



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 | |
| 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 (\pm 2.8) | 5.5 (\pm 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 (\pm 2.7) | 6.4 (\pm 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 (\pm 3.1) | 6.4 (\pm 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 (\pm 3.8) | 6.2 (\pm 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 (\pm 4.0) | 18.3 (\pm 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 (\pm 3.5) | 9.6 (\pm 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 (\pm 2.9) | 9.1 (\pm 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 (\pm 5.8) | 11.8 (\pm 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 (\pm 4.0) | 4.8 (\pm 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 (\pm 4.0) | 5.4 (\pm 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 (\pm 4.1) | 5.8 (\pm 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 (\pm 11.2) | 16.5 (\pm 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 (\pm 10.5) | 17.0 (\pm 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 (\pm 11.1) | 16.5 (\pm 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 (\pm 14.7) | 52.9 (\pm 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 (\pm 1.04) | 3.59 (\pm 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 (\pm 1.07) | 3.79 (\pm 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 (\pm 1.15) | 3.61 (\pm 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 (\pm 1.09) | 3.77 (\pm 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 (\pm 14.0) | 14.0 (\pm 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 occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 28 (3.57%) 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 occurrences (all) | 0 / 29 (0.00%) 0 | 2 / 28 (7.14%) 2 | |
| Chest tightness with wheeze subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 28 (0.00%) 0 | |
| Productive cough subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 28 (0.00%) 0 | |
| Coryzal symptoms subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 1 / 28 (3.57%) 1 | |
| Nasal congestion subjects affected / exposed occurrences (all) | 3 / 29 (10.34%) 3 | 1 / 28 (3.57%) 1 | |
| Nose bleed subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 28 (0.00%) 0 | |
| Increased effort to breathe subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 28 (3.57%) 1 | |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 1 / 28 (3.57%) 1 | |
| Low mood subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 2 | 1 / 28 (3.57%) 1 | |
| Depression subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 28 (3.57%) 1 | |
| Injury, poisoning and procedural complications Bruising and lacerations to right calf subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 28 (0.00%) 0 | |
| Cardiac disorders | | | |

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

| | | | |
|--|---------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 28 (3.57%) 1 | |
| Neutropenia subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 28 (0.00%) 0 | |
| Low HB subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 28 (0.00%) 0 | |
| Haemangioma subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 28 (3.57%) 1 | |
| Ear and labyrinth disorders Right sore ear subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 28 (3.57%) 1 | |
| Dizziness subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 2 | 5 / 28 (17.86%) 7 | |
| Sinusitis subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 2 / 28 (7.14%) 2 | |
| Vertigo subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 2 | 0 / 28 (0.00%) 0 | |
| Ringling in ears subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 28 (3.57%) 1 | |
| Eye disorders Calcium deposits to right eye subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 28 (3.57%) 1 | |
| Diabetic Maculara edema Right Eye subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 28 (3.57%) 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 occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 28 (0.00%) 0 | |
| Metabolism and nutrition disorders | | | |
| Low iron | | | |
| subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 28 (3.57%) 1 | |
| Vitamin D deficiency | | | |
| subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 2 / 28 (7.14%) 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