

# Rituximab in patients with primary Sjögren's syndrome

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		<input checked="" type="checkbox"/> Protocol
<b>Registration date</b> 09/07/2010	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan
		<input checked="" type="checkbox"/> Results
<b>Last Edited</b> 16/03/2017	<b>Condition category</b> Musculoskeletal Diseases	<input type="checkbox"/> Individual participant data

**Plain English summary of protocol**  
Not provided at time of registration

## Contact information

**Type(s)**  
Scientific

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## Additional identifiers

**Protocol serial number**  
RR10/9389

## Study information

**Scientific Title**  
A randomised double blind placebo controlled clinical trial of anti-B-cell therapy in patients with primary Sjögren's syndrome

**Acronym**  
TRACTISS

**Study objectives**

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

**Ethics approval required**

Old ethics approval format

**Ethics approval(s)**

Leeds West Ethics Committee on 25/10/2010; Protocol version 3.0 approved on 12/04/2011

**Primary study design**

Interventional

**Study design**

Multicentre randomised double-blind placebo controlled phase III trial

**Study type(s)**

Treatment

**Health condition(s) or problem(s) studied**

Primary Sjögren's syndrome (PSS)

**Interventions**

Patients will receive two doses of rituximab (1000 mg) or placebo by intravenous (IV) infusion given with IV methylprednisolone (100 mg) at 2 week intervals at T = 0 and T = 2 weeks. This will be repeated at T = 24 weeks and T = 26 weeks.

**Intervention Type**

Drug

**Phase**

Phase III

**Drug/device/biological/vaccine name(s)**

Rituximab, methylprednisolone

**Primary outcome(s)**

A 30% reduction at 48 weeks from baseline in either oral dryness or fatigue measured using visual analogue scales (VAS; range 0 - 100 mm)

**Key secondary outcome(s)**

1. Fatigue (VAS Score; range 0 - 100 mm), evaluated at baseline and weeks 16, 24, 36 and 48
2. Oral dryness (VAS Score; range 0 - 100 mm), evaluated at baseline and weeks 16, 24, 36 and 48
3. Ocular dryness (VAS Score; range 0 - 100 mm), evaluated at baseline and weeks 16, 24, 36 and 48
4. Patient global assessments (VAS Score; range 0 - 100 mm), evaluated at baseline and weeks 16, 24, 36 and 48

5. Physician global assessments (VAS Score; range 0 - 100 mm), evaluated at baseline and weeks 16, 24, 36 and 48
6. Salivary flow (stimulated and unstimulated salivary flow), performed at baseline, 16, 24, 36 and 48 weeks
7. Lachrymal flow (Schirmers I test of ocular function), performed at baseline, 16, 24, 36 and 48 weeks
8. Quality of life, evaluated at baseline and 16, 24, 36 and 48 weeks using the EULAR Sjögrens Syndrome Patient Reported Index (ESSPRI)
9. Quality of life, disease damage and disease activity indices, evaluated at baseline, 24 and 48 weeks using the following:
  - 9.1. Sjögrens Syndrome Disease Damage Index (SSDDI)
  - 9.2. Social Security Disability Insurance (SSDI)
  - 9.3. EULAR Sjögrens Syndrome Disease Activity Index (ESSDAI)
  - 9.4. Sjögrens Syndrome Disease Activity Index (SSDAI)
  - 9.5. Sjögrens Systemic Clinical Activity Index (SCAI)
  - 9.6. 36-item Short Form Health Survey (SF-36)
  - 9.7. Profile of Fatigue and Discomfort/Sicca Symptoms Inventory (PROFAD-SSI)
10. Serological and peripheral blood inflammatory features (haematology biochemistry, serology and immunology assays), taken at baseline, weeks 16, 24, 26, 36 and 48
11. Incremental cost-effectiveness ratio (EQ-5D, health economics) evaluated at baseline, weeks 24 and 48

### **Completion date**

01/07/2013

## **Eligibility**

### **Key inclusion criteria**

Current inclusion criteria as of 20/09/2011:

1. Aged between 18 and 80 years of age.
2. A confirmed diagnosis of primary Sjögrens syndrome by AECG criteria (see Appendix B).
3. Positive for anti-Ro auto-antibodies.
4. Patients with a diagnosis of primary Sjögrens syndrome (by AECG criteria) with more than 10 years disease duration must have at least one systemic feature of:
  - 4.1 Hypergammaglobulinaemia (IgG over 16)\*, or
  - 4.2 Low complement C4\*, or
  - 4.3 Cryoglobulinaemia
 OR
  - 4.4 Active/past history since diagnosis of the following (ascribed to Sjögrens Syndrome):
  - 4.5 purpura/cutaneous vasculitis,
  - 4.6 lymphadenopathy,
  - 4.7 persistent parotid salivary gland swelling not due to infection,
  - 4.8 peripheral neuropathy (previously documented by nerve conduction tests),
  - 4.9 interstitial lung disease confirmed by HRCT,
  - 4.10 renal tubular acidosis requiring treatment,
  - 4.11 CNS disease ascribed to Sjögrens syndrome (confirmed by MRI),
  - 4.12 myositis (CPK>2N and EMG or biopsy evidence of myositis),
  - 4.13 inflammatory arthritis
5. An unstimulated salivary flow rate greater than 0ml in 15 minutes.
6. Symptomatic oral dryness (≥ 5/10 on patient-completed Likert\*\*).

7. Symptomatic fatigue ( $\geq 5/10$  on patient-completed Likert\*\*).
8. Patients on corticosteroids, NSAIDS, antidepressants, methotrexate, or pilocarpine\*\*\* must have been on a stable dose for 4 weeks prior to receiving the first infusion of study medication and expected to remain on this dose throughout the study.
9. Patients who are on hydroxychloroquine at screening must have been on a stable dose throughout the preceding six-month period. If they have stopped hydroxychloroquine they should have been off it for at least 3 months prior to receiving study medication.
10. Given their written informed consent to participate in the trial and expected to be able to adhere to the study visit schedule and other protocol requirements.

\*Anti-Ro antibody test, IgG, RF and C4 assays performed within 6 months of screening may be used to confirm eligibility. If greater than 6 months repeats should be performed locally at screening to confirm eligibility.

\*\* LIKERT range 0-10 with 10 corresponding to worst severity.

\*\*\* Pilocarpine or drugs with similar pharmacological action should not be used within 12 hours of the assessment visits at screening, baseline, week 16, week 24, week 36 and week 48 (end of study).

Previous inclusion criteria:

1. Aged between 18 and 80 years of age, either sex
2. A confirmed diagnosis of primary Sjögrens syndrome by AmericanEuropean Consensus Group (AECG) criteria with:
  - 2.1. Positive labial gland biopsy\*\* and/or
  - 2.2. Positive for anti-Ro auto-antibodies greater than 1.5 upper limit of normal\*
3. A stimulated salivary flow rate of greater than or equal to 0.5 ml in 5 minutes
4. An unstimulated salivary flow rate greater than 0 in 15 minutes
5. Be positive for anti-Ro auto-antibodies greater than 1.5 upper limit of normal
6. Symptomatic oral dryness (greater than or equal to 5/10 on patient-completed Likert\*\*\*)
7. Symptomatic fatigue (greater than or equal to 5/10 on patient-completed Likert\*\*\*)
  - 8.1. At least one systemic feature of:
    - 8.1.1. Hypergammaglobulinaemia (IgG over 16)\*, or
    - 8.1.2. Low complement C4\*, or
    - 8.1.3. Cryoglobulinaemia
  - 8.2. Active/past history since diagnosis of the following (ascribed to Sjögrens syndrome):
    - 8.2.1. Inflammatory polyarthritis
    - 8.2.2. Purpura/cutaneous vasculitis
    - 8.2.3. Lymphadenopathy
    - 8.2.4. Persistent parotid salivary gland swelling not due to infection
    - 8.2.5. Peripheral neuropathy (previously documented by nerve conduction tests)
    - 8.2.6. Interstitial lung disease confirmed by high-resolution computed tomography (HRCT)
    - 8.2.7. Renal tubular acidosis requiring treatment
    - 8.2.8. Central nervous system (CNS) disease ascribed to Sjögrens syndrome (confirmed by magnetic resonance imaging [MRI])
    - 8.2.9. Myositis (creatine phosphokinase [CPK] greater than 2N and electromyogram [EMG] or biopsy evidence of myositis)
    - 8.2.10. Patients with inflammatory arthritis
    - 8.2.11. If greater than 10 years since diagnosis of primary Sjögrens syndrome, must have established systemic involvement
9. If on corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDS), hydroxychloroquine,

methotrexate, or pilocarpine; have been on a stable dose for 4 weeks prior inclusion and expected to remain on this dose throughout the study

10. Given their written informed consent to participate in the trial and expected to be able to adhere to the study visit schedule and other protocol requirements

\* Anti-Ro/La antibody test, IgG, RF and C4 assays performed within 6 months of screening may be used to confirm eligibility. If greater than 6 months repeats should be performed locally at screening to confirm eligibility.

\*\* A labial gland biopsy performed within 6 months of screening may be used to confirm eligibility. The labial gland biopsy SHOULD NOT be performed as part of the screening process.

\*\*\* LIKERT range 0 - 10 with 10 corresponding to worst severity

### **Participant type(s)**

Patient

### **Healthy volunteers allowed**

No

### **Age group**

Adult

### **Lower age limit**

18 Years

### **Sex**

All

### **Key exclusion criteria**

Current exclusion criteria as of 20/09/2011:

1. Diagnosis of secondary Sjögrens syndrome.
2. Use of DMARDs, immunosuppressant therapies or antidepressants within 4 weeks prior to the first dose administration (except for glucocorticoids, salicylates, non-steroidal anti inflammatory drugs (NSAIDs), methotrexate and analgesics which are acceptable).
3. Pregnancy, lactation or women of child-bearing potential (WCBP) unwilling to use medically approved contraception whilst receiving treatment and for 12 months after treatment has finished.
4. Men whose partners are of child-bearing potential but who are unwilling to use appropriate medically approved contraception whilst receiving treatment and for 12 months after treatment has finished.
5. Patient has active or prior hepatitis B or C, known HIV positivity or known history of tuberculosis.
6. Any history of other autoimmune diseases or other form of immunodeficiency or neutropaenia  $<1.5 \times 10^9/l$ .
7. Any AECG exclusion criteria not covered elsewhere (graft versus host disease, primary lymphoma excluding PSS, sarcoidosis).
8. Any malignancies that would normally preclude the use of rituximab within the past 5 years, including solid tumours, haematological malignancies and carcinoma in situ (except basal cell or squamous cell carcinoma of the skin that has been excised and cured)
9. Participation in a clinical study involving administration of an investigational drug within the past 4 weeks prior to the first infusion.
10. A history of major surgery within 3 months prior to first infusion or planned surgery during

the study.

11. Receipt of live/attenuated vaccine within 4 weeks prior to the first infusion.
12. Previous exposure to rituximab or any other monoclonal antibody within the past 5 years.
13. History of recurring or chronic infections or underlying conditions which may further predispose patients to serious infection.
14. History of moderate to severe congestive heart failure according to the New York Heart Association (NYHA) functional classification system (see Appendix C) or other uncontrolled heart disease, or who have a clinically significant abnormal ECG at the time of screening.
15. History of receiving human/murine recombinant products or known allergy or anaphylactic reaction to a biologic agent or any component of the active substance or any of its excipients or murine components.
16. Patients with fibromyalgia or a diagnosis of significant depression or anxiety that in the opinion of the clinician would confound the interpretation of the study results.
17. Current or a history of severe, progressive or uncontrolled renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, or cerebral disease (including demyelinating diseases such as multiple sclerosis).
18. Any history of organ transplant (with the exception of a corneal transplant >3 months prior to study entry).
19. Presence of a clinically significant illness or mental disorder within 4 weeks of the start of the trial where the safety of the individual might be at risk by entry into the trial, or where the individual does not have the capacity to consent or where the outcome of the therapy cannot be assessed by virtue of the illness or disorder. Each patient will be assessed individually and no person who wishes to participate will be unreasonably excluded by virtue of the illness or disorder.

Previous exclusion criteria:

1. Diagnosis of secondary Sjögrens syndrome
2. Use of disease modifying anti-rheumatic drugs (DMARDs) or immunosuppressant therapies within 4 weeks prior to the first dose administration (glucocorticoids, salicylates, NSAIDs, analgesics are acceptable)
3. Pregnancy, lactation or women of child-bearing potential unwilling to use medically approved contraception whilst receiving treatment and for 12 months after treatment has finished
4. Men whose partners are of child-bearing potential but who are not willing to use appropriate medically approved contraception whilst receiving treatment and for 12 months after treatment has finished, unless they are surgically sterile
5. Use of other DMARDs or immunosuppressant therapies within 4 weeks prior to the first dose administration
6. Patients who are known to have serum hepatitis or are known carriers of the hepatitis B surface antigen (HBsAg), hepatitis C antibody, or have a known human immunodeficiency virus (HIV) positivity or a known history of tuberculosis
7. Any history of other autoimmune diseases or other form of immunodeficiency or neutropaenia less than  $1.5 \times 10^9/L$
8. Any AECG exclusion criteria not covered elsewhere (graft versus host disease, primary lymphoma excluding PSS, sarcoidosis)
9. Any cancer that would normally preclude the use of rituximab within the past 5 years
10. Participation in a clinical study involving administration of an investigational drug within the past 4 weeks prior to the first infusion
11. A history of major surgery within 3 months prior to first infusion or have planned surgery during the study
12. Receipt of live/attenuated vaccine within 4 weeks prior to the first infusion
13. Previous exposure to rituximab or any other monoclonal antibody within the past 5 years
14. History of recurring or chronic infections or with underlying conditions which may further

predispose patients to serious infection

15. History of moderate to severe congestive heart failure or other uncontrolled heart disease, or who have a clinically significant abnormal electrocardiogram (ECG) at the time of screening

16. History of receiving human/murine recombinant products or known allergy to murine products or any component of the active substance or any of its excipients or murine components

17. Presence of fibromyalgia, or diagnosed significant depression or anxiety

18. Current or a history of severe, progressive or uncontrolled renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, or cerebral disease (including demyelinating diseases such as multiple sclerosis)

19. Any history of organ transplant (with the exception of a corneal transplant greater than 3 months prior to screening)

20. Presence of a clinically significant illness within 4 weeks of the start of the trial

**Date of first enrolment**

01/01/2011

**Date of final enrolment**

01/07/2013

## **Locations**

**Countries of recruitment**

United Kingdom

England

**Study participating centre**

**University of Leeds**

Leeds

United Kingdom

LS2 9JT

## **Sponsor information**

**Organisation**

University of Leeds (UK)

**ROR**

<https://ror.org/024mrx33>

## **Funder(s)**

**Funder type**

Charity

**Funder Name**

Arthritis Research UK (ref: 18810)

**Alternative Name(s)**

**Funding Body Type**

Private sector organisation

**Funding Body Subtype**

Other non-profit organizations

**Location**

United Kingdom

## Results and Publications

### Individual participant data (IPD) sharing plan

**IPD sharing plan summary**

Not provided at time of registration

**Study outputs**

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">Results article</a>	results	01/07/2017		Yes	No
<a href="#">Protocol article</a>	protocol	17/01/2014		Yes	No