	1 / 66 (1.52%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abdominal pain

subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Echinococciasis

subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders

Pulmonary embolism

subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Epiglottitis

subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Skin and subcutaneous tissue disorders

Skin cancer

subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal and urinary disorders

Cystoscopy

Additional description: Cystoscopy and TVT Release

subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urinary tract infection

subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders

Fracture

subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ankle deformity

subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chest pain

subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations

Pneumonia

subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sepsis

subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lower respiratory tract infection			
subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypotension			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Rituximab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 April 2011	Protocol v3.0 - 10 March 2011 The eligibility criteria was updated to include the following: Deletion of the word 'hydroxychloroquine' and addition of the following text: Patients on corticosteroids, NSAIDS, antidepressants, methotrexate, or pilocarpine*** must have been on a stable dose for 4 weeks prior to receiving the first infusion of study medication and expected to remain on this dose throughout the study. Addition of new inclusion criteria: Patients who are on hydroxychloroquine at screening must have been on a stable dose throughout the preceding six-month period. If they have stopped hydroxychloroquine they should have been off it for at least 3 months prior to receiving study medication. Addition of the following text: Use of DMARDs, immunosuppressant therapies or antidepressants within 4 weeks prior to the first dose administration (except for glucocorticoids, salicylates, non-steroidal anti inflammatory drugs (NSAIDs), methotrexate and analgesics which are acceptable) Addition of the following text: Any malignancies that would normally preclude the use of rituximab within the past 5 years, including solid tumours, haematological malignancies and carcinoma in situ (except basal cell or squamous cell carcinoma of the skin that has been excised and cured) Addition of the following text: History of moderate to severe congestive heart failure according to the New York Heart Association (NYHA) functional classification system (see Appendix C) or other uncontrolled heart disease, or who have a clinically significant abnormal ECG at the time of screening. Change in rituximab stock supply (from commercial to trial stock) Added requirement to monitor all pregnancies, suspected pregnancies and pregnancies occurring in participants of the study or in the female partners of male participants from time of patient randomisation 'until 30 days following the last administration of rituximab/placebo' must be reported immediately to the CTR

12 July 2012	Protocol version 4.0 dated 29 May 2012. Addition of T-cell sub-study Added new text: T-Cell sub-study Central analysis of local and systemic T-cell abnormalities in PSS and their response to B-cell depletion: • To compare peripheral blood T-cell transcriptional signatures in PSS patients with healthy and disease controls (comparator datasets held in Addenbrooke's Hospital, Cambridge (see Section 12.9)). • To compare peripheral blood T-cell transcriptional signatures in PSS patients pre- and post- B-cell depletion (these analyses will be performed on samples from patients who have received rituximab, once the trial allocations have been unblinded by CTRU at the end of the trial). • To characterise tissue distribution, phenotype, and gene expression of lesional T-cells in PSS patients pre- and post-B-cell depletion (these analyses will be performed on samples from patients who have received rituximab, once the trial allocations have been unblinded by CTRU at the end of the trial). Screening assessment changed from 14 to 28 days from the start of treatment. Eligibility criteria amended to extended list of DMARDs used to include – hydroxychloroquine, azathioprine, MMF, leflunomide, ciclosporing etc.and criteria that if patiens have stopped any of these drugs, they should have stopped these for at least 4 weeks prior to receiving the study medication. Any history of other autoimmune diseases or other form of immunodeficiency or neutropaenia <1.5 x 10^9/L – added new text (unless a diagnosis of benign ethnic neutropaenia has been confirmed i.e. neutrophil count 2.4 & 3.0 x 10^9/L for female Jamaican and Afro-Caribbean populations respectively. Added use of Participant Identification Centres (PICs) to help with recruitment.
06 March 2013	Protocol version 5.0 dated 13 February 2013. Added new safety information to Patient Information Sheet as follows: 'Rituximab use has been associated with severe blister like skin reactions, known as Toxic Epidermal Necrolysis and Stevens-Johnson syndrome, which have on very rare occasions been fatal.' Amended eligibility criteria as follows: Use of DMARS, Use of DMARDs, immunosuppressant therapies or antidepressants within 4 weeks prior to the first dose administration (except for glucocorticoids, salicylates, non-steroidal anti inflammatory drugs (NSAIDs), methotrexate and analgesics which are acceptable). Any history of other autoimmune diseases or other form of immunodeficiency or neutropaenia <1.5 x 10^9/L (unless a diagnosis of benign ethnic neutropaenia has been confirmed i.e. neutrophil count 2.4 & 3.0 x 10^9/L for female Jamaican and Afro-Caribbean populations respectively (60) Immunodeficiency or neutropaenia <1.5 x 10^9/L (unless a diagnosis of benign ethnic neutropaenia has been made in which case the neutrophil count must be > 0.9 x 10^9/L at screening for Jamaican and Afro-Caribbean populations).
24 January 2014	Protocol version 6.0 dated 20 December 2013. Added a more flexible way in which the End of Treatment (Week 48) Patient Questionnaire can be collected for patients who withdraw or are unwilling to return to the local clinics for a final visit. These patients were given the option of completing the questionnaires at home and posting them back to the local clinic. Also, a Patient follow up letter was added to remind patients to return for their End of Treatment Visit.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported