Clinical trial results:
B-cell depleting therapy (rituximab) as a treatment for fatigue in primary biliary cirrhosis

Summary

EudraCT number	2012-000145-12
Trial protocol	GB
Global end of trial date	12 September 2016

Results information

Result version number	v1 (current)
This version publication date	01 February 2018
First version publication date	01 February 2018

Trial information

Trial identification

Sponsor protocol code	5997

Additional study identifiers

ISRCTN number	ISRCTN03978701
ClinicalTrials.gov id (NCT number)	NCT02376335
WHO universal trial number (UTN)	-
Other trial identifiers	REC reference: 12/NE/0095

Notes:

Sponsors

Sponsor organisation name	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Sponsor organisation address	Level 1 Regent Point, Regent Point Road, Newcastle upon Tyne, United Kingdom, NE3 3HD
Public contact	Professor David E Jones, Newcastle University, 44 0191 2087572, david.jones@ncl.ac.uk
Scientific contact	Professor David E Jones, Newcastle University, 44 0191 2087572, david.jones@ncl.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	14 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 September 2016
Global end of trial reached?	Yes
Global end of trial date	12 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of B-cell depleting therapy in Primary Biliary Cirrhosis patients followed up for 12 months.
1. Does Rituximab therapy significantly improve the fatigue experienced by patients with PBC?
2. Does any improvement in fatigue result from a reduction in the PDH-directed antibody response in PBC and the effects that these antibodies have on muscle cell energy generation?
3. What is the safety profile of Rituximab therapy in patients with PBC?
4. How sustained is any effect of Rituximab on fatigue?

Protection of trial subjects:

No actions required.

Background therapy:

Ursodeoxycholic acid (UDCA) therapy was permitted. Usual dose was 12-15mg/kg body weight which was taken once daily although some patients took it in split dose as long as they took the total of the above calculated dose.

Evidence for comparator:

This was a placebo controlled study.

Actual start date of recruitment	01 October 2012
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: 57
Worldwide total number of subjects	57
EEA total number of subjects	57

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)	52
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited to the study between 01 October 2012 and 01 October 2015. Participants were identified either through routine clinic outpatient appointments by their treating physician at Newcastle, by their treating physician through Patient Identification Centres (PICs) in the NE region or through the UKPBC platform.

Pre-assignment

Screening details:

Screening assessments of potential participants took place at the Clinical Research Facility in Newcastle and had to occur within 4 weeks prior to baseline. An eligibility screening form was completed to document participants' fulfilment of the entry criteria for all patients considered for the study and subsequently included or excluded.

Period 1

Period 1 title	Randomisation
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Randomisation was a web based system on a 1:1 ratio (rituximab:placebo) using random-permuted blocks with random block length. The treatment arm was kept blinded from the subjects, investigators and study assessors until study completion. The randomisation system generated a treatment arm for each participant that linked to the corresponding allocated study drug (blinded).

Arms

Are arms mutually exclusive?	Yes
Arm title	Rituximab

Arm description:

Rituximab (1000mg IV) infusion on days 1 and 15

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

Dosage and administration details:

1000mg IV on days 1 and 15. First infusion at an initial rate of 50mg/h; after first 30 minutes it could be escalated in 50mg/h increments every 30 minutes, to a maximum of 400mg/h. Second dose could be infused at an initial rate of 100mg/h, and increased by 100mg/h at 30 min intervals to a max of 400mg/h.

Arm title	Placebo

Arm description:

Placebo (0.9% sodium chloride 250ml.) infusion on days 1 and 15

Arm type	Placebo
Investigational medicinal product name	N/A
Investigational medicinal product code	
Other name	Saline
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

250ml IV infusion on days 1 and 15

Number of subjects in period 1	Rituximab	Placebo
Started	29	28
Completed	29	28

Period 2

Period 2 title	Randomisation to first IMP infusion
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

As Period 1

Arms

Are arms mutually exclusive?	Yes
Arm title	Rituximab

Arm description:

Rituximab (1000mg IV) infusion on days 1 and 15

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

Dosage and administration details:

1000mg IV on days 1 and 15. First infusion at an initial rate of 50mg/h; after first 30 minutes it could be escalated in 50mg/h increments every 30 minutes, to a maximum of 400mg/h. Second dose could be infused at an initial rate of 100mg/h, and increased by 100mg/h at 30 min intervals to a max of 400mg/h.

Arm title	Placebo

Arm description:

Placebo (0.9% sodium chloride 250ml.) infusion on days 1 and 15

Arm type	Placebo
Investigational medicinal product name	N/A
Investigational medicinal product code	
Other name	Saline
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

250ml IV infusion on days 1 and 15

Number of subjects in period 2	Rituximab	Placebo
Started	29	28
Completed	27	28
Not completed	2	0
Consent withdrawn by subject	1	-
Lost to follow-up	1	-

Period 3	
Period 3 title	First IMP infusion to 12 week visit
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

As Period 1

Arms	
Are arms mutually exclusive?	Yes
Arm title	Rituximab

Arm description:

Rituximab (1000mg IV) infusion on days 1 and 15

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

Dosage and administration details:

1000mg IV on days 1 and 15. First infusion at an initial rate of 50mg/h; after first 30 minutes it could be escalated in 50mg/h increments every 30 minutes, to a maximum of 400mg/h. Second dose could be infused at an initial rate of 100mg/h, and increased by 100mg/h at 30 min intervals to a max of 400mg/h.

Arm title	Placebo

Arm description:

Placebo (0.9% sodium chloride 250ml.) infusion on days 1 and 15

Arm type	Placebo
Investigational medicinal product name	N/A
Investigational medicinal product code	
Other name	Saline
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

250ml IV infusion on days 1 and 15

Number of subjects in period 3	Rituximab	Placebo
Started	27	28
Completed	27	28

Period 4	
Period 4 title	12 week visit to 6 month visit
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

As Period 1

Arms	
Are arms mutually exclusive?	Yes
Arm title	Rituximab

Arm description:

Rituximab (1000mg IV) infusion on days 1 and 15

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

Dosage and administration details:

1000mg IV on days 1 and 15. First infusion at an initial rate of 50mg/h; after first 30 minutes it could be escalated in 50mg/h increments every 30 minutes, to a maximum of 400mg/h. Second dose could be infused at an initial rate of 100mg/h, and increased by 100mg/h at 30 min intervals to a max of 400mg/h.

Arm title	Placebo

Arm description:

Placebo (0.9% sodium chloride 250ml.) infusion on days 1 and 15

Arm type	Placebo
Investigational medicinal product name	N/A
Investigational medicinal product code	
Other name	Saline
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

250ml IV infusion on days 1 and 15

Number of subjects in period 4	Rituximab	Placebo
Started	27	28
Completed	27	28

Period 5	
Period 5 title	6 month visit to 9 month visit
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

As Period 1

Arms	
Are arms mutually exclusive?	Yes
Arm title	Rituximab

Arm description:

Rituximab (1000mg IV) infusion on days 1 and 15

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

Dosage and administration details:

1000mg IV on days 1 and 15. First infusion at an initial rate of 50mg/h; after first 30 minutes it could be escalated in 50mg/h increments every 30 minutes, to a maximum of 400mg/h. Second dose could be infused at an initial rate of 100mg/h, and increased by 100mg/h at 30 min intervals to a max of 400mg/h.

Arm title	Placebo

Arm description:

Placebo (0.9% sodium chloride 250ml.) infusion on days 1 and 15

Arm type	Placebo
Investigational medicinal product name	N/A
Investigational medicinal product code	
Other name	Saline
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

250ml IV infusion on days 1 and 15

Number of subjects in period 5	Rituximab	Placebo
Started	27	28
Completed	26	28
Not completed	1	0
Lost to follow-up	1	-

Period 6

Period 6 title	9 month visit to 12 month visit
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

As Period 1

Arms

Are arms mutually exclusive?	Yes
Arm title	Rituximab

Arm description:

Rituximab (1000mg IV) infusion on days 1 and 15

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

Dosage and administration details:

1000mg IV on days 1 and 15. First infusion at an initial rate of 50mg/h; after first 30 minutes it could be escalated in 50mg/h increments every 30 minutes, to a maximum of 400mg/h. Second dose could be infused at an initial rate of 100mg/h, and increased by 100mg/h at 30 min intervals to a max of 400mg/h.

Arm title	Placebo

Arm description:

Placebo (0.9% sodium chloride 250ml.) infusion on days 1 and 15

Arm type	Placebo
Investigational medicinal product name	N/A
Investigational medicinal product code	
Other name	Saline
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

250ml IV infusion on days 1 and 15

Number of subjects in period 6	Rituximab	Placebo
Started	26	28
Completed	24	26
Not completed	2	2
Trial terminated early	2	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Rituximab
Reporting group description:	
Rituximab (1000mg IV) infusion on days 1 and 15	
Reporting group title	Placebo
Reporting group description:	
Placebo (0.9% sodium chloride 250ml.) infusion on days 1 and 15	

Reporting group values	Rituximab	Placebo	Total
Number of subjects	29	28	57
Age categorical Units: Subjects			
Adults (18-64 years)	26	25	51
From 65-84 years	2	2	4
Not recorded	1	1	2
Age continuous Units: years			
median	55.9	53.3	
inter-quartile range (Q1-Q3)	48.8 to 60.0	49.9 to 58.8	-
Gender categorical Units: Subjects			
Female	28	27	55
Male	1	1	2
Ethnicity Units: Subjects			
White	27	28	55
Non-white	1	0	1
Not recorded	1	0	1
Smoking history Units: Subjects			
Never	16	12	28
Past	7	8	15
Current	6	8	14
Patient location			
Managed by Newcastle CRESTA centre for at least 1 year			
Units: Subjects			
Number of patients managed for at least 1 year	20	19	39
Number of patients not managed for at least 1 year	9	9	18
UDCA use			
Whether patients use UDCA			
Units: Subjects			
Use UDCA	24	27	51
Do not use UDCA	5	1	6
UDCA Responder			
Patients using UDCA, number who are responders			

Units: Subjects			
UDCA Responder	19	16	35
UDCA non-responder	5	11	16
Non UDCA user	5	1	6
Alcohol consumption			
Alcohol consumption all (including non-drinkers) units per week Units per week - drinkers: Rituximab n=17 (median=4, (IQR=2-8)) Placebo n=9 (median 4, (IQR=2-12)			
Units: Units per week (including non-drinkers)			
median	1	0	
inter-quartile range (Q1-Q3)	0 to 4	0 to 1.5	-
BMI			
Body Mass Index			
Units: Scale			
median	28.7	26.7	
inter-quartile range (Q1-Q3)	24.5 to 30.5	22.9 to 30.7	-
UK PBC risk score at 10 years			
UK PBC risk score at 10 years Number of patients for whom UK PBC risk score at 10 years available: Rituximab: 25 Placebo: 27			
Units: Scale score			
median	1.26	1.75	
inter-quartile range (Q1-Q3)	0.94 to 1.74	1.12 to 3.04	-

End points

End points reporting groups

Reporting group title	Rituximab

Reporting group description:
Rituximab (1000mg IV) infusion on days 1 and 15

Reporting group title	Placebo

Reporting group description:
Placebo (0.9% sodium chloride 250ml.) infusion on days 1 and 15

Reporting group title	Rituximab

Reporting group description:
Rituximab (1000mg IV) infusion on days 1 and 15

Reporting group title	Placebo

Reporting group description:
Placebo (0.9% sodium chloride 250ml.) infusion on days 1 and 15

Reporting group title	Rituximab

Reporting group description:
Rituximab (1000mg IV) infusion on days 1 and 15

Reporting group title	Placebo

Reporting group description:
Placebo (0.9% sodium chloride 250ml.) infusion on days 1 and 15

Reporting group title	Rituximab

Reporting group description:
Rituximab (1000mg IV) infusion on days 1 and 15

Reporting group title	Placebo

Reporting group description:
Placebo (0.9% sodium chloride 250ml.) infusion on days 1 and 15

Reporting group title	Rituximab

Reporting group description:
Rituximab (1000mg IV) infusion on days 1 and 15

Reporting group title	Placebo

Reporting group description:
Placebo (0.9% sodium chloride 250ml.) infusion on days 1 and 15

Reporting group title	Rituximab

Reporting group description:
Rituximab (1000mg IV) infusion on days 1 and 15

Reporting group title	Placebo

Reporting group description:
Placebo (0.9% sodium chloride 250ml.) infusion on days 1 and 15

Primary: Fatigue severity in PBC patients at 3 months

End point title	Fatigue severity in PBC patients at 3 months

End point description:

End point type	Primary

End point timeframe:
12 weeks (3 months)

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28		
Units: Scale Score				
arithmetic mean (standard deviation)	36.2 (± 8.4)	38.1 (± 8.7)		

Statistical analyses

Statistical analysis title	Adjusted mean difference of PBC-40 fatigue domain
Statistical analysis description:	
Adjusted mean difference of PBC-40 fatigue domain at 3 months between Rituximab and placebo arms	
Comparison groups	Rituximab v Placebo
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %

Secondary: Fatigue severity in PBC patients at 6 months

End point title	Fatigue severity in PBC patients at 6 months
End point description:	
Fatigue severity in PBC patients, assessed using the fatigue domain score of the PBC-40, a fully validated, psychometrically robust, disease specific quality of life measure, evaluated at baseline and 12 weeks, 6, 9 and 12 months (PBC-40 fatigue domain score >33 at outset).	
End point type	Secondary
End point timeframe:	
Patients with non-missing PBC-40 fatigue domain data at both baseline and 6 months	

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28		
Units: Scale Score				
arithmetic mean (standard deviation)	36.6 (± 7.6)	39.9 (± 7.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Fatigue severity in PBC patients at 9 months

End point title	Fatigue severity in PBC patients at 9 months

End point description:

End point type	Secondary

End point timeframe:

Patients with non-missing PBC-40 fatigue domain data at both baseline and 9 months

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	28		
Units: Scale Score				
arithmetic mean (standard deviation)	38.1 (± 8.3)	39.6 (± 8.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Fatigue severity in PBC patients at 12 months

End point title	Fatigue severity in PBC patients at 12 months

End point description:

End point type	Secondary

End point timeframe:

Patients with non-missing PBC-40 fatigue domain data at both baseline and 12 months

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	26		
Units: Scale Score				
arithmetic mean (standard deviation)	39.5 (± 8.2)	39.6 (± 6.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Symptom severity score for itch domain of PBC-40 questionnaire at 12 weeks

End point title	Symptom severity score for itch domain of PBC-40 questionnaire at 12 weeks
End point description:	
Symptom severity score for itch domain of PBC-40 questionnaire at 12 weeks	
End point type	Secondary
End point timeframe:	
Patients with non-missing PBC-40 itch domain data at both baseline and 12 week visits	

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28		
Units: Scale Score				
arithmetic mean (standard deviation)	4.5 (± 2.8)	5.5 (± 3.5)		

Statistical analyses

Statistical analysis title	Adjusted mean difference of PBC-40 itch domain
Statistical analysis description:	
Adjusted mean difference of PBC-40 itch domain at 3 months between Rituximab and placebo arms	
Comparison groups	Rituximab v Placebo
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	1.8

Secondary: Symptom severity score for itch domain of PBC-40 questionnaire at 6 months

End point title	Symptom severity score for itch domain of PBC-40 questionnaire at 6 months
End point description:	
End point type	Secondary
End point timeframe:	
Patients with non-missing PBC-40 itch domain data at both baseline and 6 month visits	

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28		
Units: Scale Score				
arithmetic mean (standard deviation)	4.3 (± 2.7)	6.4 (± 3.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Symptom severity score for itch domain of PBC-40 questionnaire at 9 months

End point title	Symptom severity score for itch domain of PBC-40 questionnaire at 9 months

End point description:

End point type	Secondary

End point timeframe:

Patients with non-missing PBC-40 itch domain data at both baseline and 9 month visits

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28		
Units: Scale Score				
arithmetic mean (standard deviation)	4.4 (± 3.1)	6.4 (± 3.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Symptom severity score for itch domain of PBC-40 questionnaire at 12 months

End point title	Symptom severity score for itch domain of PBC-40 questionnaire at 12 months

End point description:

End point type	Secondary

End point timeframe:

Patients with non-missing PBC-40 itch domain data at both baseline and 12 month visits

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	26		
Units: Scale Score				
arithmetic mean (standard deviation)	4.7 (± 3.8)	6.2 (± 3.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Symptom severity score for cognitive domain of PBC-40 questionnaire at 3 months

End point title	Symptom severity score for cognitive domain of PBC-40 questionnaire at 3 months
End point description:	
Symptom severity score for cognitive domain of PBC-40 questionnaire.	
End point type	Secondary
End point timeframe:	
Patients with non-missing PBC-40 cognitive domain data at both baseline and 3 month visits.	

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28		
Units: Scale Score				
arithmetic mean (standard deviation)	19.3 (± 4.0)	18.3 (± 5.7)		

Statistical analyses

Statistical analysis title	Adjusted mean difference PBC-40 cognitive domain
Statistical analysis description:	
Adjusted mean difference of PBC-40 cognitive domain at 3 months between Rituximab and placebo arms	
Comparison groups	Rituximab v Placebo
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Regression, Linear
Parameter estimate	Median difference (final values)
Point estimate	0.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	3.3

Secondary: Symptom severity score for cognitive domain of PBC-40 questionnaire at 9 months

End point title	Symptom severity score for cognitive domain of PBC-40 questionnaire at 9 months

End point description:

End point type	Secondary

End point timeframe:

Patients with non-missing PBC-40 cognitive domain data at both baseline and 9 month visits.

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	28		
Units: Scale Score				
arithmetic mean (standard deviation)	19.2 (± 4.5)	19.0 (± 4.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Symptom severity score for cognitive domain of PBC-40 questionnaire at 12 months

End point title	Symptom severity score for cognitive domain of PBC-40 questionnaire at 12 months

End point description:

End point type	Secondary

End point timeframe:

Patients with non-missing PBC-40 cognitive domain data at both baseline and 12 month visits

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	26		
Units: Scale Score				
arithmetic mean (standard deviation)	19.6 (± 3.0)	20.0 (± 4.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Symptom severity score for social domain of PBC-40 questionnaire at 12 weeks

End point title	Symptom severity score for social domain of PBC-40 questionnaire at 12 weeks

End point description:

End point type	Secondary

End point timeframe:

Patients with non-missing PBC-40 social domain data at both baseline and 12 weeks visit

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28		
Units: Scale Score				
arithmetic mean (standard deviation)	32.6 (± 7.1)	30.8 (± 7.4)		

Statistical analyses

Statistical analysis title	Adjusted mean difference of PBC-40 social domain

Statistical analysis description:

Adjusted mean difference of PBC-40 social domain at 3 months between Rituximab and placebo arms

Comparison groups	Rituximab v Placebo
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	5

Secondary: Symptom severity score for social domain of PBC-40 questionnaire at 6 months

End point title	Symptom severity score for social domain of PBC-40 questionnaire at 6 months

End point description:

End point type	Secondary

End point timeframe:

Patients with non-missing PBC-40 social domain data at both baseline and 6 month visits

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28		
Units: Scale Score				
arithmetic mean (standard deviation)	31.9 (± 8.3)	32.9 (± 8.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Symptom severity score for social domain of PBC-40 questionnaire at 9 months

End point title	Symptom severity score for social domain of PBC-40 questionnaire at 9 months

End point description:

End point type	Secondary

End point timeframe:

Patients with non-missing PBC-40 social domain data at both baseline and 9 month visits

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	28		
Units: Scale Score				
arithmetic mean (standard deviation)	32.2 (± 7.6)	31.3 (± 8.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Symptom severity score for social domain of PBC-40 questionnaire at 12 months

End point title	Symptom severity score for social domain of PBC-40 questionnaire at 12 months

End point description:

End point type	Secondary

End point timeframe:

Patients with non-missing PBC-40 social domain data at both baseline and 12 month visits

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	26		
Units: Scale Score				
arithmetic mean (standard deviation)	32.5 (± 7.6)	30.3 (± 7.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Symptom severity score for emotional domain of PBC-40 at 12 weeks

End point title	Symptom severity score for emotional domain of PBC-40 at 12 weeks

End point description:

End point type	Secondary

End point timeframe:

Patients with non-missing PBC-40 social emotional data at both baseline and 12 week visits

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28		
Units: Scale Score				
arithmetic mean (standard deviation)	9.3 (± 3.3)	9.0 (± 3.2)		

Statistical analyses

Statistical analysis title	Adjusted mean difference PBC-40 emotional domain

Statistical analysis description:

Adjusted mean difference of PBC-40 emotional domain at 3 months between Rituximab and placebo arms

Comparison groups	Placebo v Rituximab
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	2

Secondary: Symptom severity score for emotional domain of PBC-40 at 6 months

End point title	Symptom severity score for emotional domain of PBC-40 at 6 months

End point description:

End point type	Secondary

End point timeframe:

Patients with non-missing PBC-40 social emotional data at both baseline and 6 months

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28		
Units: Scale Score				
arithmetic mean (standard deviation)	9.3 (± 3.5)	9.6 (± 3.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Symptom severity score for emotional domain of PBC-40 at 9 months

End point title	Symptom severity score for emotional domain of PBC-40 at 9 months

End point description:

End point type	Secondary

End point timeframe:

Patients with non-missing PBC-40 social emotional data at both baseline and 9 months

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	28		
Units: Scale Score				
arithmetic mean (standard deviation)	9.1 (± 3.5)	9.6 (± 3.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Symptom severity score for emotional domain of PBC-40 at 12 months

End point title	Symptom severity score for emotional domain of PBC-40 at 12 months

End point description:

End point type	Secondary

End point timeframe:

Patients with non-missing PBC-40 social emotional data at both baseline and 12 months

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	25		
Units: Scale Score				
arithmetic mean (standard deviation)	9.0 (± 2.9)	9.1 (± 3.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Symptom severity for other symptoms domain of PBC-40 at 12 weeks

End point title	Symptom severity for other symptoms domain of PBC-40 at 12 weeks

End point description:

End point type	Secondary

End point timeframe:

Patients with non-missing PBC-40 other symptoms domain data at both baseline and 12 week visits

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28		
Units: Scale Score				
arithmetic mean (standard deviation)	16.9 (± 3.7)	17.6 (± 3.3)		

Statistical analyses

Statistical analysis title	Adjusted mean difference PBC-40 symptoms domain
Statistical analysis description:	
Adjusted mean difference of PBC-40 symptoms domain at 3 months between Rituximab and placebo arms	
Comparison groups	Rituximab v Placebo
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	1.5

Secondary: Symptom severity for other symptoms domain of PBC-40 at 6 months

End point title	Symptom severity for other symptoms domain of PBC-40 at 6 months
End point description:	
End point type	Secondary
End point timeframe:	
Patients with non-missing PBC-40 other symptoms domain data at both baseline and 6 month visits	

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28		
Units: Scale Score				
arithmetic mean (standard deviation)	18.2 (± 4.9)	18.2 (± 3.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Symptom severity for other symptoms domain of PBC-40 at 9 months

End point title	Symptom severity for other symptoms domain of PBC-40 at 9 months

End point description:

End point type	Secondary

End point timeframe:

Patients with non-missing PBC-40 other symptoms domain data at both baseline and 9 months

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	28		
Units: Scale Score				
arithmetic mean (standard deviation)	17.8 (± 5.1)	18.1 (± 4.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Symptom severity for other symptoms domain of PBC-40 at 12 months

End point title	Symptom severity for other symptoms domain of PBC-40 at 12 months

End point description:

End point type	Secondary

End point timeframe:

Patients with non-missing PBC-40 other symptoms domain data at both baseline and 12 month visits

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	26		
Units: Scale Score				
arithmetic mean (standard deviation)	18.5 (± 4.7)	18.9 (± 4.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: ESS at 12 weeks

End point title	ESS at 12 weeks
End point description:	
Epworth Sleepiness Scale (ESS) score to assess daytime somnolence at baseline, 12 weeks, 6, 9 and 12 months	
End point type	Secondary
End point timeframe:	
Patients with non missing data at both baseline and 12 week visits	

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	28		
Units: Scale Score				
arithmetic mean (standard deviation)	10.9 (± 6.1)	11.9 (± 5.1)		

Statistical analyses

Statistical analysis title	Adjusted mean difference of ESS domain
Statistical analysis description:	
Adjusted mean difference of ESS domain at 3 months between Rituximab and placebo arms	
Comparison groups	Rituximab v Placebo
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	1.6

Secondary: ESS at 6 months

End point title	ESS at 6 months

End point description:

End point type	Secondary

End point timeframe:

ESS score at 6 months

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	27		
Units: Scale Score				
arithmetic mean (standard deviation)	11.4 (± 5.5)	12.6 (± 5.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: ESS at 9 months

End point title	ESS at 9 months

End point description:

End point type	Secondary

End point timeframe:

ESS score at 9 months

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	28		
Units: Scale Score				
arithmetic mean (standard deviation)	10.8 (± 5.9)	13.3 (± 5.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: ESS at 12 months	
End point title	ESS at 12 months
End point description:	
End point type	Secondary
End point timeframe:	
ESS score at 9 months	

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	26		
Units: Scale Score				
arithmetic mean (standard deviation)	11.2 (± 5.8)	11.8 (± 4.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: OGS at 12 weeks	
End point title	OGS at 12 weeks
End point description:	
Orthostatic Grading Scale (OGS) score to assess vasomotor autonomic symptoms at baseline, 12 weeks, 6, 9 and 12 months	
End point type	Secondary
End point timeframe:	
OGS score at 12 weeks	

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	28		
Units: Scale Score				
arithmetic mean (standard deviation)	4.7 (± 4.0)	4.8 (± 4.1)		

Statistical analyses

Statistical analysis title	Adjusted mean difference of OGS domain
Statistical analysis description:	
Adjusted mean difference of OGS domain at 3 months between Rituximab and placebo arms	
Comparison groups	Rituximab v Placebo

Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	1.9

Secondary: OGS at 6 months

End point title	OGS at 6 months

End point description:

End point type	Secondary

End point timeframe:

OGS score at 6 months

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: Scale Score				
arithmetic mean (standard deviation)	5.5 (± 4.1)	5.7 (± 4.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: OGS at 9 months

End point title	OGS at 9 months

End point description:

End point type	Secondary

End point timeframe:

OGS score at 9 months

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	28		
Units: Scale Score				
arithmetic mean (standard deviation)	5.7 (± 4.0)	5.4 (± 3.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: OGS at 12 months

End point title	OGS at 12 months

End point description:

End point type	Secondary

End point timeframe:

OGS score at 12 months

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	25		
Units: Scale Score				
arithmetic mean (standard deviation)	4.7 (± 4.1)	5.8 (± 4.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: PROMIS-HAQ at 6 months

End point title	PROMIS-HAQ at 6 months

End point description:

End point type	Secondary

End point timeframe:

6 months

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	27		
Units: Scale Score				
arithmetic mean (standard deviation)	11.2 (± 11.2)	16.5 (± 14.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: PROMIS-HAQ at 9 months

End point title	PROMIS-HAQ at 9 months

End point description:

End point type	Secondary

End point timeframe:

9 months

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	28		
Units: Scale Score				
arithmetic mean (standard deviation)	12.4 (± 10.5)	17.0 (± 17.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: PROMIS-HAQ at 12 months

End point title	PROMIS-HAQ at 12 months

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	26		
Units: Sclae Score				
arithmetic mean (standard deviation)	12.6 (± 11.1)	16.5 (± 15.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: COGFAIL at 12 weeks

End point title	COGFAIL at 12 weeks
End point description:	
Cognitive Failure questionnaire score at baseline, 12 weeks, 6, 9 and 12 months	
End point type	Secondary
End point timeframe:	
COGFAIL Score at 12 weeks	

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	28		
Units: Scale Score				
arithmetic mean (standard deviation)	59.7 (± 14.7)	52.9 (± 17.2)		

Statistical analyses

Statistical analysis title	Adjusted mean difference of COGFAIL domain
Statistical analysis description:	
Adjusted mean difference of COGFAIL domain at 3 months between Rituximab and placebo arms	
Comparison groups	Rituximab v Placebo
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.7
upper limit	8.6

Secondary: COGFAIL at 6 months

End point title	COGFAIL at 6 months

End point description:

End point type	Secondary

End point timeframe:
6 months

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	26		
Units: Sclae Score				
arithmetic mean (standard deviation)	57.6 (± 15.7)	54.2 (± 19.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: COGFAIL at 9 months

End point title	COGFAIL at 9 months

End point description:

End point type	Secondary

End point timeframe:
9 months

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	28		
Units: Scale Score				
arithmetic mean (standard deviation)	57.1 (± 16.2)	54.4 (± 20.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: COGFAIL at 12 months	
End point title	COGFAIL at 12 months
End point description:	
End point type	Secondary
End point timeframe:	
12 months	

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	26		
Units: Scale Score				
arithmetic mean (standard deviation)	57.8 (± 14.7)	55.7 (± 17.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: HADS at 12 weeks	
End point title	HADS at 12 weeks
End point description:	
Hospital Anxiety and Depression Scale (HADS) score to assess depressive and anxiety-related symptoms at baseline, 12 weeks, 6, 9 and 12 months	
End point type	Secondary
End point timeframe:	
HADS score at 12 weeks	

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	28		
Units: Scale Score				
arithmetic mean (standard deviation)	12.4 (± 6.5)	12.3 (± 6.7)		

Statistical analyses

Statistical analysis title	Adjusted mean difference of HADS domain
Statistical analysis description:	
Adjusted mean difference of HADS domain at 3 months between Rituximab and placebo arms	
Comparison groups	Rituximab v Placebo

Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.8
upper limit	1.2

Secondary: HADS at 6 months

End point title	HADS at 6 months

End point description:

End point type	Secondary

End point timeframe:

6 months

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: Scale Score				
arithmetic mean (standard deviation)	13.8 (± 7.9)	14.0 (± 7.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: HADS at 9 months

End point title	HADS at 9 months

End point description:

End point type	Secondary

End point timeframe:

9 months

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	26		
Units: Scale Score				
arithmetic mean (standard deviation)	13.7 (± 8.6)	14.2 (± 7.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: HADS at 12 months

End point title	HADS at 12 months

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	25		
Units: Scale Score				
arithmetic mean (standard deviation)	13.0 (± 6.6)	13.0 (± 7.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Average perceived fatigue score at 12 weeks

End point title	Average perceived fatigue score at 12 weeks

End point description:

Average perceived fatigue score calculated from participant held diaries at baseline, 12 weeks, 6, 9 and 12 months. The diaries measure fatigue using a scale of 1 to 6, where 1 represents no fatigue and 6 represents extreme fatigue.

End point type	Secondary

End point timeframe:

12 weeks

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	20		
Units: Scale Score				
arithmetic mean (standard deviation)	3.51 (± 1.04)	3.59 (± 1.11)		

Statistical analyses

Statistical analysis title	Adjusted mean difference of fatigue diary score
Statistical analysis description: Adjusted mean difference of fatigue diary score at 3 months between Rituximab and placebo arms	
Comparison groups	Rituximab v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.7

Secondary: Average perceived fatigue score at 6 months

End point title	Average perceived fatigue score at 6 months
End point description:	
End point type	Secondary
End point timeframe: 6 months	

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	20		
Units: Scale Score				
arithmetic mean (standard deviation)	3.34 (± 1.07)	3.79 (± 1.10)		

Statistical analyses

No statistical analyses for this end point

Secondary: Average perceived fatigue score at 9 months

End point title	Average perceived fatigue score at 9 months

End point description:

End point type	Secondary

End point timeframe:
9 months

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	20		
Units: Scale Score				
arithmetic mean (standard deviation)	3.48 (± 1.15)	3.61 (± 1.07)		

Statistical analyses

No statistical analyses for this end point

Secondary: Average perceived fatigue score at 12 months

End point title	Average perceived fatigue score at 12 months

End point description:

End point type	Secondary

End point timeframe:
12 months

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	18		
Units: Scale Score				
arithmetic mean (standard deviation)	3.8 (± 1.09)	3.77 (± 0.97)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: PROMIS-HAQ at 12 weeks

End point title	PROMIS-HAQ at 12 weeks

End point description:	
Patient-Reported Outcomes Measurement Information System Health Assessment Questionnaire (PROMIS-HAQ) to assess functional status at baseline, 12 weeks, 6, 9 and 12 months	
End point type	Other pre-specified
End point timeframe:	
12 weeks	

End point values	Rituximab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	28		
Units: Scale Score				
arithmetic mean (standard deviation)	13.7 (± 14.0)	14.0 (± 13.1)		

Statistical analyses

Statistical analysis title	Adjusted mean difference of PROMIS-HAQ
Statistical analysis description:	
Adjusted mean difference of PROMIS-HAQ domain at 3 months between Rituximab and placebo arms	
Comparison groups	Rituximab v Placebo
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	7.3

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All non serious adverse events were reported from visit 2 until visit 19 (final study visit at 12 months). Serious Adverse Events (SAEs) were reported throughout the study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	None
Dictionary version	1.0

Reporting groups

Reporting group title	Rituximab

Reporting group description:

Rituximab (1000mg IV) infusion on days 1 and 15

Reporting group title	Placebo

Reporting group description:

Placebo (0.9% sodium chloride 250ml.) infusion on days 1 and 15

Serious adverse events	Rituximab	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 29 (0.00%)	2 / 28 (7.14%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Abdominal pain			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Neuritis	Additional description: Right optic neuritis followed by left optic neuritis.		
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Rituximab	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 29 (93.10%)	28 / 28 (100.00%)	
Surgical and medical procedures			
Coronary angiogram			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Carpal tunnel operation left hand			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Adverse reaction to flu jab (bilateral swelling arms)			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Fall			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Vacant memory			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	3 / 29 (10.34%)	4 / 28 (14.29%)	
occurrences (all)	5	4	
Extreme fatigue			
subjects affected / exposed	2 / 29 (6.90%)	1 / 28 (3.57%)	
occurrences (all)	4	2	
Restless feeling			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Itching of head and throat			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Erythema at cannula site			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Insomnia			

subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Tooth extraction			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Facial flushing			
subjects affected / exposed	7 / 29 (24.14%)	3 / 28 (10.71%)	
occurrences (all)	7	4	
Hot flushes			
subjects affected / exposed	2 / 29 (6.90%)	3 / 28 (10.71%)	
occurrences (all)	2	3	
Facial rash			
subjects affected / exposed	0 / 29 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
Facial spots			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Hiatus hernia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Lethargy			
subjects affected / exposed	2 / 29 (6.90%)	0 / 28 (0.00%)	
occurrences (all)	2	0	
Tremulous			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Severe hot flushes			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
shivering			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Shaking to body			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Feeling sluggish			

subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Systemic itch			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Blocked nose			
subjects affected / exposed	1 / 29 (3.45%)	1 / 28 (3.57%)	
occurrences (all)	2	1	
Running nose			
subjects affected / exposed	2 / 29 (6.90%)	2 / 28 (7.14%)	
occurrences (all)	2	2	
Sore throat			
subjects affected / exposed	5 / 29 (17.24%)	7 / 28 (25.00%)	
occurrences (all)	6	7	
Cold/sore throat			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Flu like symptoms			
subjects affected / exposed	4 / 29 (13.79%)	1 / 28 (3.57%)	
occurrences (all)	4	1	
Cough and cold			
subjects affected / exposed	3 / 29 (10.34%)	0 / 28 (0.00%)	
occurrences (all)	3	0	
Common cold			
subjects affected / exposed	5 / 29 (17.24%)	1 / 28 (3.57%)	
occurrences (all)	5	1	
Cough			
subjects affected / exposed	1 / 29 (3.45%)	4 / 28 (14.29%)	
occurrences (all)	1	4	
Dry cough			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Chesty cough			

subjects affected / exposed	0 / 29 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
Chest tightness with wheeze			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Productive cough			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Coryzal symptoms			
subjects affected / exposed	1 / 29 (3.45%)	1 / 28 (3.57%)	
occurrences (all)	1	1	
Nasal congestion			
subjects affected / exposed	3 / 29 (10.34%)	1 / 28 (3.57%)	
occurrences (all)	3	1	
Nose bleed			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Increased effort to breathe			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 29 (3.45%)	1 / 28 (3.57%)	
occurrences (all)	1	1	
Low mood			
subjects affected / exposed	2 / 29 (6.90%)	1 / 28 (3.57%)	
occurrences (all)	2	1	
Depression			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Bruising and lacerations to right calf			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			

Syncopal disorder			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Paroxysmal atrial fibrillation			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Lightheaded			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Tachycardia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Vasovagal syncope			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Hypotension			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Heavy feeling/dull ache to chest			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 29 (44.83%)	10 / 28 (35.71%)	
occurrences (all)	22	14	
Migraine			
subjects affected / exposed	0 / 29 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			
Swollen ankles			
subjects affected / exposed	2 / 29 (6.90%)	0 / 28 (0.00%)	
occurrences (all)	2	0	
Numb hands			

subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Neutropenia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Low HB			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Haemangioma			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Right sore ear			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	2 / 29 (6.90%)	5 / 28 (17.86%)	
occurrences (all)	2	7	
Sinusitis			
subjects affected / exposed	0 / 29 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
Vertigo			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	2	0	
Ringing in ears			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Eye disorders			
Calcium deposits to right eye			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Diabetic Macularaedema Right Eye			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Glaucoma			

subjects affected / exposed	2 / 29 (6.90%)	0 / 28 (0.00%)	
occurrences (all)	2	0	
Right Eye Infection			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Tired eyes			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Bleed in left eye			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal bloating			
subjects affected / exposed	3 / 29 (10.34%)	1 / 28 (3.57%)	
occurrences (all)	3	1	
Abdominal cramps			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Vomited			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Mild abdominal pains			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Rectal bleeding			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Colic pain			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
subjects affected / exposed	1 / 29 (3.45%)	1 / 28 (3.57%)	
occurrences (all)	1	1	
Acid reflux			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	

Diarrhoea			
subjects affected / exposed	7 / 29 (24.14%)	2 / 28 (7.14%)	
occurrences (all)	7	2	
Nausea			
subjects affected / exposed	6 / 29 (20.69%)	6 / 28 (21.43%)	
occurrences (all)	7	8	
Nausea and vomiting			
subjects affected / exposed	2 / 29 (6.90%)	0 / 28 (0.00%)	
occurrences (all)	2	0	
Nausea and diarrhoea			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Tiredness			
subjects affected / exposed	1 / 29 (3.45%)	2 / 28 (7.14%)	
occurrences (all)	2	2	
Loss of appetite			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Lower abdominal pain			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Loose stool			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Indigestion			
subjects affected / exposed	3 / 29 (10.34%)	1 / 28 (3.57%)	
occurrences (all)	3	1	
Stomach pain			
subjects affected / exposed	0 / 29 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
Stomach ache			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Right upper quadrant pain			
subjects affected / exposed	1 / 29 (3.45%)	1 / 28 (3.57%)	
occurrences (all)	1	1	

Skin and subcutaneous tissue disorders			
Sensitivity of skin			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Worsening skin irritation to hands and arms			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Lichen planus	Additional description: Mouth		
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Reaction to local anaesthetic			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	3	
Eczema			
subjects affected / exposed	0 / 29 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
Patches dry/flaky skin			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Itch			
subjects affected / exposed	1 / 29 (3.45%)	3 / 28 (10.71%)	
occurrences (all)	1	3	
Itchy legs			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Itchy on left hand			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Cold sore			
subjects affected / exposed	2 / 29 (6.90%)	2 / 28 (7.14%)	
occurrences (all)	2	3	
Rash			

subjects affected / exposed	2 / 29 (6.90%)	2 / 28 (7.14%)	
occurrences (all)	2	2	
Tingling in right arm and jaw			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
4 small cyst-type growths on upper and lower lids, left eye			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Skin erythema			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Redness/Itchiness to stomach			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Hyperthyroidism			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Renal and urinary disorders			
UTI			
subjects affected / exposed	4 / 29 (13.79%)	0 / 28 (0.00%)	
occurrences (all)	5	0	
Frequency urine			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Query scaphoid bone fracture			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Bruising left knee			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Aches and pains			
subjects affected / exposed	2 / 29 (6.90%)	2 / 28 (7.14%)	
occurrences (all)	2	2	
Aching muscles			

subjects affected / exposed	0 / 29 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
Arthritic pain			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Backache			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Restless leg			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	2	0	
Bruised ribs secondary to fall			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Swelling to right clavicle			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Muscle ache			
subjects affected / exposed	1 / 29 (3.45%)	1 / 28 (3.57%)	
occurrences (all)	2	1	
Painful ribs			
subjects affected / exposed	0 / 29 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	3	
Pain to both breasts			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Painful left knee			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Painful right knee			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Right sided muscular pain			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Painful legs			

subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Leg cramp			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Left Tennis Elbow			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Plantar fibromatosis, right foot			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Right sided swelling below clavicle			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Right sided shoulder pain			
subjects affected / exposed	1 / 29 (3.45%)	1 / 28 (3.57%)	
occurrences (all)	1	1	
Lower back pain			
subjects affected / exposed	1 / 29 (3.45%)	1 / 28 (3.57%)	
occurrences (all)	1	1	
Neck and back pain			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Fracture Right Radial			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Painful left ankle			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Pain knuckles			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Pain and burning feeling to muscles			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Right ankle sprain			

subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Pulled muscle (intercostals, right side)			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Right foot tenderness			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Right shoulder tenderness			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Joint aches			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Joint pains			
subjects affected / exposed	1 / 29 (3.45%)	1 / 28 (3.57%)	
occurrences (all)	1	1	
Cramp in hands			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Broken wrist			
subjects affected / exposed	1 / 29 (3.45%)	1 / 28 (3.57%)	
occurrences (all)	1	1	
Whiplash			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Infections and infestations			
Mouth ulcer			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Thrush (vaginal)			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Infection to right calf			

subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Swollen neck glands			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Swollen throat glands			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Swollen glands and sore throat			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Itch to insect bite left leg			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Gum infection			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Tooth pain			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Tooth infection			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Tooth abscess			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Flu virus			
subjects affected / exposed	3 / 29 (10.34%)	0 / 28 (0.00%)	
occurrences (all)	3	0	
Chest infection			
subjects affected / exposed	0 / 29 (0.00%)	7 / 28 (25.00%)	
occurrences (all)	0	7	
Viral illness			
subjects affected / exposed	1 / 29 (3.45%)	1 / 28 (3.57%)	
occurrences (all)	1	1	
Shingles			

subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Low iron			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Vitamin D deficiency			
subjects affected / exposed	0 / 29 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 March 2013	Addition of Expression of Interest Form, inclusion of Patient Identification Centres, change to Clinical Research Facility Rituximab Infusion Guidelines (protocol appendix 5) and amended Fatigue Diary (protocol appendix 4).
10 December 2013	Addition of random lipid profile blood tests, addition of Urea and Electrolyte blood tests and clarification of placebo in protocol. Change to SmPC in appendix 1 (dated 04/12/2013).
10 December 2014	Change to inclusion criteria for women - contraception should be continued for 12 months in line with updated SmPC rather than 3 months. SmPC updated in appendix 1 (dated 06/06/2014). Clarification regarding Hepatitis B, HBV serology and Hepatitis B serology.
21 September 2015	6-month extension, amended study population and power, addition of UKPBC platform and additional administrative changes to protocol, PIS and ICF.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported