SUPPLEMENTARY TEXT

Planned sample size

When the protocol was written, there were no high-quality data available to form the basis for accurate sample size calculations for a study based on the RAMRIS, as no large observational studies or randomized controlled trials were available involving a study population similar to that planned for the present study. However, a study using 60 patients in each treatment arm was calculated to have approximately 80% power to detect a standardized difference between treatment arms of approximately 0.50 units. This effect size is smaller than the standardized effect sizes reported by Jones et al. (Jones G, et al. *Rheumatology*. 2003;42:6–13.) for infliximab and leflunomide radiographic studies, and comparable with most of the effect size estimates reported in that paper for a range of DMARDs, given the expected greater sensitivity of the RAMRIS score.

Assignment to treatment group/sequence

Eligible patients were randomly assigned to treatment groups through an interactive voice response system (IVRS) prior to receiving any study medication. The specifications of the randomization algorithm were determined by the Roche randomization group in Basel, Switzerland and provided to Perceptive Informatics (Nottingham, UK) who provided the IVRS service. Central randomization was performed by the IVRS and stratified by duration of MTX treatment prior to entering the study (< 6 months or ≥ 6 months) and by presence or absence of bone erosions using the randomization list provided by the Sponsor.

Patient eligibility information was provided to the IVRS by the investigator at the time of randomization. During randomization, the patient was assigned a unique medication/ randomization number, which the investigator noted in the appropriate place on the eCRF.

Once randomized, the patient received treatment according to the schedule described in the main text. Rituximab infusions were to be given on an outpatient basis; however, it was acceptable to hospitalize a patient for 24 hours if required.

Blinding

This was a double-blind study. Consequently, details of the randomization list were available only to the 2 Randomization List Managers (Jean-Claude Farina and Norbert Neumann) and were not available at the study center, to the Sponsor's monitors, project statisticians or to the Sponsor's project team at any time prior to the Week 24 analysis.

It was only permissible to unblind a patient's treatment assignment when knowledge of the treatment was essential for the further management of the patient, such as in the event of an SAE or if an independent pharmacological analysis of biological samples was required. In such cases, it was necessary to ensure that adequate procedures were in place to ensure integrity of the data.

The investigator had to make every attempt to contact the Sponsor before unblinding the treatment assignment for any patient, but if this was not possible, he/she had to contact the Sponsor within 1 working day after the event and, if appropriate, complete an AE form. In the event of accidental unblinding, all the above procedures had to be followed, but no AE form had to be completed.

If emergency unblinding was required, the investigator or designee contacted the IVRS prior to unblinding a patient. The IVRS then provided the site with the patient's unblinding code.

Additionally, to maintain the blind after screening, sites did not receive data related to RF, anti-CCP, CD19, rituximab serum levels or HACA results. CD19+ cell counts were made available to the investigator at the end of the first year of SFU in order that a decision could be made as to whether or not to continue to follow the patient.

The first database lock for the study occurred for the purposes of the Week 24 analysis, which included primary, secondary and exploratory efficacy analyses and safety summaries, once all data up to that point had been collected and cleaned. Treatment assignments were unblinded to the Sponsor at this point. However, all patients and investigators/assessors remained blinded to treatment assignments until the end of the study.

SUPPLEMENTARY TABLES

Table S1 Summary of reasons for premature withdrawal from treatment (ITT population)

	Placebo (n = 63)	**Rituximab 500 mg (n = 62)**	**Rituximab 1000 mg (n = 60)**
Number of withdrawals	14 (22.2)	3 (4.8)	4 (6.7)
Reason for withdrawals			
Safety	2 (3.2)	–	–
Adverse event/intercurrent illness	–	–	–
Infusion reaction event	–	–	–
Death			
Non-safety			
Insufficient therapeutic response	2 (3.2)	–	1 (1.7)
Failure to return	1 (1.6)	–	–
Protocol violation	3 (4.8)	2 (3.2)	–
Refused treatment/did not cooperate	1 (1.6)	–	–
Withdrew consent	5 (8.0)	–	3 (5.0)
Code broke	–	–	–
Administrative/other	–	1 (1.6)	–

Note: Percentages are based on the number of subjects treated.

Table S2 Summary of adverse events with frequency >2% in any treatment group, by system organ class and preferred term (safety population)

	Placebo (n = 63)	**Rituximab 500 mg (n = 62)**	**Rituximab 1000 mg (n = 60)**
Patients with any TEAE, n (%)	41 (65.1)	35 (56.5)	36 (60.0)
Infections and infestations	*14 (22.2)*	*23 (37.1)*	*22 (36.7)*
Bronchitis	2 (3.2)	4 (6.5)	6 (10.0)
Viral infection	2 (3.2)	4 (6.5)	3 (5.0)
Nasopharyngitis	2 (3.2)	2 (3.2)	3 (5.0)
Rhinitis	2 (3.2)	3 (4.8)	2 (3.3)
Upper respiratory tract infection	1 (1.6)	2 (3.2)	4 (6.7)
Gastroenteritis	1 (1.6)	2 (3.2)	1 (1.7)
Oral herpes	–	1 (1.6)	3 (5.0)
Pharyngitis	1 (1.6)	2 (3.2)	1 (1.7)
Sinusitis	2 (3.2)	2 (3.2)	–
Tracheobronchitis	1 (1.6)	2 (3.2)	1 (1.7)
Urinary tract infection	1 (1.6)	3 (4.8)	–
Herpes simplex	–	2 (3.2)	–
Musculoskeletal and connective tissue disorders	*14 (22.2)*	*12 (19.4)*	*10 (16.7)*
Rheumatoid arthritis	8 (12.7)	3 (4.8)	1 (1.7)
Back pain	1 (1.6)	1 (1.6)	4 (6.7)
Arthralgia	1 (1.6)	4 (6.5)	–
Myalgia	2 (3.2)	–	1 (1.7)
Neck pain	–	2 (3.2)	1 (1.7)
Musculoskeletal pain	2 (3.2)	–	–
Investigations	*8 (12.7)*	*8 (12.9)*	*3 (5.0)*
Blood pressure increased	–	3 (4.8)	–
Hepatic enzyme increased	1 (1.6)	–	2 (3.3)
Transaminase increased	1 (1.6)	2 (3.2)	–
Gastrointestinal disorders	*7 (11.1)*	*5 (8.1)*	*4 (6.7)*
Gastritis	3 (4.8)	–	1 (1.7)
Dyspepsia	2 (3.2)	1 (1.6)	–
Mouth ulceration	–	2 (3.2)	–
Nervous system disorders	*9 (14.3)*	*5 (8.1)*	*2 (3.3)*
Headache	1 (1.6)	4 (6.5)	–
Dizziness	1 (1.6)	2 (3.2)	–
Somnolence	2 (3.2)	1 (1.6)	–
Skin and subcutaneous tissue disorders	5 (7.9)	5 (8.1)	4 (6.7)
Erythema	2 (3.2)	–	–
Respiratory, thoracic, and mediastinal disorders	4 (6.3)	4 (6.5)	5 (8.3)

Pharyngolaryngeal pain	2 (3.2)	1 (1.6)	1 (1.7)
Cough	2 (3.2)	–	1 (1.7)
General disorders and administration site conditions	7 (11.1)	3 (4.8)	3 (5.0)
Fatigue	2 (3.2)	1 (1.6)	–
Vascular disorders	5 (7.9)	2 (3.2)	5 (8.3)
Hypertension	4 (6.3)	–	1 (1.7)
Blood and lymphatic system disorders	4 (6.3)	–	2 (3.3)
Anemia	2 (3.2)	–	1 (1.7)
Iron deficiency anemia	2 (3.2)	–	–
Psychiatric disorders	4 (6.3)	1 (1.6)	1 (1.7)
Depression	2 (3.2)	–	1 (1.7)
Insomnia	2 (3.2)	–	–

Abbreviation: TEAE, treatment-emergent adverse event.

Adverse events were coded with MedDRA version 11.2. Multiple occurrences of the same adverse event in one individual were counted only once. Only preferred terms where AE had a frequency in any one treatment group >2% are shown.

Table S3 Summary of serious adverse events by system organ class and preferred term (safety population)

	Placebo (n=63)	Rituximab 500 mg (n=62)	Rituximab 1000 mg (n=60)
Any serious adverse event, n (%)	**5 (7.9)**	**3 (4.8)**	**4 (6.7)**
Infections and infestations	–	*1 (1.6)*	*2 (3.3)*
Bronchitis	–	–	1 (1.7)
Omphalitis	–	–	1 (1.7)
Soft tissue infection	–	1 (1.6)	–
Musculoskeletal and connective tissue disorders	*2 (3.2)*	–	–
Rheumatoid arthritis	2 (3.2)	–	–
Cardiac disorders	*1 (1.6)*	–	–
Acute coronary syndrome	1 (1.6)	–	–
Gastrointestinal disorders	*1 (1.6)*	–	–
Colonic polyp	1 (1.6)	–	–
Intestinal diverticulum	1 (1.6)	–	–
General disorders and administration site conditions	*1 (1.6)*	–	–
General physical health deterioration	1 (1.6)	–	–
Metabolism and nutrition disorders	–	*1 (1.6)*	–
Hyperglycemia	–	1 (1.6)	–
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	–	–	*1 (1.7)*
Papillary serous endometrial carcinoma	–	–	1 (1.7)
Pregnancy, puerperium, and perinatal conditions	–	–	*1 (1.7)*
Omphalorrhexis	–	–	1 (1.7)
Renal and urinary disorders	–	*1 (1.6)*	–
Renal colic	–	1 (1.6)	–
Respiratory, thoracic, and mediastinal disorders	–	–	*1 (1.7)*
Bronchitis chronic	–	–	1 (1.7)

SUPPLEMENTARY FIGURE

Figure S1. Patient disposition. ITT, intent-to-treat; MTX, methotrexate; RTX, rituximab.