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Assessment Report
For
Mabthera
(rituximab)

Procedure No.: EMEA/H/C/000165/II/0065

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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1. Scientific discussion

1.1 Introduction

Mabthera contains the active substance rituximab (RTX) which is a chimeric murine/human monoclonal antibody that binds CD20. CD20 is a hydrophobic transmembrane protein which is present on the cell surface of pre-B- and mature B-lymphocytes. In contrast the protein is considered absent on hematopoietic stem cells, pro–B–cells, normal plasma cells as well as other tissues.

CD20 is also present on malignant B-cells in most patients with mature B-cell lymphoma or B-cell leukaemia. The binding of rituximab to CD20 on lymphocytes could lead to the elimination of these cells by means of several different mechanisms. The mechanisms include antibody dependent cellular cytotoxicity (ADCC), complement dependent cytotoxicity (CDC) and apoptosis.

Rituximab was approved in July 2006 in the EU for use in combination with methotrexate (MTX) to reduce the signs and symptoms in adult patients with severe active Rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs (DMARD) including one or more tumour necrosis factor (TNF) inhibitor therapies. Data to support this indication were presented in the original submission (EMEA/H/C/165/II/39).

In this application, the MAH submitted data from two pivotal studies IMAGE and SERENE as well as four supportive studies MIRROR, SUNRISE, REFLEX (2 years extension data from REFLEX study which has been submitted as part of the initial application for the RA indication) and DANCER, to support an extension of the current RA indication to earlier stages of RA, in MTX naïve patients (1st line treatment) and in MTX inadequate response (MTX-IR) patients (2nd line treatment).

The evaluation procedure started as an Extension procedure. Following withdrawal of the extension application, the procedure was finalised as a Type II variation to update section 4.1 with information of improvement in physical function and reduction in the rate of joint damage as measured by x-ray, when given in combination with methotrexate and sections 4.2, 4.4, 4.5, 4.8 and 5.1 have been updated as a consequence. The Package Leaflet has been updated accordingly.
In addition to this, sections 5.1 and 5.2 of the SmPC have been updated with additional information from studies in patients with early arthritis.
Furthermore changes were made to the SmPC, labelling and Package Leaflet to bring them in line with the current QRD template.
Finally Annex II has been updated in order to reflect the latest version of the RMP.

1.2 Clinical pharmacology

In this variation, pharmacokinetic (PK) and pharmacodynamic (PD) data for rituximab are available from the 4 newly submitted phase III clinical trials supporting this application (IMAGE, SERENE, MIRROR, and SUNRISE, see Table 5) in which rituximab was administered either as 0.5 g or 1 g dose in combination with MTX in RA patients.

Pharmacokinetics

The PK of rituximab was assessed following two IV doses of 0.5 or 1 g on Days 1 and 15. As blood sampling was limited, only Cmax and $t_{1/2}$ were calculated. Estimated PK parameters in all RA studies are summarized in Table 1. The same two colorimetric sandwich enzyme-linked immunosorbent assays (ELISAs) were used for quantisation of rituximab in human serum.

Table 1: Mean PK Parameters for Rituximab from all Four Studies. Values are mean±SD (N=number of subjects)

	C_{first} (µg/mL)	C_{second} (µg/mL)	Ratio of C_{second}/ C_{first}	C_{first} Ratio Course 2/ Course 1	C_{second} Ratio Course 2/ Course 1	$t_{1/2}$ (days)
2 x 0.5 g in Course 1						
IMAGE	171 ± 54 (242)	198 ± 58 (234)	1.16			14.8 ± 5.8 (229)
SERENE	157 ± 46 (164)	183 ± 55 (16)	1.17			15.7 ± 5.1 (163)
MIRROR	164 ± 41 (233)	193 ± 61 (247)	1.18			16.4 ± 6.1 (230)
2 x 0.5 g in Course 2						
IMAGE	170 ± 38 (184)	ND	ND	0.99	ND	ND
SERENE	ND	ND	ND	ND	ND	ND
MIRROR	175 ± 41 (142)	207 ± 69 (145)	1.18	1.1	1.1	19.4 ± 6.0 (140)
2 x 1 g in Course 1						
IMAGE	341 ± 84 (240)	404 ± 102 (230)	1.18			16.9 ± 5.4 (235)
SERENE	318 ± 85.8 (164)	381 ± 98.3 (159)	1.20			18.5 ± 5.8 (166)
MIRROR	312 ± 103 (119)	365 ± 126 (120)	1.14			18.0 ± 6.2 (113)
SUNRISE	298 ± 91.2 (265)	355 ± 112 (269)	1.19			21.2 ± 8.2 (80)
2 x 1 g in Course 2						
IMAGE	370 ± 101 (191)	ND	ND	1.1	ND	ND
SERENE	ND	ND	ND	ND	ND	ND
MIRROR	348 ± 89 (189)	386 ± 132 (195)	1.11	1.1	1.1	21.8 ± 6.4 (184)
SUNRISE	317 ± 107 (277)	377 ± 120 (272)	1.19	1.1	1.1	20.9 ± 5.8 (184)

C_{first} = post-infusion concentration after first infusion (day 1); C_{second} = post-infusion concentration after second infusion (day 15). Second course based on clinical symptoms is administered > 24 weeks.
ND = not determined

A population PK analysis of rituximab was conducted using data drawn from the combined dataset of six clinical studies in patients with RA: two Phase II clinical studies (Phase IIa study WA16291/U2789s and DANCER), and four Phase III clinical studies. The objectives were to estimate the typical values and inter-patient variability of the PK parameters and to assess the effect of physiological co-variates. The population PK analysis consisted of a total of 24,165 rituximab samples from 2005 patients who received two IV doses (of either 2 x 1 g or 2 x 0.5 g) of rituximab on Days 1 and 15, followed by a subsequent rituximab treatment course.
The PK of rituximab was assessed using non-linear mixed-effects modelling. A first-order conditional estimation with interaction was used for parameter estimation throughout this analysis. A nominal p-value of 0.005 was selected for model selection and covariate selection. The final model for physiologic covariates was elaborated by testing the full model against restricted models by removing each covariate in turn. In addition, a covariate was removed from the model if the 95% CI included 0, indicating lack of covariate effect on a parameter. GOFs (Goodness of Fit) were provided and bootstrap was performed to assess stability of the model.

The best structural model was a two-compartment model with first-order elimination. After inclusion of the statistically significant covariates on CL and V_c, the typical population estimate of rituximab CL, V_c and the peripheral compartment volume of distribution (V_p) from the 2005 patients with RA was 0.335 L/day, 3.10 L and 3.39 L, respectively. The inter-patient variability for CL, V_c and V_p was 29.3% (estimation of CV = 4.74%), 10.7% (estimation of CV = 14.0%), and 22.5% (estimation of CV = 15.3%) respectively. The mean terminal half-life of rituximab was 18.0 days (range, 5.17–77.5 days). Weight, sex, and C-reactive protein (CRP) were the most significant covariates on CL. HACA, ESR, CD19, age, RF, cyclophosphamide, MTX, corticosteroids, with or without previous treatment with TNF inhibitors were not significant covariates on CL. The V_c and the V_p of rituximab proportionally increased with body weight. However, body weight, sex, and CRP explained a small magnitude of the overall inter-individual variability of the respective physiologically relevant parameters.

Pharmacodynamics

Treatment with rituximab plus MTX resulted in a near-complete depletion of peripheral $CD19^+$ B cells. The effect was rapid, with B-cell counts in most patients declining to below 10 cells/μL by the end of the second infusion. In the majority of patients following administration of the first course, peripheral B-cell depletion was maintained over 24 weeks, with only a small proportion of patients (5.9%) showing signs of peripheral B-cell recovery (i.e., B-cell counts greater than the lower limit of normal [LLN], 80 cells/μL) by Week 24. No clear difference in B-cell depletion and recovery characteristics were noted between the 2 x 0.5 g and 2 x 1 g rituximab dose groups (see Table 2).

Table 2: Proportion of Patients with CD19 Counts above Baseline or the Lower Limit of Normal Value by Visit after First Infusion on Day 1 (Safety Population): IMAGE, SERENE, MIRROR

Study	Timepoint (week)	CD19 ≥baseline or LLN
IMAGE	Rituximab 2 × 0.5 g+MTX (n=167)	
	8	0/242 (0%)
	16	3/226 (1.3%)
	24	13/235 (5.5%)
	Rituximab 2 × 1 g+MTX (n=170)	
	8	0/238 (0%)
	16	0/233 (0%)
	24	6/235 (2.6%)
SERENE	Rituximab 2 × 0.5 g+MTX (n=167)	
	8	0/161 (0%)
	16	2/156 (1.3%)
	24	6/154 (3.9%)
	Rituximab 2 × 1 g+MTX (n=170)	
	8	1/163 (0.6%)
	16	2/160 (1.3%)
	24	12/154 (7.8%)
MIRROR	Rituximab 2 × 0.5 g (n=253)	
	8	0/237 (0%)
	16	2/234 (0.9%)
	24	15/221 (6.8%)
	Rituximab 2 × 1 g (n=124)	
	8	0/124 (0%)
	16	0/124 (0%)
	24	7/124 (5.6%)

LLN Lower limit of normal

The extent and duration of B-cell depletion was similar for each treatment course with repeat treatments. Subsequent treatment was based on clinical symptoms and not on the patients' CD19+ counts, which may or may not have returned to LLN/baseline prior to the next treatment. The recovery of B cells was similar for subsequent courses of rituximab. There was no clear difference in B-cell depletion and recovery characteristics between the 2 x 0.5 g and 2 x 1 g doses. However, the PRN (as needed) retreatment strategy resulted in more patients having B cell counts above the LLN at the time of each repeat treatment (~40% of patients) than did the treatment to remission strategy (~5% to 10% of patients ≥ LLN at each repeat treatment course baseline, data not shown).

Peripheral T-Cell Counts

There was no clear difference between any of the treatment groups in overall peripheral T-cell counts (CD3), or any of the T-cell subsets: T helper (CD4), cytotoxic T-cell (CD8), CD3 or CD4 memory, or naive or transitional subsets, with levels remaining relatively stable over one year in all treatment arms. Peripheral T-cell counts decreased after each infusion but recovered to baseline within 2 weeks, after which cell counts remained relatively stable (data not shown).

HACA (human anti-chimeric antibodies)

HACA were routinely measured pre-dose on Day 1, at each course's baseline, at Week 24 and approximately every six months thereafter (exact visit depending on study), upon patient withdrawal from the treatment phase and upon completion of safety follow-up. As the minimum quantifiable

concentration of rituximab HACA in a sample was 5 RU/mL, a patient was defined as HACA positive if their HACA titer was ≥ 5 RU/mL and immunodepleteable with rituximab. A patient was defined as being HACA negative if the result was < 5 RU/mL, or ≥ 5 RU/mL and not immunodepleteable with rituximab. The incidence of HACA in four clinical studies submitted as part of this variation is summarized in Table 3.

Table 3: HACA Incidence in four Clinical Studies at Week 24

Study, Phase	Dosing Regimen	Patients with Positive HACA Response
IMAGE, Phase III	placebo rituximab 2 × 0.5 g rituximab 2 × 1 g	1.4% (3/222) 11.9% (28/235) 7.8% (18/230)
SERENE, Phase III	placebo, rtx 2 × 0.5 g rituximab 2 × 0.5 g rituximab 2 × 1 g	3.6 % (5/137) 7.9% (12/152) 5.4% (8/149)
SUNRISE	2 × 1 g, no re-treatment 2 × 1 g, placebo 2 × 1 g, 2 × 1 g	6.5% (2/31) 6.7% (10/150) 5.9% (17/288)
MIRROR, Phase III	rituximab 2 × 0.5 g rituximab 2 × 1 g,	6.2% (14/227) 1.8% (2/114)

HACA = human anti-chimeric antibody.
Note: A positive HACA is defined as ≥ 5 RU/mL and immunodepletable with rituximab. A negative HACA is < 5 RU/mL or ≥ 5 RU/mL and not immunodepletable with rituximab

The majority of patients who developed HACA-positive titers for the first time after receipt of rituximab were identified following the first course of treatment. Overall, a total of 410 rituximab-treated patients had positive HACA at any time following receipt of rituximab (out of 3095 patients in the pooled All Exposure population). Among these 410 patients, 18 patients had HACA-positive titers before their treatment with rituximab at baseline. Thus the overall incidence of HACA post-rituximab treatment was 392/3095 (12.7%) in the all-exposure population. In MIRROR, at Week 24, there was a higher detection of positive HACA titers in patients receiving the 2 x 0.5 g dose as first course (6.2%), than in those receiving the 2 x 1 g dose (1.8%),. This trend was also seen in IMAGE with incidence of HACA of 11.9% vs. 7.8% at Week 24 for the 2 x 0.5 g dose and 2 x 1 g dose, respectively.

Effect of HACA on PK of rituximab

Serum rituximab concentrations in the majority of HACA-positive patients were generally within the range of levels in HACA-negative patients. Overall there was no difference in $C_{post\text{-}infusion}$ between the HACA-positive and HACA-negative patients, during the first or the second course in a pooled analysis of SERENE, MIRROR and SUNRISE. Further, the population PK analysis indicated that HACA was not a significant covariate on either the clearance or central volume of distribution (data not shown).

Effect of HACA on PD of rituximab

The effect of a positive HACA on the PD of B cell depletion was explored by identifying patients who appeared to have partial B cell depletion following treatment with rituximab. A definition of a CD19 count that never decreased below 40 cells/µl after the day 1 infusion of any course, or that returned to ≥ 40 cells/µl by week 8 post-treatment was used.
The proportion of patients who met this definition after developing a HACA positive titre was similar to that in patients who were consistently HACA negative (5.5% vs. 3.7% respectively). Of those patients who developed a positive HACA titre and had subsequent partial B cell depletion, two patients had a reduced efficacy response. ACR responses were maintained or improved in 80% of patients following development of a positive HACA titre.
Of the 225 patients who developed a positive HACA titre and who received further courses of rituximab, five (2.2%) subsequently reported infusion reactions that were either serious or that led to withdrawal. In contrast 11/2126 (0.52%) patients who were HACA negative experienced infusion related reactions (IRRs) that were serious or led to withdrawal following second course or beyond.
In conclusion, while the development of HACA that potentially influenced either efficacy or safety was uncommon, an association between the development of HACA and subsequent poorer tolerance to infusions of rituximab cannot be excluded.

Discussion on clinical pharmacology
The PK data from the 4 studies submitted with this application are consistent with the PK profile of rituximab in patients with RA, which was characterized in the original submission (EMEA/H/C/165/II/39) following an initial course of treatment.

In all these studies, rituximab PK were dose proportional from 0.5 g to 1 g. Mean maximum plasma concentration C_{max} for serum rituximab following first infusion (C_{first}) ranged from 157 to 171 µg/mL for the 2 x 0.5 g dose and ranged from 298 to 341 µg/mL for the 2 x 1 g dose. Mean C_{max} was 16 to 19% higher following the second infusion compared with the first infusion for both doses. Mean terminal elimination half-life ranged from 15 to 16.5 days for the 2 x 0.5 g dose group and 17 to 21 days for the 2 x 1 g dose group. The PK profile following a second course of treatment was similar to that following the initial course of treatment in the SERENE, IMAGE and MIRROR studies.

In the population PK analysis, body weight, sex, and CRP explained a small magnitude of the overall inter-individual variability of the respective physiologically relevant PK parameters (CL, V_c and V_p). Therefore, results from this analysis suggest that dosing of rituximab should not be adjusted according to demographic or physiologic variables.
PD data from the new studies were consistent with previous experience. In summary, all patients showed near-complete depletion of peripheral CD19+ B cells by 2 weeks after the first dose. CD19 is a marker of B cells used to measure B cell depletion, as the administration of rituximab could confound CD20 assay measurements. In the majority of patients, peripheral B-cell depletion was maintained over the entire 24 weeks, with only a small proportion of patients showing signs of peripheral B-cell recovery by Week 24, when serum rituximab concentrations fell below 1−10 µg/mL. The extent and duration of B-cell depletion were similar for each treatment course. Repeat treatments were given as per the protocol, with treatment based on clinical symptoms and not on patients' CD19+ counts, which may or may not have returned to the LLN or baseline value. T-cell counts remained stable after a transient decrease, likely because of concomitant treatment with corticosteroids.

The overall incidence of HACA post-rituximab treatment was 392/3095 (12.7%) in the all-exposure population. The low incidence (18/410, 0.6%) of HACA responses prior to rituximab treatment may be attributable to human anti-mouse antibodies or other pre-existing antibodies, including rheumatoid factors, recognizing an epitope shared with rituximab. The detection of higher HACA titers in patients receiving the 2 x 0.5 g dose as first course than in those receiving the 2 x 1 g dose in the MIRROR and IMAGE studies may be due to residual rituximab in serum interfering with HACA detection with higher doses. Finally, while the development of HACA that potentially influenced either efficacy or safety was uncommon, an association between the development of HACA and subsequent poorer tolerance to infusions of rituximab cannot be excluded.

1.3 Clinical efficacy

Four new phase III studies have been submitted by the MAH: two pivotal (IMAGE and SERENE) and two supportive (MIRROR and SUNRISE) (Table 4).

Table 4: Pivotal and Supporting Phase III Studies

Studies	Population	Design	Treatment groups[a] Rituximab dose	Primary endpoint objectives	Status
IMAGE (WA17047)	MTX-naïve	double-blind, randomised, placebo-controlled	2 x 0.5 g/ 2 x 0.5 g 2 x 1 g/ 2 x 1 g Placebo/Placebo	Radiographic progression (Week 52)	Terminated due to unfavourable risk: benefit balance in MTX-naïve patients.
SERENE (WA17045)	MTX-IR	double blind, randomised, placebo controlled	2 x 0.5 g/ 2 x 0.5 g 2 x 1 g/ 2 x 1 g Placebo/ Placebo	ACR20 (Week 24)	Ongoing - repeat treatment and assessment of long-term outcomes
MIRROR (WA17044)	MTX-IR/ TNF-IR[b]	double-blind, randomised study	2 x 0.5 g/ 2 x 0.5 g 2 x 0.5 g/ 2 x 1 g 2 x 1 g/ 2 x 1 g	ACR20 (Week 48) Efficacy of dose escalation	
SUNRISE U3384g	TNF-IR	double blind, randomized, placebocontrolled retreatment	2 x 1 g/ 2 x 1 g 2 x 1 g/Placebo	ACR20 (week 48) Efficacy of repeat treatment	Completed

a All patients received MTX
b Patients treated with one prior biologic (which may have been a non-TNF inhibitor) were permitted

In addition, extension data from studies submitted previously (DANCER and REFLEX), including 2-year radiographic outcomes from REFLEX have been provided.
The data from DANCER study (not shown) are based on a very small number of patients and as such of limited importance.

Furthermore, SUNRISE study was a randomised withdrawal study designed to evaluate whether re-treatment with rituximab after 24 weeks is useful. Patient with inadequate response to MTX+TNF were eligible.
This study only included treatment experience TNF-IR patients, therefore the data (not shown) are not relevant for the present application for early RA (MTX naive and MTX-IR patients).

Main studies

IMAGE Study
IMAGE study is a phase III, randomised, controlled, double-blind, parallel group, multicentre study designed to evaluate the efficacy and safety of rituximab in combination with MTX compared to MTX alone in MTX-naïve patients with active RA.

METHODS

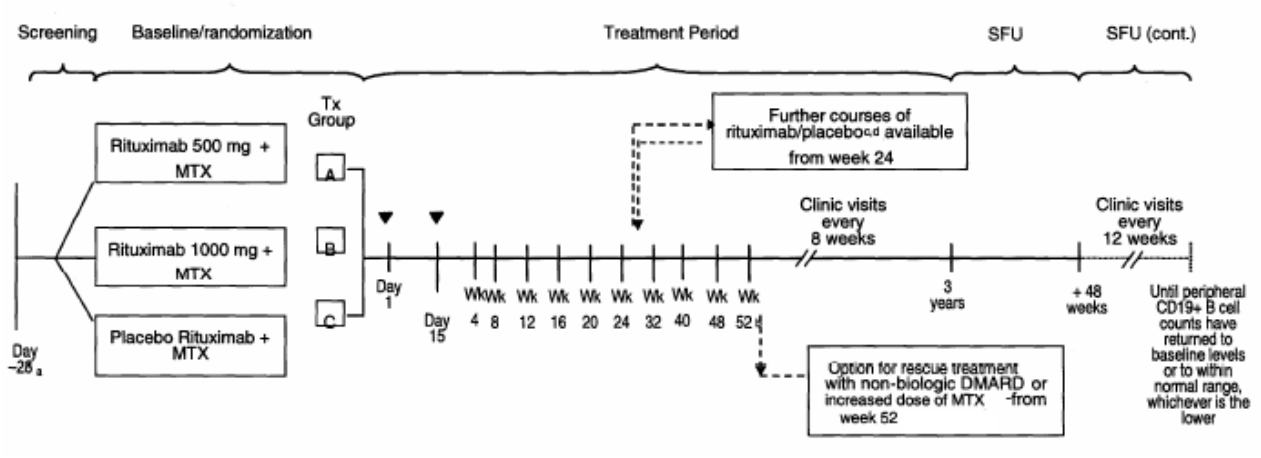
Study Participants
Both RF positive and RF negative patients were potentially eligible, with the overall proportion of RF negative patients being limited to ~20% of the total sample size. RF negative patients had to have existing erosive joint damage.
The inclusion criteria were the following:
• Patients with RA diagnosed between 8 weeks and 4 years prior to baseline according to the revised 1987 American College of Rheumatology (ACR) criteria.
• Minimum age of 18 years.
• Patients naïve to, and considered to be candidates for, treatment with MTX.
• Swollen joint count (SJC) ≥ 8 (66 joint count), and tender joint count (TJC) ≥ 8 (68 joint count) at both screening and baseline.
• At screening CRP ≥ 1.0 mg/dL (10 mg/L).
• Glucocorticoids ≤ 10 mg/day prednisolone or equivalent permitted if stable for at least 4 weeks prior to baseline.
• Use of NSAIDs permitted if stable for at least 2 weeks prior to baseline.

• For rheumatoid factor (RF) negative patients only, radiographic evidence of at least one joint with definite erosion attributable to RA.

Key exclusion criteria related to RA, or treatments for RA were as follows:
• Rheumatic autoimmune disease other than RA, or significant systemic involvement secondary to RA (including but not limited to vasculitis, pulmonary fibrosis or Felty's syndrome). Secondary Sjögren's syndrome or secondary limited cutaneous vasculitis with RA is permitted.
• Functional class IV as defined by the ACR Classification of Functional Status in RA.
• History of, or current, inflammatory joint disease other than RA (including, but not limited to, gout, reactive arthritis, psoriatic arthritis, seronegative spondyloarthropathy, Lyme disease) or other systemic autoimmune disorder (including, but not limited to, systemic lupus erythematosus, inflammatory bowel disease, scleroderma, inflammatory myopathy, mixed connective tissue disease or any overlap syndrome).
• Diagnosis of juvenile idiopathic arthritis (JIA) or juvenile rheumatoid arthritis (JRA) and/or RA before age 16.
• Previous treatment with any approved or investigational biologic agent for RA.
• Previous treatment with an anti-alpha 4 integrin antibody or co-stimulation modulator.
• Concurrent treatment with any biologic agent or DMARD other than MTX. Treatment must be discontinued 14 days prior to baseline, except for the following: azathioprine for ≥ 28 days; leflunomide for ≥ 8 weeks (or ≥ 14 days after 11 days of standard cholestyramine or activated charcoal washout).
• Previous treatment with any cell depleting therapies, including investigational agents.
• Intra-articular or parenteral glucocorticoids within 4 weeks prior to baseline. Safety-related exclusion criteria included patients with active infections, HIV-positive patients, positive hepatitis B surface antigen (HBsAg) or hepatitis C serology, or for HBV core antibody if associated with positive HBV DNA. Significant cardiac or pulmonary disease was excluded, as was any other uncontrolled, clinically significant condition.

Treatments
Patients were randomised to receive one of two doses of rituximab (either 2 x 0.5g [low dose group] or 2 x 1g [high dose group]) or placebo together with MTX. Patients received a first course of two infusions of rituximab or placebo on Days 1 and 15. MTX was initiated at 7.5 mg/week and escalated up to 20 mg/week by week 8. After a minimum of 24 weeks, and depending on disease activity (if Disease Active Score-28 joint count-Erythrocyte Sedimentation Rate (DAS28-ESR) ≥ 2.6), patients were eligible to receive further courses of rituximab or placebo.
Patients who withdrew from the study at any point were to return for safety follow-up assessments for a period of 1 year (or until B cells returned to baseline levels or within the normal range if this is later). The trial design is shown in Figure 1.

Figure 1 Overview of Study Design



▼ Rituximab or placebo infusion
[a] For patients requiring washout from leflunomide – this could be extended to 56 days and for patients requiring vaccination the screening period could be extended to 42 days.
[b] The primary efficacy endpoint was the change in mTSS at week 52
[c] Patients were to receive the same dose of rituximab throughout the study. Placebo patients could become eligible to receive rituximab 0.5 g × 2 + MTX from week 104.
[d] Patients were to be assessed for eligibility to receive a further course from week 24.

Study treatment comprised the following:
Rituximab/placebo IV infusion on days 1 and 15 (first course).
Subsequent course to be administered at least 24 weeks apart if DAS ≥ 2.6.
MTX administered once per week, starting dose of 7.5 mg per os (p.o.) escalated at 2.5 mg p.o. per week every 1-2 weeks to achieve:
15 mg p.o. per week by week 4
20 mg p.o. per week by week 8
Folic acid stable dose (5mg/week) to be maintained for duration of study.
Glucocorticoids 100 mg IV methylprednisolone prior to each rituximab/placebo infusion.

Objectives
The objectives of the study were as follows:
1. To determine the efficacy of rituximab in the prevention of progression in structural joint damage and to evaluate the safety of rituximab in patients with active rheumatoid arthritis initiating treatment with MTX.
2. To evaluate the efficacy of rituximab in improving patient's physical function and signs and symptoms of RA.
3. To investigate by a population analysis approach the PK of rituximab in the target RA patient population and the influence of covariates on the PK parameters.
4. To explore the long-term efficacy and safety of further courses of rituximab.

Outcomes/endpoints
The primary endpoint was the radiographic endpoint change in total sharp Genant score (mTSS) at week 52. The mTSS consists of a sum of scores of erosion (E-score) and joint-space narrowing (JSN-score) in hands, wrists and feet. For the total E-score, a 8-point scale till maximal 3.5 points was used for each bone (2 x 20 in total). For the JSN-score, a 9-point scale till maximal 4.0 points was used for each joint (2 x 19 in total). The maximal total score is 290, after normalisation for differences in number of bone sites for E- and JSN- scores. Subjects with an mTSS difference from baseline =<0 were classified as patients without progression.
Radiographs (by X-Ray) were made before inclusion, and at Week 24 and 52. Radiographs were also made in the open-label continuation phase every six months.

Secondary endpoints included:

<u>Physical endpoints</u>:

1. Change in HAQ-DI at Week 52: The Health Assessment Questionnaire Disability index is a patient-reported questionnaire specific for RA. It consists of 20 questions referring to eight component sets: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities.
2. Change in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-fatigue) score at week 52: The FACIT-fatigue is a 13-item questionnaire with patients requested to score each question on a five-point scale ranges from 0 (no fatigue) to 52 (extreme fatigue) and a clinically relevant improvement was defined as a decrease of at least 4 points.

Clinical endpoints:
1. ACR50 at Week 52: ACR50 means a 50 % improvement compared with baseline in both TJCs and SJCs as well as a 50 % improvement in three of the following measurements:
Physician's global assessment of disease activity
Patient's global assessment of disease activity
Patient's assessment of pain
Health Assessment Questionnaire
An acute phase reactant: CRP or, if CRP value was missing, ESR
2. ACR20, ACR70, ACR90 at week 52.
3. Disease Activity Score 28 (DAS28) remission at week 52 and DAS28-ESR low disease activity at week 52.
The following parameters are included in the calculation of DAS:
Number of joints tender to the touch (TEN)
Number of swollen joints (SW)
Erythrocyte sedimentation rate (ESR)
Patient assessment of disease activity (VAS; mm)
A EULAR response reflects an improvement in disease activity and an attainment of a lower degree of disease activity. For example, a good response is defined as an improvement in the DAS of >1.2 compared with baseline, and attainment of a DAS28of <3.2.

3. Major clinical response and complete clinical response at week 52.

Sample Size
The planned sample size was 750 patients: 250 patients per group. The sample size of 750 patients was expected to give >90% power to detect differences between each rituximab treatment group and the placebo group. The power estimate was based on simulations using distributions that match the data from the ASPIRE study, using nonparametric tests and the closure principle for multiplicity adjustment. Predicted change in mTSS were mean change=0.5; SD=5.6 (percentiles: 25%, 50%, 75%, 98% = -1.0, 0.0, 1.3, 9.03) for Rituximab 2 x 0.5 g + MTX and for Rituximab 2 x 1 g + MTX, and mean change=3.7; SD=9.6 (percentiles: 25%, 50%,75%, 89% = 0.0, 0.43, 4.5, 9.03) for Placebo + MTX, respectively.

Randomisation
Central randomisation was performed. Randomisation was stratified by region [United States (US) or rest of world (ROW)] and RF (positive or negative) using the randomisation list provided by the Sponsor.

Blinding
The study was a double-blind study.

Statistical Hypothesis and Planned Sample Size
All populations were based on randomised patients who had received any part of an infusion of study medication. Four analysis populations were defined:
- Modified ITT (MITT): Patients with a screening and at least one post-BL radiographic evaluation, grouped as randomised
- ITT: All patients randomised and treated, grouped as randomised
- Per Protocol (PP): Patients without major protocol violations, grouped as treated
- Safety: All patients randomised and treated, grouped as treated

The primary analysis was a comparison based on the Kruskal-Wallis test statistic to test equality of population medians among the three treatment arms. The three treatment arms were to be considered different if the test result was statistically significant at $\alpha = 0.05$ level stratifying for region and RF status using the MITT population.
The Closure Principle was used to adjust for multiple comparisons for the primary endpoint. Given a significant result above, each of the rituximab groups was to be compared with the placebo group using the Van Elteren test statistic. Each of the rituximab treated arms was to be considered superior to placebo if the test result was statistically significant at $\alpha = 0.05$ level.

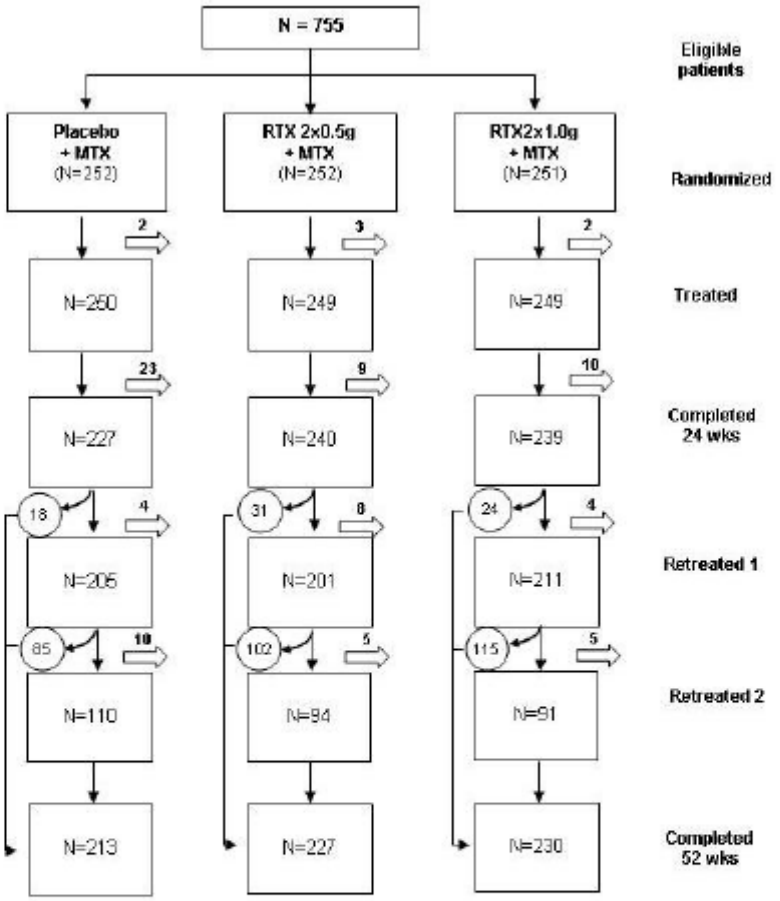
A hierarchical approach was taken in testing further secondary endpoints. In principle, if the primary radiographic endpoint was significant (global test), the primary clinical endpoint (ACR50 at Week 52) followed by the primary functional endpoint (mean change in HAQ-DI at Week 52) were to be tested to support the other claims of relief of signs and symptoms and improvement in physical function. Sub-hierarchies of secondary endpoints under each of the three main endpoints were predefined.

Handling of missing data (primary imputation method) for the primary endpoint was based on linear extrapolation (based on slope between two non-missing assessments). Concerning secondary endpoints, non responder imputation was used for categorical variables (ACR 20 50 70, 90, major and complete clinical response, EULAR response, % of patients with LDA/remission, minimally important difference in HAQ-DI/FACIT/SF36) whereas last observation carried forward was used for continuous variables (change from baseline in DAS28, ACRn, individual ACR core set parameters, FACIT-Fatigue, SF-36, AUC of ACRn).

RESULTS

Participant flow
Of the 755 patients randomised, 748 (evenly distributed between arms as 1:1:1) received a first course of treatment. Of these treated patients, similar proportions in each group received a second course (placebo+MTX: 81%, rituximab 2x0.5g+MTX: 80%, rituximab 2x1g+MTX: 84%). More patients in the placebo group received a third course of treatment than patients in the rituximab groups (44% in placebo+MTX vs. 37-38% in rituximab+MTX). Most retreated patients received their second course between Week 24 and Week 32 (placebo + MTX: 80%, rituximab 2 x 0.5 g + MTX: 85%, rituximab 2 x 1 g + MTX: 80%). In total, 670 (89.6%) of treated patients completed the study up to week 52. The proportion of patients completing 52 weeks was higher in the rituximab + MTX arms (90.1% in the rituximab 2 x 0.5 g + MTX arm and 91.6% in the rituximab 2 x 1.0 g + MTX arm) than in the placebo + MTX arm (84.5%). The patient disposition is presented in Figure 2.

Figure 2 Patient Disposition



○ = Received no further treatment but completed trial up to week 52

⇨ = Permanently withdrew from trial

Patients displayed as treated
Note that three patients received incorrect medication for their first treatment course (see also section 3.2)
Patient 7703, randomized to placebo + MTX, received rituximab 2 x 0.5 g
patient 6811, randomized to rituximab 2 x 1 g + MTX, received placebo + MTX
patient 6812, randomized to rituximab 2 x 0.5 g + MTX received placebo + MTX
For the safety analysis, these patients were analysed under the treatment they were given for the first course
Patient 5473 randomised to rituximab 2 x 0.5 g + MTX actually received rituximab 2 x 1 g + MTX, but has been analysed under 2 x 0.5 g for all analyses

Recruitment
The study period was from 05 Jan 2006 to 30 Sep 2008. A total of 755 patients were recruited in 169 centres across 27 countries. Approximately one quarter of patients were recruited in the US (182 patients). In non-US countries, patients were recruited mainly from Europe (95 patients in Eastern Europe and 159 patients from the rest of Europe), Asia (100 patients), Central America (97 patients), and South America (78 patients).

Conduct of the study
Four amendments were made to the protocol, none of which had a major impact on the conduct of the study.

Baseline data
Data are presented in tables 5 and 6.

Table 5: Summary of Demographic data (ITT)

	Placebo + MTX (N=249)	Rituximab 2x0.5g + MTX (N=249)	Rituximab 2x1.0g + MTX (N=250)
Sex			
n	249	249	250
Female	192 (77.1%)	203 (81.5%)	212 (84.8%)
Male	57 (22.9%)	46 (18.5%)	38 (15.2%)
Region			
n	249	249	250
US	60 (24.1%)	61 (24.5%)	60 (24.0%)
ROW	189 (75.9%)	188 (75.5%)	190 (76.0%)
Race			
n	249	249	250
Caucasian/White	161 (64.7%)	164 (65.9%)	160 (64.0%)
Black	12 (4.8%)	11 (4.4%)	12 (4.8%)
Oriental	34 (13.7%)	27 (10.8%)	31 (12.4%)
Native American	0 (0.0%)	1 (0.4%)	2 (0.8%)
Other	42 (16.9%)	46 (18.5%)	45 (18.0%)
Ethnicity			
n	249	249	250
Hispanic	76 (30.5%)	78 (31.3%)	84 (33.6%)
Non-Hispanic	173 (69.5%)	171 (68.7%)	166 (66.4%)
Age (years)			
n	249	249	250
Mean	48.06	47.87	47.89
SD	12.692	13.391	13.324
Median	50.00	49.00	47.50
Minimum	18.0	18.0	18.0
Maximum	77.0	77.0	79.0
Weight (kg)			
n	248	249	244
Mean	71.70	71.42	71.41
SD	18.008	18.881	17.828
Median	68.50	68.00	67.40
Minimum	41.0	40.0	38.1
Maximum	140.4	170.0	143.6
Height (cm)			
n	248	249	244
Mean	162.73	162.58	161.30
SD	10.525	9.480	10.060
Median	161.00	163.00	161.00
Minimum	140.0	132.0	131.0
Maximum	190.0	193.0	193.0

ROW = Rest of World
Native American has been selected from the free text of the other category.
Oriental includes patients recorded as Asian from the free text of the other category.
The race category 'other' consists of: BRASILIAN, WHITE GREEK, MULATTO, MIXED WHITE/BLACK, MESTIZO, MESTIZA, MESTIZE, HISPANIC, MEXICAN, MEXICAN - AMERICAN, CAPE VERDIAN, FIRST NATION, CHINESE/CARIB INDIAN/SPANISH, EAST INDIAN, MEZTIZE

Table 6: Baseline Disease Characteristics (ITT)

	Placebo + MTX (N=249)	Rituximab 2x0.5g + MTX (N=249)	Rituximab 2x1.0g + MTX (N=250)
RA disease duration (years)			
n	249	249	250
Mean	0.907	0.990	0.923
SD	1.1293	1.0735	1.2549
Median	0.416	0.452	0.404
Minimum	0.01	0.00	0.01
Maximum	8.37*	3.95	11.88*
Previous DMARDS (excluding methotrexate)			
n	249	249	250
No	174 (69.9%)	178 (71.5%)	172 (68.8%)
Yes	75 (30.1%)	71 (28.5%)	78 (31.2%)
Number of previous DMARDS (excluding methotrexate) in patients previously exposed			
n	75	71	78
Mean	1.1	1.2	1.1
SD	0.41	0.49	0.39
Median	1.0	1.0	1.0
Minimum	1	1	1
Maximum	3	3	3
Swollen Joint Count (66 joints) [SJC]			
n	249	249	250
Mean	20.0	22.4	21.6
SD	12.03	12.77	10.95
Median	16.0	19.0	19.0
Minimum	7	4	8
Maximum	66	66	66
Tender Joint Count (68 joints) [TJC]			
n	249	249	250
Mean	32.7	34.0	33.2
SD	16.64	15.67	14.97
Median	29.0	32.0	31.0
Minimum	8	5	8
Maximum	68	68	68
C-Reactive Protein (mg/dl) [CRP]			
n	249	249	250
Mean	3.1871	3.4432	3.0282
SD	2.79306	3.10356	2.72083
Median	2.4600	2.7100	2.4350
Minimum	0.068	0.105	0.105
Maximum	18.700	20.100	17.500
HAQ-DI			
n	249	248	250
Mean	1.835	1.774	1.733
SD	0.6073	0.6972	0.6617
Median	1.875	1.875	1.813
Minimum	0.13	0.00	0.00
Maximum	3.00	3.00	3.00
Disease Activity Score [DAS28-ESR]			
n	246	248	248
Mean	7.07	7.11	7.04
SD	0.983	0.994	0.982
Median	7.18	7.17	7.13
Minimum	4.0	3.4	3.4
Maximum	9.0	9.1	9.1
Rheumatoid Factor Status			
n	249	249	250
RF negative	32 (12.9%)	33 (13.3%)	37 (14.8%)
RF positive	217 (87.1%)	216 (86.7%)	213 (85.2%)
Total Genant-Modified Sharp Score			
n	246	248	250
Mean	7.354	7.668	6.880
SD	10.8712	11.7461	10.6281
Median	3.325	3.800	2.700
Minimum	0.00	0.00	0.00
Maximum	66.95	94.20	81.50

RF negative patients are those patients with a concentration < 20 IU/ml.
RF positive patients are those patients with a concentration >= 20 IU/ml.
Source: TDE11dc_1 and TDE11blc_1.
* 4 patients had a disease duration of > 4 years - these patients were excluded from the PP analysis

Numbers analysed

All patients who were randomised and received at least one or part of an infusion were included in the ITT and Safety populations. These populations differed slightly because three patients received a treatment other than that to which they were randomised (for their first course of treatment only, receiving the correct treatment for the second course). These patients were analyzed according to their randomised treatment for efficacy (ITT and MITT) and according to the treatment they received in the

first course for safety. Thirty-three patients did not have both a screening and post-BL radiographic assessment and were excluded from the MITT population, while a further 76 patients were excluded from the per protocol analysis due to significant protocol violations, predefined as reasons for exclusion. Principal reasons (not mutually exclusive) were:
•received study medication that underwent a temperature excursion (16 patients)
•started oral glucocorticoids at a dose ≥ 5mg/day and continued for ≥ 6 months (13 patients)
•received <80% of planned dose of each course of study medication (13 patients)
•blind broken or compromised (12 patients)
•received incorrect study medication or incorrect randomisation number (10 patients)
The summary of analysis population is presented in Table 7.

Table 7: Summary of Analysis Population

	Placebo + MTX	Rituximab (2 × 0.5 g) +MTX	Rituximab (2 x 1g) +MTX
No of patients randomized	251	252	252
No included in ITT	249	249	250
Excluded (received no study tmt)	2	3	2
No included in Safety*	250	249	249
No included in MITT	232	239	244
Excluded (did not have BL and post-BL radiolographic assessment)	17	10	6
No in Per Protocol	202	219	218
Excluded (due to significant protocol violations)	30	20	26

Patients displayed as randomized, except for safety
* patients receiving medication other than that to which they were randomized are counted under the treatment they actually received at the first treatment course, with one exception: patient 5473 randomised to rituximab 2 x 0.5 g + MTX actually received rituximab 2 x 1 g + MTX, but has been analysed under 2 x 0.5 g

Outcomes and estimation
The comparison between the three treatment arms showed statistically significant differences (global p value = 0.0016). Table 8 presents the results from radiographic endpoints (primary and secondary) between the treatment arms at week 52.

Table 8: Week 52 Outcomes of IMAGE Study in MTX naïve patients (early RA)

Endpoints (ITT/mITT (n))	RTX low dose, Group A **249/239**	RTX high dose, Group B **250/244**	Placebo, Group C **249/232**	Group comparisons, p-values (95% CI of difference)
*Radiographic progression (*mITT)				
mTSS mean change from baseline (SD)	**+0.646 (1.9)**	**+0.359 (1.0)**	**+1.079 (4.0)**	**A vs. C: ns; B vs. C: 0.0004, A vs. B: 0.036**
Mean baseline value (SD):	**7.46 (11.7)**	**6.85 (10.6)**	**7.10 (10.4)**	
% no progression of joint damage	57.7	63.5	53.4	**A vs. C: ns (-4.3-16), B vs. C: 0.03 (1.5-18.6)**

Maintenance of effect IMAGE Study: Radiographic progression

Preliminary data of the open-label extension period are available from about 20% of the study population (n=151). Patients on rituximab treatment in the first randomised period of the study could continue their rituximab treatment with 1000 mg dose, and patients on placebo (MTX alone) could be transferred to rituximab 1000 mg courses.

The effect of rituximab on prevention of bone erosion was maintained until observational period of 2 years in the patients who had been previously treated with rituximab in the blind phase. In patients

that had been treated with rituximab placebo (MTX alone) in the trial phase, progression in bone erosion still continued after transfer to active rituximab treatment, though to a lesser extent than in the first year (see Table 9 below).

Table 9: Annualised Progression Rates of Modified Total Sharp Score (Observed Cases) (mITT)

Patients on rituximab 0.5 g or Placebo were converted to rituximab 1 g after 1 year.

	MTX-Naïve		
	IMAGE (Week 104 Subset)		
Annualized Progression Rate of mTSS	**Placebo +MTX**	**RTX 0.5g +MTX**	**RTX 1g +MTX**
0 to 24 weeks	0.418 (n=43)	0.583 (n=54)	0.712 (n=53)
24 weeks to 1 year[a]	1.066 (n=43)	0.245 (n=53)	-0.073 (n=52)
1 Year to 2 years	0.695 (n=44)	-0.082 (n=53)	0.001 (n=52)

[a] Week 52 for IMAGE, Week 56 for REFLEX

The MAH submitted data comparing the efficacy of rituximab and other biologics therapies in early RA patients naïve to MTX. The table 10 below presents the radiographic and clinical outcomes of rituximab therapy (IMAGE study) compared to those observed with other biologic therapies as abatacept (AGREE study), adalimumab (PREMIER study), infliximab (ASPIRE study) and etanercept (COMET study).

Table 10: Comparison of efficacy across studies with biologic therapies in early RA

	IMAGE	**AGREE**	**PREMIER**	**ASPIRE**	**COMET**
Regimen	MTX vs. MTX + Rituximab	MTX vs. MTX + Abatacept	MTX vs. MTX + Adalimumab	MTX vs. MTX + Infliximab	MTX vs. MTX + Etanercept
Patient population*					
MTX naïve	Yes	Yes	Yes	Yes	Yes
Mean Disease Duration (years)	0.9	0.5	0.7	0.9	0.8
Mean DAS28-ESR	7.1	6.3†	6.3	6.7	6.5
Radiographic Outcomes*					
Degree of inhibition over MTX alone (%)	67%	41%	77%	86%	89%
Patients with no progression (%)	64%	61%	64%	nr	80%
Clinical Outcomes (difference from control)**					
ACR20 (%)	16%	nr	10%	12%	19%
ACR50 (%)	23%	15%	16%	18%	22%
ACR70 (%)	22%	16%	18%	16%	20%
DAS28 LDA (%)	23%	nr	nr	nr	23%
DAS28 remission (%)	18%	18	22%	16%	22%

* Data from MTX+"biologic" arm using approved doses. Rituximab 2 x 1g group data ** Differential between MTX + biologic group and MTX control group. † DAS28-CRP, nr: not reported

SERENE study

SERENE study is a randomised, placebo controlled, double-blind, parallel group, international study designed to evaluate the safety and efficacy of rituximab in combination with MTX, compared to MTX monotherapy, in patients with active RA.

METHODS

Study Participants
The target population for this study was patients with active RA, who had had an inadequate response to MTX. Both RF positive and RF negative patients were potentially eligible, but the overall proportion of RF negative patients was intended to be limited to 20% of the total sample size.

The inclusion criteria were the following:
• Patients with active RA for at least six months and patients who have had an inadequate therapeutic response to MTX.
• ≥ 8 SJC (66 joint count), and ≥ 8 TJC (68 joint count) at screening and baseline.
• CRP ≥ 0.6 mg/dL (6 mg/L) or ESR ≥ 28 mm/h.
• Use of NSAIDs permitted if stable for at least 2 weeks prior to baseline.
• Age 18-80 years.
• Glucocorticoids ≤ 10 mg/day prednisolone or equivalent permitted if stable for at least 4 weeks prior to baseline.

The exclusion criteria were the following:
• Rheumatic autoimmune disease other than RA, or significant systemic involvement secondary to RA (including but not limited to vasculitis, pulmonary fibrosis or Felty's syndrome). Secondary Sjögren's syndrome or secondary limited cutaneous vasculitis with RA is permitted.
• Functional class IV as defined by the ACR Classification of Functional Status in RA.
• History of, or current, inflammatory joint disease other than RA (including, but not limited to, gout, reactive arthritis, psoriatic arthritis, seronegative spondyloarthropathy, Lyme disease) or other systemic autoimmune disorder (including, but not limited to, systemic lupus erythematosus, inflammatory bowel disease, scleroderma, inflammatory myopathy, mixed connective tissue disease or any overlap syndrome).
• Diagnosis of JIA or JRA and/or RA before age 16.

Treatments
Patients were randomised to one of three treatment arms: low dose rituximab (2 x 0.5 g), high dose rituximab (2 x 1 g) or placebo. The infusions were preceded with methylprednisolone 100 mg IV, to prevent infusion reactions. All patients continued to receive concomitant MTX 10-25 mg/week at a stable dose, and 5 mg/week folic acid or equivalent to counteract MTX toxicity, and could remain on background stable oral glucocorticoid (<= 10 mg/day prednisolone or equivalent) and stable NSAIDs. After receiving study medication on day 1 and day 15 the patients returned for safety and efficacy assessments at weeks 4, 8, 12, 16, 20 and 24. Evaluation of the primary endpoint (ACR20) occurred at week 24 (placebo-controlled comparison), with additional analysis being performed at week 48 (active dose comparison). The table 11 presents the schedule of treatments.

Table 11: Schedule of treatments

Group	Rituximab or Placebo (Infusions on Days 1 and 15)	Glucocorticoids (IV on Days 1 and 15)	MTX (weekly)
Group A	Rituximab 500 mg i.v.	100 mg i.v. methylprednisolone	10-25 mg/wk, p.o. or parenteral (as prescribed)
Group B	Rituximab 1000 mg i.v.	100 mg i.v. methylprednisolone	10-25 mg/wk, p.o. or parenteral (as prescribed)
Group C	Placebo Rituximab i.v,	100 mg i.v. methylprednisolone	10-25 mg/wk, p.o. or parenteral (as prescribed)

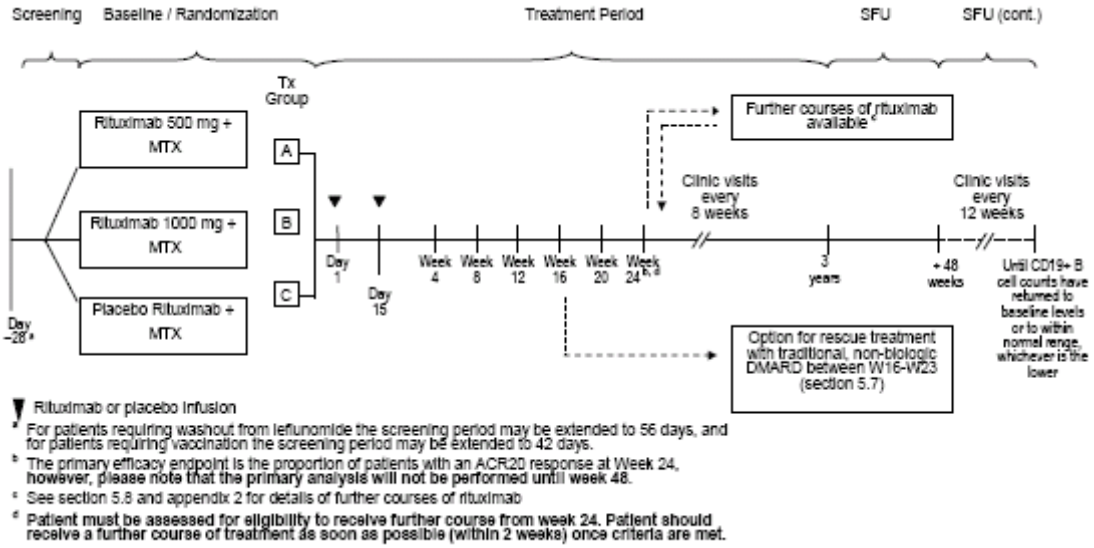
Between week 16 and week 23, patients who had less than a 20% improvement in both TJC and SJC compared to baseline were allowed to initiate "rescue" treatment with one non-biologic DMARD, the choice of which is at the discretion of their treating physician. These patients could receive further courses of rituximab if eligible, but were considered to be non-responders for all categorical efficacy endpoints at week 24. Rescue medication had to remain stable for the duration of the study except for safety reasons. Switching of or additional DMARDs were not permitted.
Beginning at week 24 and for up to three years in this study, all patients were evaluated at every study visit (every eight weeks) for their eligibility to receive retreatment courses of active rituximab (including patients randomised to placebo + MTX).
Patients who experienced a flare in disease activity could also be assessed at unscheduled visits. From week 24 onwards, all patients were retreated every 24 weeks if they were not in clinical remission

(defined as a Disease Activity Score (DAS28-ESR) $\leq$ 2.6) and they also met all the safety criteria specified in the protocol.

All patients who withdrew from the study at any point or completed the total 3-year treatment period were/are to return for safety follow up (SFU) assessments at weeks 4, 12, 24, 36 and 48 after withdrawal or completion, effectively following the patient for approximately 1 year after withdrawal from or completion of the study. If a patient's peripheral B cell count had/have not returned to their baseline level or to within the normal range, whichever was lower, after 1 year, Safety Follow-up visits were/are to be performed at 12 week intervals until B cell repletion occurred.

The trial design is shown in Figure 4.

Figure 4: Overall of study design



Objectives
The objectives of the study were as follows:
1. To determine the efficacy and safety at week 24 of rituximab 2 x 0.5 g and rituximab 2 x 1.0 g in combination with MTX compared to continued MTX monotherapy in patients with active RA who had had an inadequate clinical response to MTX.
2. To explore a dose separation of rituximab 2 x 0.5 g IV from rituximab 2x 1.0 g IV at week 48.
3. To investigate by a population analyses approach the PK of rituximab in the target RA patient population and the influence of covariates on the PK parameters.
4. To explore the long-term efficacy and safety of further courses of rituximab.

Outcomes/endpoints
The primary efficacy endpoint was ACR20 at Week 24.
Secondary efficacy endpoints were: ACR50, ACR70 at week 24 and week 48, change in DAS28-ESR at week 24 and week 48 and DAS28-ESR low disease activity at week 24 and week 48.

A number of additional secondary endpoints were also prespecified, including radiographic, clinical and physical function endpoints.

Sample Size
The target population for the study was 500 patients with 167 patients randomised to each group. The sample size was expected to give 90% power to detect differences between each rituximab treatment group and the placebo group.

Randomisation
Randomisation was stratified by region (US versus ROW) and RF status (positive versus negative) using the randomisation list provided by the sponsor.

Blinding
The Randomisation List was not available at the study centre, to the sponsor monitors, project statisticians or to the sponsor's project team. A patient's treatment assignment was only unblinded

when knowledge of the treatment was essential for the further management of the patient. Procedures were in place to ensure integrity of the data after such unblinding.

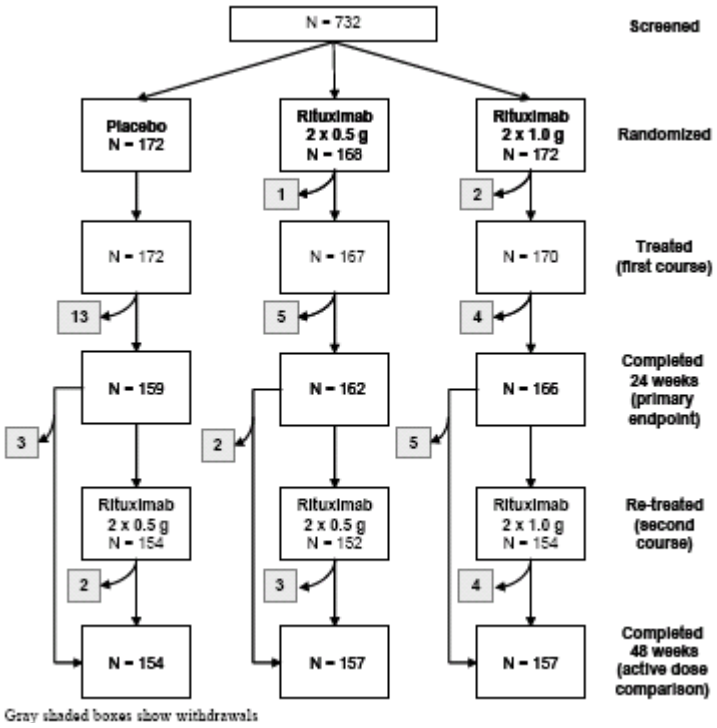
Statistical Hypothesis and Planned Sample Size

Four analysis populations were defined:
- ITT: All patients who were randomised and received any part of an infusion of study medication were included in the ITT population.
- PP: Patients from the ITT population excluding patients who significantly deviated from the inclusion criteria, exclusion criteria or study protocol.
- Safety: All patients who were randomised and received any part of an infusion of the study drug
- PK: All patients who received at least one infusion of rituximab and provided at least one serum sample for PK evaluation were considered as pharmacokinetically evaluable patients.

Primary as well as secondary endpoints were analysed using the Cochran-Mantel Haenszel test statistic, stratifying by region and RF status. Analysis was adjusted for multiplicity with a 0.025 two-sided significance level.
ACR20 response rates at Week 24 were also analysed by logistic regression. No adjustments were made for multiplicity for this analysis. Non-responder imputation was applied for missing data. All analyses were stratified by region and RF status. Claims were tested hierarchically, according to a pre-defined decision tree.

RESULTS
Participant flow
A total of 511 patients were recruited and randomised between 25 Oct 2005 and 15 Nov 2006.
A further 220 patients were screened but failed to meet the eligibility criteria.
Of the 511 patients randomised, 509 received at least one infusion, 487 completed 24 weeks, and 468 completed 48 weeks. A second course of treatment was given to 460 patients, 451 of whom completed 48 weeks in the study.
The proportion of patients who completed week 24 was high in all groups; 92.4% of randomised patients in the placebo + MTX arm and 96.4% and 96.5% in the rituximab 2 x 0.5 g + MTX and 2 x 1.0 g + MTX arms, respectively. The proportion of patients completing 48 weeks in the study was 89.5% in the placebo/rituximab 2 x 0.5 g + MTX arm, 93.5% in the rituximab 2 x 0.5 g + MTX arm, and 91.3% in the rituximab 2 x 1.0 g + MTX arm.
Around 90% of patients in all three arms were retreated after week 24. Of these re-treated patients around 75% had received the first infusion of the second course by week 28 for both rituximab arms, and this percentage rose to 89% for 2 x 0.5 g + MTX and 85% for 2 x 1.0 g + MTX by week 32. The patient disposition is presented in Figure 5.

Figure 5: Disposition of patients up to week 48



Recruitment
The study period was from 25 October 2005 to 15 November 2007. A total of 512 patients were recruited in 102 centres across 11 countries: Canada (3 centres), France (3 centres), Germany (4 centres), Guatemala (1 centre), Mexico (5 centres), Poland (2 centres), Romania (4 centres), Slovenia (1 centre), Sweden (3 centres), United Kingdom (8 centres) and the USA (68 sites).

Conduct of the study
Two amendments were made to the protocol, none of which had a major impact on the conduct of the study.

Baseline data
Data are presented in tables 12 and 13.

Table 12: Summary of Demographic Data (Safety Population)

	Placebo + MTX / Rituximab 2x0.5g + MTX (N=172)	Rituximab 2x0.5g + MTX (N=167)	Rituximab 2x1.0g + MTX (N=170)
Sex			
n	172	167	170
Female	147 (85.5%)	133 (79.6%)	138 (81.2%)
Male	25 (14.5%)	34 (20.4%)	32 (18.8%)
Region			
n	172	167	170
US	80 (46.5%)	78 (46.7%)	78 (45.9%)
ROW	92 (53.5%)	89 (53.3%)	92 (54.1%)
Race			
n	172	167	170
Caucasian/White	142 (82.6%)	134 (80.2%)	137 (80.6%)
Black	5 (2.9%)	8 (4.8%)	7 (4.1%)
Oriental	1 (0.6%)	0 (0.0%)	1 (0.6%)
Native American	2 (1.2%)	1 (0.6%)	1 (0.6%)
Other	22 (12.8%)	24 (14.4%)	24 (14.1%)
Ethnicity			
n	172	167	170
Hispanic	36 (20.9%)	33 (19.8%)	32 (18.8%)
Non-Hispanic	136 (79.1%)	134 (80.2%)	138 (81.2%)
Age (years)			
n	172	167	170
Mean	52.16	51.91	51.30
SD	12.390	12.926	12.644
Median	54.00	54.00	53.00
Minimum	18.0	20.0	18.0
Maximum	79.0	78.0	79.0
Weight (kg)			
n	172	167	170
Mean	77.83	76.57	78.26
SD	18.617	22.000	21.373
Median	74.90	70.30	74.75
Minimum	40.8	41.4	41.0
Maximum	136.7	149.5	168.2
Height (cm)			
n	172	167	170
Mean	162.56	164.40	163.79
SD	8.276	10.045	10.143
Median	162.50	163.00	164.00
Minimum	126.0	141.0	137.0
Maximum	183.0	196.0	188.0
Body Surface Area (m**2) [BSA]			
n	172	167	170
Mean	1.82	1.82	1.83
SD	0.218	0.261	0.258
Median	1.81	1.78	1.81
25% Percentile	1.66	1.62	1.67
75% Percentile	1.97	2.00	2.02
Minimum	1.3	1.3	1.3
Maximum	2.5	2.5	2.7

	Placebo + MTX / Rituximab 2x0.5g + MTX (N=172)	Rituximab 2x0.5g + MTX (N=167)	Rituximab 2x1.0g + MTX (N=170)
Smoking History			
n	172	167	170
Never Smoked	95 (55.2%)	103 (61.7%)	94 (55.3%)
Current Smokers	31 (18.0%)	23 (13.8%)	36 (21.2%)
Past Smokers	46 (26.7%)	41 (24.6%)	40 (23.5%)
Time since smoking cessation (years) - Past Smokers			
n	46	41	40
Mean	15.52	12.62	18.57
SD	10.677	9.936	13.949
Median	13.84	12.00	16.88
Minimum	0.1	0.2	0.3
Maximum	38.0	45.0	56.0
Frequency of Smoking (Current Smokers), Number of cigarettes/day			
n	31	23	36
0	0 (0.0%)	2 (8.7%)	0 (0.0%)
1-10	17 (54.8%)	13 (56.5%)	23 (63.9%)
11-20	7 (22.6%)	7 (30.4%)	9 (25.0%)
21-30	6 (19.4%)	1 (4.3%)	4 (11.1%)
>30	1 (3.2%)	0 (0.0%)	0 (0.0%)
Frequency of Smoking (Current Smokers), Number of cigars/day			
n	31	23	36
0	30 (96.8%)	21 (91.3%)	35 (97.2%)
1	1 (3.2%)	0 (0.0%)	0 (0.0%)
2-5	0 (0.0%)	1 (4.3%)	0 (0.0%)
6-10	0 (0.0%)	1 (4.3%)	1 (2.8%)
Frequency of Smoking (Current Smokers), Number of pipes/day			
n	31	23	36
0	31 (100.0%)	23 (100.0%)	36 (100.0%)
Female Reproductive Status			
n	147	133	138
Childbearing potential with contraceptive protection	30 (20.4%)	34 (25.6%)	30 (21.7%)
Surgically sterilised	43 (29.3%)	27 (20.3%)	43 (31.2%)
Postmenopausal	64 (43.5%)	62 (46.6%)	58 (42.0%)
Naturally sterile	1 (0.7%)	0 (0.0%)	0 (0.0%)
Abstinence/partner surgically sterile	9 (6.1%)	10 (7.5%)	7 (5.1%)

ROW - Rest of World
Native American has been selected from the free text of the other category. Races specified under the other category are: MESTIZA, MESTIZE, MESTIZO, MEZTIZO, MIXED

Table 13: Summary of Baseline Disease Activity (Safety Population)

	Placebo + MTX / Rituximab 2x0.5g + MTX (N=172)	Rituximab 2x0.5g + MTX (N=167)	Rituximab 2x1.0g + MTX (N=170)
Swollen Joint Count (66 joints) [SJC]			
n	172	167	170
Mean	20.9	18.6	19.5
SD	11.26	9.62	10.32
Median	18.0	16.0	17.0
Minimum	8	2	8
Maximum	66	55	66
Tender Joint Count (68 joints) [TJC]			
n	172	167	170
Mean	30.2	27.1	28.7
SD	15.94	14.10	14.98
Median	27.0	25.0	25.0
Minimum	8	2	8
Maximum	68	68	68
HAQ-DI			
n	172	166	170
Mean	1.647	1.558	1.589
SD	0.6053	0.6328	0.6347
Median	1.625	1.500	1.625
Minimum	0.13	0.13	0.00
Maximum	3.00	2.88	3.00
Patients Global Assessment of Disease Activity (mm)			
n	171	167	169
Mean	62.9	62.6	60.7
SD	19.71	19.07	22.89
Median	65.0	65.0	61.0
Minimum	4	10	4
Maximum	100	100	100
Patients Assessment of Pain (mm)			
n	171	167	169
Mean	58.5	56.2	53.5
SD	19.57	20.60	21.89
Median	60.0	58.0	54.0
Minimum	3	10	3
Maximum	100	100	100
Physicians Global Assessment of Disease Activity (mm)			
n	172	167	170
Mean	62.5	61.5	60.8
SD	17.35	18.37	18.17
Median	62.5	65.0	61.5
Minimum	7	8	5
Maximum	99	100	98
C-Reactive Protein (mg/dl) [CRP]			
n	172	167	170
Mean	2.2381	2.0519	1.9820
SD	2.40696	1.92735	2.39851
Median	1.3000	1.4900	1.2000
Minimum	0.063	0.036	0.020
Maximum	15.900	10.200	18.500
Erythrocyte Sedimentation Rate (mm/h) [ESR]			
n	172	167	170
Mean	43.56	42.54	44.18
SD	25.586	22.582	26.910
Median	40.00	39.00	40.00
Minimum	4.0	7.0	0.0
Maximum	140.0	121.0	140.0
Disease Activity Score [DAS28-ESR]			
n	171	167	168
Mean	6.54	6.40	6.49
SD	1.015	0.951	1.061
Median	6.51	6.36	6.49
Minimum	3.0	3.9	2.8
Maximum	8.7	8.7	9.1
Disease Activity Score [DAS28-CRP]			
n	171	167	169
Mean	5.95	5.81	5.86
SD	0.972	0.912	0.967
Median	5.83	5.84	5.90
Minimum	3.0	2.9	3.0
Maximum	8.1	8.0	8.2

Eligibility criteria for CRP and ESR were not based on baseline values.
RF negative patients are those patients with a concentration < 20 IU/ml.
RF positive patients are those patients with a concentration >= 20 IU/ml.

Number analysed

The summary of analysis population sis presented in table 14.

Table 14: Summary of Analysis Population (All Patients)

	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX	Total
Number Randomized	172	168	172	511
Main Study Populations				
ITT Population	172	167	170	509
PP Population	139	138	147	424
Safety Population	172	167	170	509
PK Population		167	169	336

Outcomes and estimation
The table 15 presents the outcomes at Week 24 (rituximab low and high dose, placebo) and week 48 rituximab high and low dose. Patients from placebo arm who were converted to rituximab low dose at Week 24 (blinded) were excluded from analyses at Week 48.

Table 15: Outcomes of SERENE Study

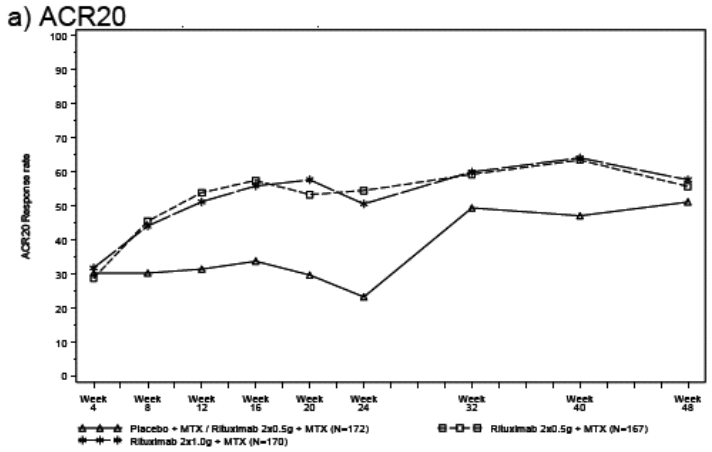
	Placebo + MTX (N=172)	Rituximab 2 × 0.5 g +MTX (N=167)	Rituximab 2 x 1 g + MTX (N=170)
Primary endpoint			
ACR20 response (%)	40 (23.3%)	91 (54.5%)	86 (50.6%)
p-value		<0.0001	<0.0001
Secondary endpoints			
ACR50 response (%)	16 (9.3%)	44 (26.3)***	44 (25.9%)***
ACR70 response (%)	9 (5.2%)	15 (9.0%)	17 (10.0%)
Mean change in DAS28-ESR score from baseline [a]	-0.75	-1.76***	-1.69***
EULAR Responses (%)			
Moderate	50 (29.1%)	82 (49.1%)***	87 (51.2%)***
Good	8 (4.7%)	29 (17.4%)***	20 (11.8%)***
DAS28-ESR endpoints			
Low disease activity (DAS-28-ESR ≤ 3.2) (%)	8 (4.7%)	29 (17.5%)**	21 (12.4%)*
Clinical remission DAS28-ESR <2.6) (%)	4 (2.3%)	16 (9.6%)**	16 (9.4%)**
HAQ-DI Improvement, mean change from baseline ≥ MCID = 0.22 (%)	82 (47.7%)	109 (66.1%)**	99 (58.2%)**
FACIT-Fatigue mean change from baseline Adjusted mean	2.119	5.513**	6.525***
SF-36 mean change from baseline			
SF36 Summary Score adjusted mean			
Mental Component Summary	1.656	3.311	4.576**
Physical Component Summary	2.489	5.912***	5.704***
Improvement, mean change from baseline			
Mental Health ≥ MCID = 6.33	35 (23.8%)	51 (33.6%)	54 (34.8%)*
Physical Health ≥ MCID = 5.42	45 (30.6%)	70 (46.1%)**	75 (48.4%)**

MCID = minimum clinically important difference
a: negative change = improvement.
* p<0.05. **p<0.01 ***p ≤ 0.0001

Maintenance of effect:

The Study is still ongoing. Data after week 48 are not available yet. The results of ACR20 at week 48 are presented in figure 6:

Figure 6: ACR20 Responder Rates SERENE Study



Supportive studies

REFLEX study

REFLEX study was a Phase III, randomised, placebo-controlled, double-blind, multicentre study that investigated the safety and efficacy of rituximab in combination with MTX in patients with active RA who had had an inadequate response to anti-TNFα therapies.

Data from REFLEX study have been submitted as part of the initial application for the RA indication and re-evaluated with data from the REFLEX extension study (including two-year radiographic outcomes) to support this type II variation.

METHODS

Study Participants
The target population for this study was patients with active RA, for at least 6 months, who had experienced an inadequate response to previous treatments with anti-TNFα therapies.

Treatments
Eligible patients were randomised to receive infusions of rituximab (1.0 g, Group A) or placebo (Group B) i.v. on days 1 and 15. Both groups also received stable concomitant doses of MTX (10-25 mg/week p.o. or parenteral) and folate (≥ 5 mg/week or equivalent). In addition, all patients received a corticosteroid regimen consisting of methylprednisolone, 100 mg i.v. administered 30 minutes prior to both infusions of rituximab or placebo, and prednisone, 60 mg p.o. on days 2-7, 30 mg p.o. on days 8-14, returning to baseline dose by day 16. Patients continued to receive any background corticosteroid (≤ 10 mg/day prednisone or equivalent) throughout the study, including during the rituximab/placebo treatment period (days 1-15).

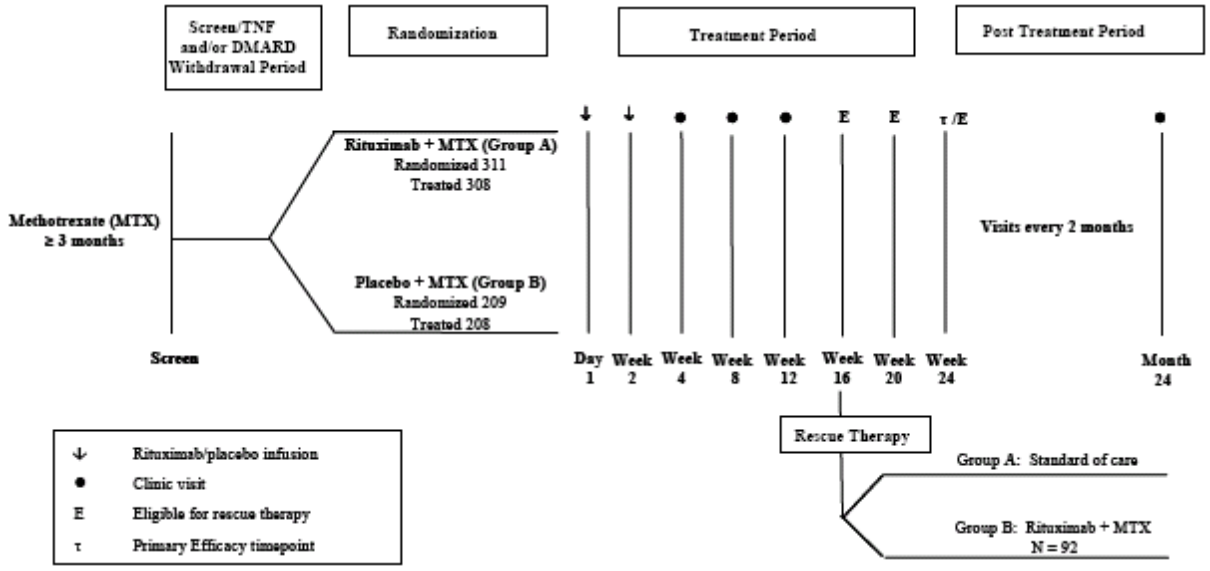
All patients who withdrew from the study at any time, and did not enter the rescue arm or the retreatment protocol, were encouraged to return for five observation period assessments (safety follow-up [SFU]), at weeks 4, 12, 24, 36, and 48 after withdrawal. Further 3 monthly follow-up visits continued in patients who remain B-cell depleted, until these cells returned to their original baseline or normal levels.

Rescue Therapy
Patients who had failed to achieve a 20% improvement from baseline in SJC and TJC between weeks 16 and 24 were to be considered for withdrawal as treatment failures. These patients were then potentially eligible to receive a single course of open-label, rituximab rescue therapy. Patients who had

initially been randomised to Group B (placebo) were eligible to receive rescue therapy with open-label rituximab 2 x 1 g, at the discretion of the investigator. Patients who were initially randomised to receive rituximab 2 x 1 g (Group A) were not eligible to receive rituximab rescue therapy and were withdrawn into the safety follow-up period, where they were permitted to receive standard of care treatment.

The trial design is shown in Figure 7.

Figure 7.Overall Study design



Study endpoints

The primary endpoint of the study was the proportion of patients with an ACR20 response at week 24.

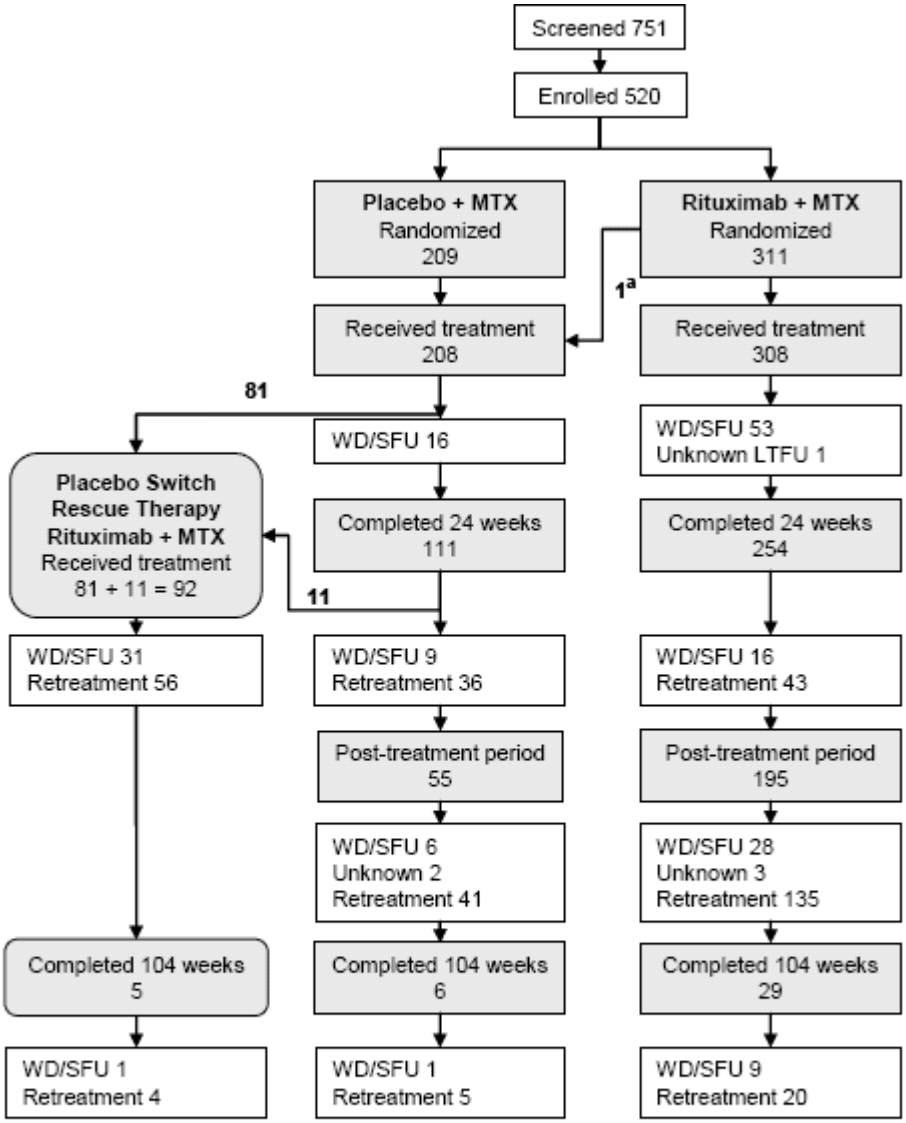
Secondary endpoints included ACR20/50/70 at week 104, major clinical response (ACR70 over 6 consecutive months), DAS28, EULAR response, HAQ, FACIT, SF36, and pharmacodynamic parameters.

RESULTS

Participant flow

The patient disposition is presented in Figure 8.

Figure 8. Disposition of patients



MTX: methotrexate
WD: early withdrawal
SFU: Safety follow up (Section 2.1)
Unknown = LTFU (lost to follow-up)
Retreatment given under separate protocol (WA17531/IDEC 102-21)
a: Patient 36679/5823 was shown in the rituximab arm in the week 24 CSR [1]

Baseline data
Data are presented in table 16.

Table 16. Summary of Demographic Data and Baseline Disease Characteristics

	Safety Population		ITT Population		Completers Population		Placebo Switch Population
	Placebo	Rituximab	Placebo	Rituximab	Placebo	Rituximab	
N	208	308	200	298	6	26	92
Males (%)	40 (19%)	57 (19%)	37 (19%)	56 (19%)	1	6 (23%)	15 (16%)
Caucasians (%)	181 (87%)	269 (87%)	174 (87%)	261 (88%)	4	21 (81%)	82 (89%)
Mean age at screening	52.8	52.3	52.9	52.3	61.3	53.6	50.5
Mean weight (kg)	80.36	77.14	80.52	77.65	82.92	72.23	80.57
Mean height	165.1	164.9	165.0	165.1	164.7	164.5	165.3
Mean BSA	1.87	1.83	1.87	1.84	1.90	1.78	1.87
Mean RA duration (yr)	11.67	12.07	11.75	12.15	10.08	10.58	11.67
Mean SJC	22.9	23.4	23.0	23.4	17.2	19.9	25.0
Mean TJC	33.0	33.9	33.0	33.9	27.8	25.7	36.0
Mean DAS	6.82	6.89	6.82	6.88	6.84	6.56	6.97
Mean HAQ-DI	1.95	1.90	1.94	1.90	1.63	1.60	2.04
Mean Sharp-Genant	48.0	48.3	48.3	48.0	47.8	42.4	47.6
Mean CRP	3.79	3.72	3.78	3.75	2.80	3.19	4.38
Mean ESR	48.47	47.96	48.47	47.87	51.83	45.12	50.05
B-cell count <LLN at baseline (%)[a]	22.4%	21%	.	.	4/5	27%	.
RF positive at baseline	164 (79%)	237 (77%)	159 (80%)	230 (77%)	6	15 (58%)	74 (80%)
Median previous DMARDS[b]	2.0	2.0	2.0	3.0	3.0	3.0	2.5
Median previous TNFs	1.0	1.0	1.0	1.0	1.0	1.0	1.5

a CD19 count LLN =80cells/µL
b: excluding methotrexate

Number analysed
The number of patients in each analysis population is presented in table 17.

Table 17. Analysis population

Number of Patients	Placebo	Rituximab
Main Study Arms		
Patients randomized	209	311
Safety population	208	308
ITT population	200	298
Completers population	6	26
Placebo Switch Arm		
Placebo switch safety population	92	92

Outcomes and estimation

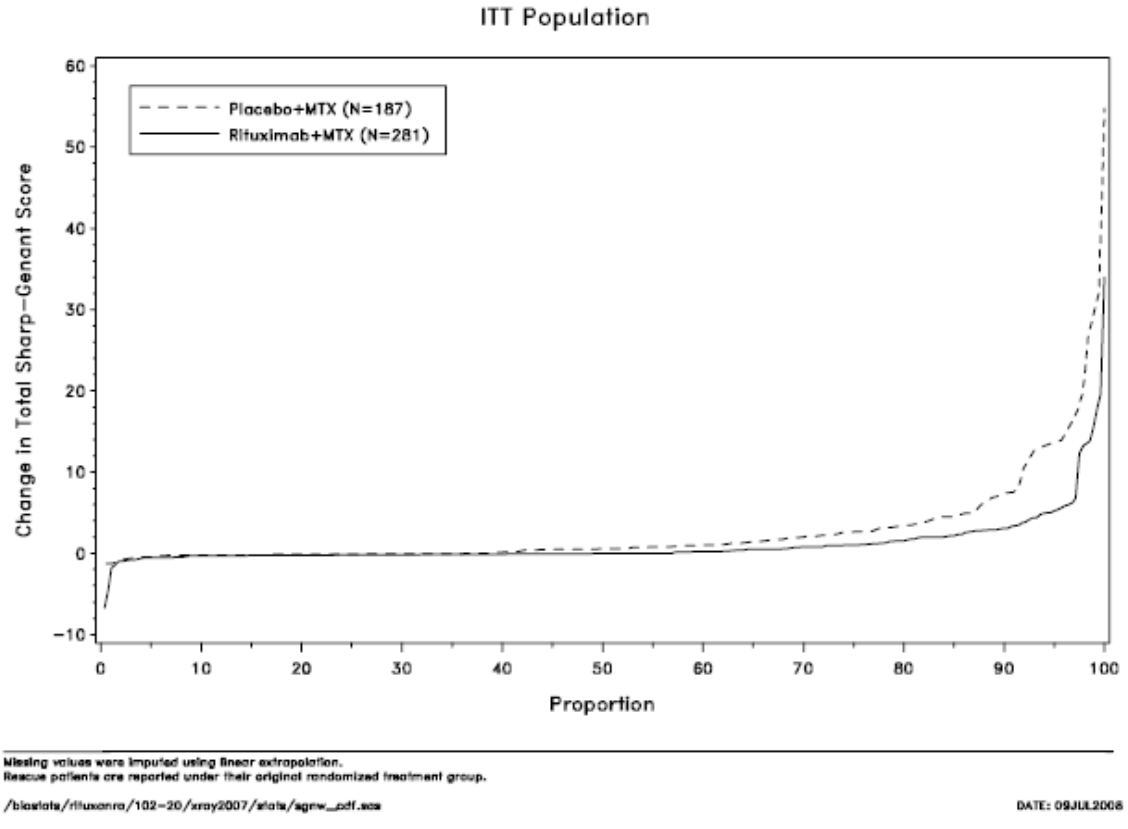
Table 18. Overview of efficacy results

Clinical Endpoints at Week 104 (Placebo Switch Data Excluded)

Parameter	Placebo +MTX N=208	Rituximab + MTX N=308
Patients who completed 104 weeks	6 (2.8%)	29 (9.4%)
ACR20 response	4 (2.0%)	17 (5.7%)
ACR50 response	1 (0.5%)	9 (3.0%)
ACR70 response	0	5 (1.7%)
Major Clinical Response (ACR70 duration ≥ 6 months)	0	11 (4%)
Mean change from baseline in DAS28 score	-1.95	-2.53
Good EULAR response	1 (0.5%)	6 (2.0%)
DAS28 Low disease activity	1 (0.5%)	6 (2.0%)
DAS28 Clinical remission	0	6 (2.0%)
Improved HAQ-DI score	3 (1.5%)	13 (4.4%)
Mean change from baseline in FACIT-F	-4.83	-7.19
Improved SF-36 mental health summary score	1 (0.5%)	8 (2.7%)
Improved SF-36 physical health summary score	3 (1.55)	11 (3.7%)

The cumulative distribution of change in mTTS over two years is presented in Figure 9.

Figure 9. Cumulative Distribution of Change in mTSS from baseline to week 104 (REFLEX)



The summary of radiographic outcomes of the REFLEX study and the two-year REFLEX-extension study is presented in Table 19.

Table 19. Summary of Radiographic Outcomes at 2 Years in Patients with an Inadequate Response to TNF-inhibitors (REFLEX, REFLEX-extension)

	Pbo/RTX 1g +MTX[a]	**RTX 1g/1g +MTX**
Outcomes at week 104 (2 Years)		
n	**187**	**281**
Mean change from baseline:		
Modified Total Sharp Score	2.81	1.14***
Erosion score	1.80	0.72***
Joint space narrowing score	1.00	0.42**
Number (proportion) of patients with no progression from baseline at Week 104 in mTSS	72 (39%)	160 (57%)***
Number (proportion) of patients with no progression from baseline to week 104 in erosion score	82 (44%)	170 (60%)**
Number (proportion) of patients with no progression at one year who maintained no progression at Week 104	71/86 (83%)	146/168 (87%)

Results on the physical function endpoints (REFLEX study) are presented in figure 10 and table 20.

Figure10. Mean Change in HAQ-DI over 24 weeks in patients with an adequate response toTNF-inhibitors (REFLEX)

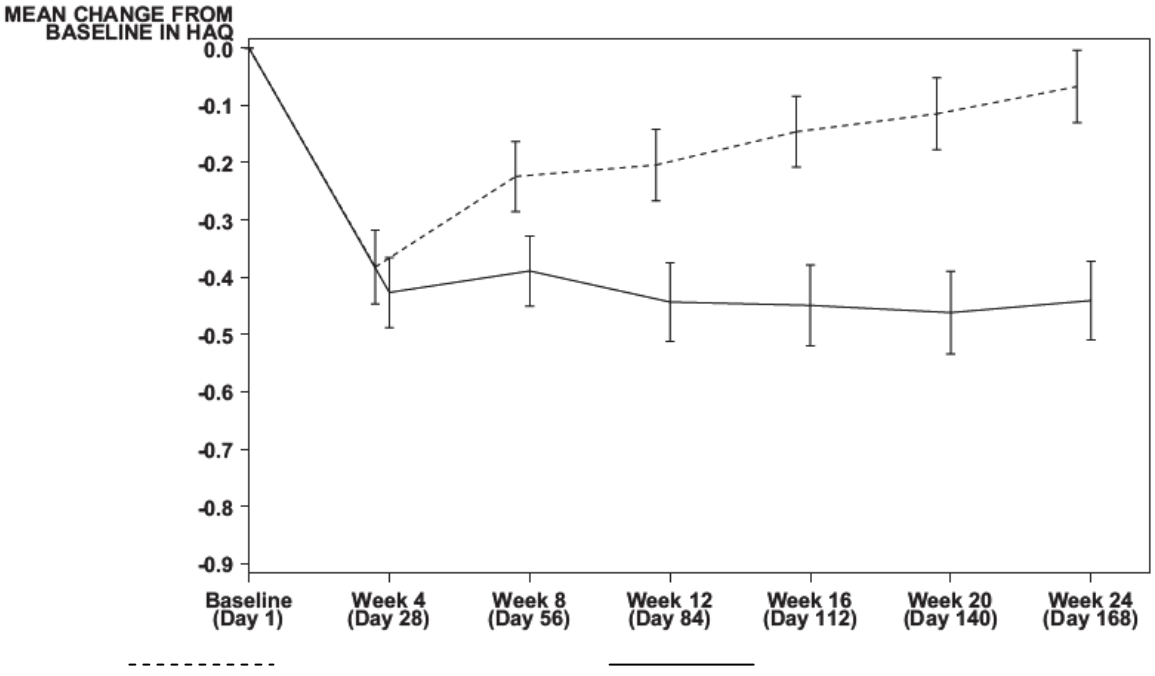


Table 20: Summary of Assessment of Physical Function at Week 24 in patients with an inadequate response to TNF-inhibitors (REFLEX)

	Placebo + MTX (n = 201)	Rituximab 2 × 1 g + MTX (n = 298)	p-value
Health Assessment Questionnaire (HAQ-DI)			
Mean Change in HAQ-DI (SD)	-0.1 (0.45)	-0.4 (0.60)	< 0.0001
Proportion of patients with improvement ≥0.25	20%	51%	na
SF-36 Physical Health Domains			
Mean Change in Physical Health (SD)	0.9 (5.65)	5.8 (8.47)	< 0.0001

na Not available
p-value from Analysis of Covariance with covariates being region and RF factor

MIRROR study
MIRROR study is a phase III, randomised, double-blind, parallel group, multicentre study in patients with active RA who were showing an inadequate clinical response to MTX therapy at the time of study entry.

Patients, who had previously been treated with no more than one biological agent approved for RA, were also eligible to enter the study (up to a maximum of 30% of the total sample size). Both RF positive and RF negative patients were eligible.

In this study, the use of dose escalation of rituximab was evaluated. Subjects (ITT=363) with inadequate response to MTX and/or MTX+TNF treatment were randomised to either dose extension arm (first course: 500 mg, second course: 1000 mg), stable low dose (1st & 2nd course 500 mg), or stable high dose (1st & 2nd course 1000 mg). Re-treatment with the 2nd course took place at Week 24. As this study was designed to investigate the effects of a repeat treatment, all patients were to receive a 2nd course.

Primary endpoint was ACR-20 response at Week 48. Subgroup analyses based on ACR20 response at week 24 were made to explore the impact of re-treatment. Data were analysed conform statistical methods in SERENE study. Stratification took place based on RF status, region and prior biologic use (about 30% of the population).

Of the 378 patients randomised, all but one received at least one infusion, 365 (97%) completed 24 weeks of follow up, 352 (93%) received a second course of treatment, and 340 (90%) went on to complete the full 48 weeks period of the study.

The results of MIRROR study are summarised in Table 21:

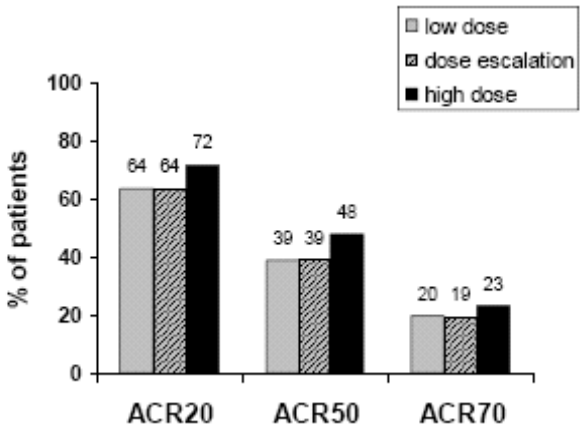
Table 21: Summary of clinical efficacy at week 48

The ACR 20/50/70 response at Week 48 after two courses of 1000 mg (high dose), two courses of 500 mg (low dose) or dose escalation (1st dose 500 mg, 2nd dose 1000 mg) are presented in figure 11.

	Rituximab (2 x 0.5g, 2x 0.5 g) + MTX	Rituximab (2 × 0.5 g, 2 x 1g) +MTX	Rituximab (2 x 1g, 2 x 1g) +MTX
ITT	N=123	N=127	N=113
Primary endpoint	79 (64)	82 (65)	77 (68)
ACR20 (%)			
p-value[a]		0.886	0.671
ITT-M2	N=134	N=119	N=93
ACR20 (%)	86 (64)	76 (64)	67 (72)
p-value[a]		0.816	0.242
ACR50 (%)	52 (39)	46 (39)	45 (48)
ACR70 (%)	27 (20)	23 (19)	21 (23)
Change in DAS28 n	n=132	n=118	n=93
[Mean (SD)]	-2.3 (1.3)	-2.4 (1.5)	-2.6 (1.4)
EULAR Response (%)			
None	36 (27)	33 (28)	10 (11)
Moderate	68 (51)	66 (56)	58 (62)
Good	30 (22)	20 (17)	25 (27)
Low disease activity	31 (23)	20 (17)	25 (27)
DAS remission	12 (9)	15 (13)	18 (19)
HAQ-DI ≥ MCID[b] (%)	93 (69)	86 (72)	67 (72)
SF36 domains ≥ MCID[c] (%)	n=121	n=112	n=86
Mental Health	58 (43)	48 (41)	37 (40)
Physical Health	69 (52)	66 (56)	53 (57)
FACIT-F ≥ MCID[d] (%)	n=125	n=115	n=91
	72 (58)	74 (64)	63 (69)

MCID = minimum clinically important difference
a p-value from CMH test, analysis was stratified by region, prior biologic use, RF status and treatment
b defined as decrease of ≥0.22
c defined as decrease of ≥6.33 for mental health score and change ≥5.42 for physical health score
d defined as increase ≥ 4
Source outputs: ETs16f_1_ACRX3NR_48_3A, ETs16f_6_ACRX3NR_48_3B, ETs16f_6_ACRX4NR_48_3B, ETs11u_6_C28E2L, ETs15f_6_EULINR_48_3B, ETs16f_6_D28E3L_48_3B, ETs16f_6_D28E4L_48_3B, ETs15f_6_HAQSLO_48_3B, ETs12f_6_CTLM6SI, ETs12f_6_CTLFCSI

Figure 11: ACR 20/50/70 Response at Week 48 after two courses of 1000 mg (high dose), two courses of 500 mg (low dose) or dose escalation (1st dose 500 mg, 2nd dose 1000 mg).



Re-treatment

Subgroup analyses based on ACR20 response at week 24 were made to explore the impact of re-treatment. Approximately 40% to 50% of non-responders by ACR criteria at week 24 subsequently responded after the second course of treatment. The majority (83%) ACR20 responders to the first course of treatment at week 24 maintained their response (at least ACR20) after the second course of treatment (week 48), also irrespective of the dose.

Subgroup analyses based on prior biologic use and RF status showed that ACR20 response rates were 61% in patients with prior biologic use versus 65% in patients without prior biologic use and 59% in RF negative versus 65% in RF positive patients.

Clinical studies in special populations (Ancillary analyses)

RF/anti-CCP status and efficacy

The MAH provided subgroup analyses based on RF-anti-CCP status. The CHMP concluded that interpretation of responses in seropositive/seronegative subgroups within individual studies is confounded by small numbers of patients.

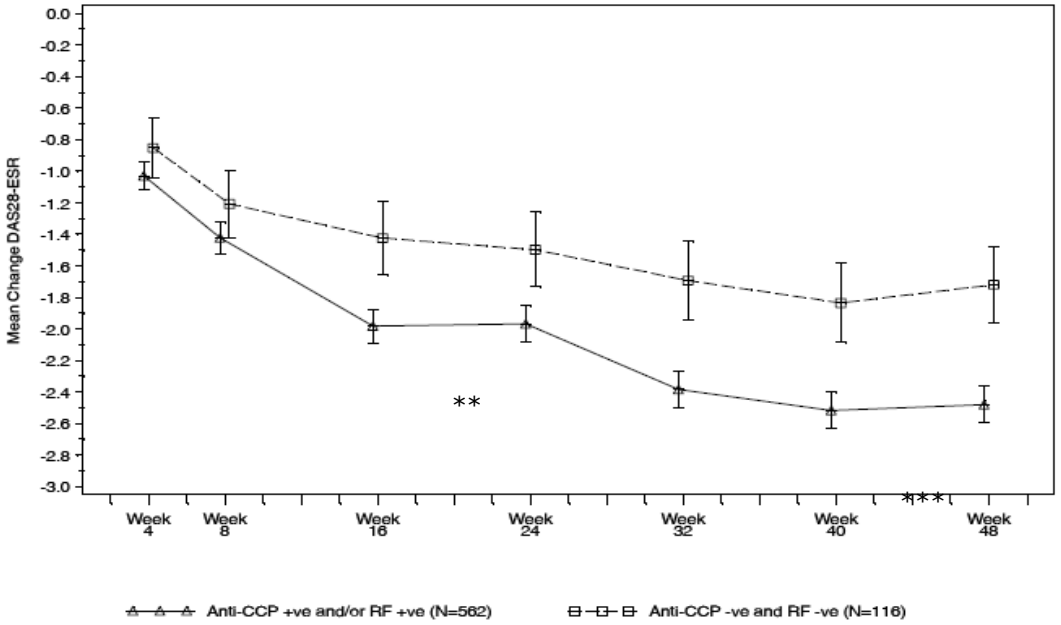
In reply to CHMP concern regarding the size of the sample, the MAH provided a pooled, retrospective analysis of rituximab (0.5 g and 1 g) treated patients from the SERENE and MIRROR studies based on autoantibody status. The results are presented in table 22 and Figure 12.

Table 22: Summary of ACR, EULAR and DAS28-ESR Outcomes by Baseline Autoantibody Status (Pooled MIRROR and SERENE Patients, all doses)

	Week 48		Odds Ratio (95% CI)
	Seronegative	Seropositive	(ref = seronegative group)
ACR Responses (n)	**101**	**506**	
ACR20 (%)	51.5	71. 1*	2.26* (1.3822, 3.5816)
ACR50 (%)	22.8	44.9**	2.72** (1.5752, 4.6983)
ACR70 (%)	6.9	20.9*	3.3* (1.3899, 7.8182)
EULAR Outcomes (n)	**101**	**496**	
EULAR Response (%)	72.3	84.3*	na
Mean change DAS28-ESR	-1.72	-2.48***	na
DAS28-ESR Categories (n)	**101**	**499**	
Low Disease (%)	12.9	26.5*	2.29* (1.1973, 4.3803)
DAS28-ESR Remission (%)	5.9	13.2	2.33 (0.9024, 6.0379)

Significance levels were defined as * p<0.05 **p<0.001, ***p<0.0001.

Figure 12: Change from baseline of DAS28-ESR by Baseline Autoantibody Status (Pooled MIRROR and SERENE Patients)



Source: EGs17f_st_R162_CD28E2. **p< 0.001, ***p<0.0001.

CHMP discussion on efficacy data

IMAGE study

There was a statistically significant reduction in radiographic progression in the 1.0 x 2 g rituximab group both compared to placebo but also to the low-dose 0.5 g x 2 rituximab dose but the additional effect of RTX in prevention of radiographic progression is marginal compared to MTX alone, and confidence intervals are wide.
The difference was modest and of questionable clinical significance, in particular as no correlation was found between AUC of ACRn and radiographic outcome at week 52. Radiographic progression may be considered as an important endpoint, as prevention of joint damage is relevant in treatment of early RA patients with low baseline damage, and progression of joint damage is often more prominent in early active phase of the disease. It is however questionable whether radiographic progression should be the sole primary endpoint. There was no clear relationship between radiographic and clinical outcomes. A significant effect on radiographic progression without an improvement of clinical symptoms is not acceptable.

In addition to this, RA is a chronic disease, and rituximab treatment may be applied for years on. Claims regarding maintenance of effect are not sufficiently justified based on these data, considering short follow-up in relation to disease duration.

The clinical endpoint was in favour of the rituximab groups with a higher proportion obtaining the ACR20/50/70/90 compared to placebo. This also accounted for the DAS and HAQ scores. However, there was no significant difference between the 2 rituximab groups with respect to clinical outcome.
The effect of rituximab on prevention of radiographic progression seems less than reported for TNF-alpha blockers.

SERENE study
For the primary endpoint, ACR20, the incidence difference was 27.3 (NNT 95% CI 3-6). Also for ACR50 and remission rate, add-on therapy with rituximab was significantly better than MTX alone.
In logistic regression analysis, adjusted for RF status and region, the odds of achieving an ACR20 week 24 response of patients who received rituximab either dose was > 3 fold higher than placebo plus MTX [low dose: 3.9 (95% CI 2.4-6.3) ; high dose: 3.3 (2.1-5.3)] . Neither RF status nor region affected the likelihood of a patient achieving an ACR20 response significantly.
In both rituximab arms, subjects achieved optimal clinical effect around week 40, after re-treatment at week 24. Subjects who received placebo at the first dose, improved significantly after (blinded) conversion to MTX 500 mg treatment at week 24. However, by week 48, they still had not caught up to the response level of the group who had received active treatment from baseline on. The pattern of the ACR20 response is representative for the secondary clinical outcomes.

The diminished effect of rituximab in subjects who were converted from placebo-MTX to rituximab – MTX at week 24 is to be expected, as the subjects in the SERENE study were already irresponsive to MTX at baseline, and RA further progressed during placebo period. These data support that rituximab is added to MTX treatment once patients show inadequate response to MTX.

REFLEX study
This study is an extension of the original 24 week protocol which supported the Marketing Authorisation of rituximab in RA. The aim was to follow-up on a single course of rituximab or placebo for a total of 104 weeks. Borderline statistical significance was obtained for the primary efficacy endpoint, ACR20, in favour of rituximab (2% vs 5.7%).

However the mean change in mTTS, erosion scores and JSN scores were all significantly lower in the rituximab + MTX group compared with the placebo + MTX group. The cumulative distribution of change in mTTS indicating that a higher proportion of patients had no progression of joint damage, and that, in progressing patients, the rate of progression was reduced. Furthermore, patients receiving rituximab +MTX had significantly greater improvement in HAQ-DI scores compared to those receiving placebo + MTX (proportion of patients with improvement ≥ 0.25 are 20% v.s 51 % in favour of rituximab group).

MIRROR study
There were no significant differences between the treatment arms.
A repeat rituximab course at week 24 further improved the outcome. Over 40% of ACR non-responders at week 24 were subsequently ACR responders at week 48. Patients previously treated with biologicals (almost exclusively TNF antagonists) performed equally well. There was no difference in response between RF positive and RF negative patients.

In the RF/anti-CCP status pooled analyses, seropositivity significantly increased the probability of achieving ACR20 ACR50 and ACR70 responses compared with seronegative patients, with the odds ratios (95% CI) of 2.23 (1.38–3.58), 2.72 (1.58–4.70) and 3.3 (1.40–7.82) respectively. The probability of achieving low disease activity (defined as a DAS28-ESR ≤3.2) was also significantly increased. The analysis also showed that at both weeks 24 and 48 there were significantly greater falls in disease activity (as measured by DAS28-ESR) in seropositive treated patients compared to seronegative treated patients.

Further to the assessment of the data submitted in the variation application and in the responses to the CHMP requests for supplementary information, the CHMP considered that efficacy data to support the 1st and 2nd line treatment was insufficient. However the CHMP considered acceptable the update of section 4.1 with information on improvement in physical function and reduction in the rate of joint damage as measured by x-ray, when given in combination with methotrexate.

Clinical safety

The data from 2 pivotal and supportive studies accompanying this application have not changed the overall safety profile associated with the clinical use of rituximab. The most commonly reported Adverse Events (AEs) were worsening of RA, IRRs, and infections. Serious adverse event (SAEs) in the lower Gastrointestinal (GI) tract and cardiovascular systems were also reported. In addition, the potential risk for malignancies has been presented as well.

IMAGE study

The table 23 summarises the safety results of IMAGE study.

Table 23: Summary of safety IMAGE trial

		Placebo + MTX (N=250)	Rituximab (2 × 0.5 g) +MTX (N=249)	Rituximab (2 x 1g) +MTX (N=249)
AE incidence: no of patients (%)				
Any AE		203 (81.2)	189 (75.9)	197 (79.1)
Any serious AE		26 (10.4)	23 (9.2)	24 (9.6)
AE leading to withdrawal		12 (4.8)	4 (1.6)	5 (2.0)
Death on study		0	0	0
Death during safety FU		3 (1.2)	0	0
Infusion related reaction				
First course[a]		36 (14)	44 (18)	50 (20)
Second course[a]		26[b] (12.7)	23 (11.4)	24[c] (11.4)
Third course[a]		7 (6.3)	2 (2.1)	10 (11.0)
Infection	Any	124 (49.6)	127 (51.0)	129 (51.8)
	Serious[d]	13 (5.2)	6 (2.4)	8 (3.2)
Lower GI event	Any	22 (9)	26 (10)	33 (13)
	Serious	4 (2)	1 (<1)	2 (<1)
Cardiac event	Any	3 (1)	3 (1)	8 (3)
	Serious	0	2 (<1)	3 (1)
Malignancy	Any	5 (2)	2 (<1)	1 (<1)
	Serious	4 (2)	2 (<1)	1 (<1)
AE rates per 100 pat-years (95% CI)				
Overall infection rate		115 (102: 130)	104 (92: 118)	127 (113:142)
Serious infection[d] rate		6.09 (3.61: 10.29)	4.61 (2.55: 8.32)	3.73 (1.94: 7.18)
Lower GI event rate		12.19 (8.41: 17.65)	12.56 (8.78: 17.97)	18.67 (13.94: 25.00)

a % incidence based on number receiving each treatment course
b one patient received placebo+MTX for their first course followed by rituximab+MTX in the second course during which they experienced a mild IRR – all the patient's data are summarized under placebo+MTX
c one of these IRRs was reported as serious
d Reported as serious and/or treated with IV antibiotics

IRRs occurred most frequently with the first course of MTX, decreasing with subsequent courses to rates similar to placebo. There was a trend towards more serious IRRs in the high dose rituximab group compared to low dose group: Of the five IRR cases that led to study withdrawal, one occurred in the low dose group, four after a high dose, and none occurred in the placebo group. One case was classified as serious AE (anaphylactic reaction which occurred during 2nd course high dose group. Of

the 10 subjects that developed antibodies against rituximab (HACA), 2 developed IRR (one of these was the serious case).
Lower GI events consisted mainly of constipation and diverticulosis. No lymphoma was reported after rituximab. The table 24 presents the malignancies diagnoses in IMAGE trial.

Table 24: Malignancies in IMAGE trial

Patient	Preferred Term	CTC grade	Day of Onset	Relevant history/comeds	Outcome/ comment	Discont or Dose Adjusted
Placebo + MTX						
6101	Primary mediastinal large B-cell lymphoma	3	225		U	Dis
7624	Myelodysplastic syndrome	2	58		R-NS	N
6191	Colon cancer	3	80		U	Dis
6933	Metastatic malignant melanoma		314			Dis
Rituximab 2 x 0.5g, + MTX						
7703	Carcinoma in situ of skin	2	229	Squamous cell carcinoma of skin	R-NS	DM
7439	Endometrial cancer metastatic		229			Dis
Rituximab 2 x 1.0 g, + MTX						
5568	Cervix carcinoma	3	218 No		R-WS	N

R-NS, resolved with no sequel; R-WS resolved with sequelae; U, unresolved; N, none; Dis discontinued; DM, dosage modified

SERENE Study
The tables 25 and 26 below summarise the safety overview of SERENE study at week 0-24 and week 25-48 respectively.

Table 25: Safety overview SERENE Study Week 0-24

	Placebo +MTX N=172 (%)	Rituximab 2 x 0.5 g +MTX N=167 (%)	Rituximab 2 x 1.0 g +MTX N=170 (%)
Treated first course	172	167	170
Total patient years of follow-up	79.24 years	79.63 years	81.36 years
Number of patients with AEs (%)			
Any AE	128 (74)	128 (77)	130 (76)
Any related AE	25 (15)	25 (15)	17 (10)
Deaths	0	0	0
Deaths after withdrawal and before week 24	0	0	0
Serious AE	15 (9)	6 (4)	15 (9)
Any related serious AE	3 (2)	1 (<1)	2 (1)
AE leading to withdrawal (excluding RA flare)	2 (1)	2 (1)	3 (2)
Infusion related reaction[a]			
Day 1 infusion			
Any	24 (14)	31 (19)	42 (25)
Serious	0	0	0
Day 15 infusion			
Any	14 (8)	12 (7)	10 (6)
Serious	0	0	0
Infection			
Any	74 (43)	69 (41)	61 (36)
Serious [b]	4 (2)	1 (<1)	2 (1)
Malignancy	1 (<1)	1 (<1)	2 (1)
AE rates per 100 patient-years (95% CI)			
Overall infection rate	159.00 (133.53:189.34)	138.13 (114.59:166.52)	120.45 (98.81: 146.82
Serious infection[b] rate	8.83 (4.21: 18.53)	1.26 (0.18: 8.92)	2.46 (0.61: 9.83)

Table 26: Safety overview SERENE Study Week 25-48 (IRR, infections, malignancy)

	Rituximab 2 x 0.5 g +MTX N=167 (%)	Rituximab 2 x 1.0 g +MTX N=170 (%)
Treated first course	167	170
Treated second course	152	154
Total patient-years of follow-up	152.43 years	153.36 years
AE incidence – no of patients (%)		
Any AE	143 (86)	138 (81)
Any related AE	31 (19)	28 (16)
Deaths	2 (1)	0
Deaths after withdrawal and before week 48	1 (<1)	1 (<1)
Serious AE	13 (8)	17 (10)
Any related SAE	1 (<1)	3 (2)
AE leading to withdrawal (excluding RA flares)	3 (2)	8 (5)
Infusion related reaction [a]		
1st course: Day 1 infusion (any)	31 (19)	42 (25)
1st course: Day 15 infusion (any)	12 (7)	10 (6)
2nd course: Day 1 infusion (any)	19 (11)	17 (10)
2nd course: Day 15 infusion (any)	6 (4)	8 (5)
Any serious IRR	0	0
Infection		
Any	96 (57)	85 (50)
Serious [b]	3 (2)	3 (2)
Malignancy	1 (<1)	2 (1)
AE rates per 100 patient-years (95% CI)		
Overall infection rate	133.83 (116.67: 153.52)	106.94 (91.76: 124.63)
Serious infection[b] rate	2.62 (0.98, 6.99)	1.96 (0.63, 6.07)

The incidence rates of AEs did not significantly increase after second course at Week 24. The incidence of infusion reactions to the second course was comparable for both rituximab doses, and was lower than that seen with the first course. Altogether three patients withdrew due to IRRs, all from the rituximab 2 x 1.0 g + MTX arm.

There were no deaths before week 24, but two occurred between week 24 and week 48 in the low rituximab arm. One patient died approximately 20 weeks after her second course of rituximab 2 x 0.5 g treatment, of the aftermath of an intestinal perforation of the ileum (due to vasculitis) on study day 314. There was no evidence of infection and no antibiotics were given. After surgery, the event improved sufficiently for the patient to be discharged from hospital on day 320. Two days later however, the patient returned to hospital and died of abdominal sepsis. The abdominal sepsis and the death were considered possibly related to the disease, the use of DMARDs including NSAIDs and corticosteroids, or the study drug rituximab.
The second patient experienced SAE of pneumonia, intestinal perforation, intra-abdominal haematoma, incisional hernia, and interstitial lung disease, and then died (while still participating in the study) due to interstitial lung disease. Besides the study drug, the death could have been related to underlying disease or the use of MTX and prednisone.

REFLEX Study

An overview of AEs in the safety population is presented in Table 27.

Table 27. Overview of adverse events in the safety population (placebo switched data excluded)

	Placebo N = 208	Rituximab N = 308
Patient-years in the study		
Week 24 analysis	82.14	134.58
Week 104	131.36	358.02
Number of patients with any AE	186 (89%)	274 (89%)
Related AEs	77 (37%)	127 (41%)
Infections	85 (41%)	164 (53%)
Number of s with serious AEs	24 (12%)	39 (13%)
Serious infections	3 (1%)	15 (5%)
Deaths	1 (0.4%)	1 (0.3%)
Withdrawals due to AEs	3 (1.4%)	12 (3.9%)
AEs per patient year	5.49	3.68
SAEs per patient year	0.205	0.165
Serious infections per patient year	0.030	0.059

The rituximab arm had more infection events. The second class of AEs that was more common in the rituximab arm was the skin disorders. Here the most common event was rash, at similar frequencies in both placebo and rituximab patients (4% and 5% respectively), followed by pruritus(1% and 5% respectively) and urticaria (1% and 3% respectively).

The table 28 below presents the serious infections per 100 patients years at week 24 and 104.

Table 28. Serious infections per 100 patients years at week 24 and 104

Serious Infections per 100 Patient Years to Week 24

	Placebo+MTX (N=209)	Rituximab+MTX (N=308)
Total patient years	82.14	134.58
Number of Serious Infections	3	7
Serious Infections per 100 patient years	3.65	5.2
Serious Infections per patient year	0.0365	0.052

Serious Infections per 100 Patient Years to Week 104

	Placebo + MTX (N=208)	Rituximab + MTX (N=308)
Total patient years	131.36	358.02
Number of Serious Infections	4	21
Serious Infections per 100 patient years	3.05	5.87
95% CI for Rate/100 pt years	(1.14, 8.13)	(3.83, 9.00)
Serious Infections per patient year	0.0305	0.0587
95% CI for Rate/pt year	(0.0114,0.0813)	(0.0383, 0.09)

Rescue data is excluded.
Safety Follow-Up data is excluded.
Multiple occurrences of the same event in one individual are counted multiple times
Adverse Events with a start date prior to the last valid visit date are included
*=Reported as serious and/or treated with IV antibiotics

Deaths

Altogether there were four deaths in the study: one in a patient who received placebo, one who received rituximab, and two patients who received placebo followed by rituximab rescue treatment. None of the deaths were judged related to trial treatment. One had cardiac arrest 702 days after the second placebo infusion. One had intestinal carcinoma 176 days after the second rituximab infusion.

One had myelodysplastic syndrome 217 days after the second rituximab infusion. And one patient died in her sleep 339 days after the second rescue treatment with rituximab.

Malignancies
AEs classed as "neoplasms benign, malignant and unspecified" were observed in 7 (3%) placebo patients and 8 (3%) rituximab patients. There were a number of skin cancers, none of which was reported as serious. In the treatment phase there were two in the placebo arm (a basal cell carcinoma and a skin neoplasm) and one in a rituximab arm patient (the malignant melanoma in patient 36693/1282). In the post-treatment phase there were four skin cancers in the rituximab arm (two basal cell carcinomas and two squamous cell carcinomas) that were resolved without sequelae during the study. The serious malignancies were all single instances of different cancers, occurring in two patients from each study arm (breast and gastric cancer in the placebo arm and intestinal adenocarcinoma and prostate cancer in the rituximab arm). There were no cases of lymphoma during the 104-week study period.

MIRROR Study

The number of SAEs reported at the three groups were as follows: low dose 15 (11%), escalation 21 (18%), high dose 16 (17 %).The number of administration site reactions leading to dose modification or interruption of treatment was as follows: low dose 11(8%), escalation14 (12%), high dose 15 (165). There were no deaths in the study.
Five patients reported events coding to a MedDRA-defined malignancy term. Two events, basal cell carcinoma and Hodgkin's disease, were reported as serious. A reported basal cell carcinoma and thyroid neoplasm were later confirmed to be non-malignant, and a squamous cell carcinoma of the skin did not meet the criteria of a serious event.

Safety All Exposure population

Patient exposure

At the time of initial submission of the current application, the rituximab all exposure population comprised 3095 patients with 7198.49 years of patient observation. In reply to CHMP concern regarding the lack of long-term safety data, the MAH provided supplementary long-term safety data (cut-off date 30 September 2009). Therefore, the observed safety data from clinical trials now extended to 3189 RA patients providing 9342 patient-years of exposure, up to 15 courses of treatment and up to 9 years follow-up (table 29 and table 30).

Table 29: Duration of Exposure

Treatment Course	Duration of Observation	Number (Cumulative Percentage)
All Courses	Sample	**N = 3189**
	Duration ≤ 6 months	123 (3.9)
	6 months < Duration ≤ 12 months	138 (8.2)
	12 months < Duration ≤ 18 months	201 (14.5)
	18 months < Duration ≤ 24 months	255 (22.5)
	24 months < Duration ≤ 36 months	932 (51.7)
	36 months < Duration ≤ 48 months	855 (78.5)
	48 months < Duration ≤ 60 months	98 (81.6)
	60 months < Duration ≤ 72 months	277 (90.3)
	72 months < Duration ≤ 84 months	222 (97.2)
	84 months < Duration ≤ 96 months	17 (97.8)
	96 months < Duration ≤ 108 months	55 (99.5)
	Duration > 108 months	16 (100.0)
	Total patient years of observation	**9342.29**

Duration of observation = day of first exposure to rituximab to date of last contact. Date of last contact is the last available date of efficacy, complete medication start, date, laboratory, adverse event assessments, early withdrawal visit, date of last contact, or date of death. Note: includes placebo patients from point of first exposure to rituximab.

Table 30: Summary of Duration of Observation from First Exposure to Rituximab (All Exposure Population)

	Submission data cut (2008) N = 3095		New data cut 30 September 2009 N=3189	
Treatment courses	**n**	**PY observation**	**n**	**PY observation**
1	3095	2967.00	3189	3165.80
2	2365	2197.56	2417	2574.40
3	1581	1131.89	1724	1483.56
4	1038	603.98	1392	1029.40
5	497	203.20	1036	607.20
6	132	53.20	656	313.41
7	51	23.50	357	106.89
8	29	10.13	101	26.82
9	13	5.20	37	17.93
10	8	1.94	25	8.25
11	4	0.53	13	4.31
12	1	0.36	9	3.26
13	1	0	2	0.44
14			1	0.38
15			1	0.24
Total PY of observation	**7198.49**		**9342.29**	

The new cut-off date provided extra data of 94 newly exposed subjects and about 1 year extra follow-up of the original data base of 3095 subjects.

Of note, 82% of this clinical trial database consists of patients who are MTX-IR (n=1207) or TNF-IR (patients with an inadequate response to one or more TNF-inhibitor, n=1373).
To determine the specific influence of safety data emerging after prolonged exposure to rituximab, a population of patients with long-term exposure to rituximab has also been identified. This "long term" population was defined as patients with at least 5 years (>60 months) of follow-up and, as of 30 September 2009, consisted of 587 patients. This long-term population had received up to 15 courses of rituximab with 298/587 (51%) having received at least 4 treatment courses. All 587 patients in this population were reflective of the proposed indication with 57.8% being TNF-IR and 42.2% biologic naive (MTX-IR). In addition to this long-term population, 1036 patients have received at least 5 courses of treatment.

Adverse events
The overall summary of safety in all patient populations is presented in table 31 below:

Table 31: Overall Safety Profile (cut-off date Sept 09) in All Exposure, Long-Term, 5-Course and Placebo Populations

	Placebo population (N=818)	All Exposure population (Sept 09) (n=3189)	Patients with >60 mth exposure All Doses (N=587)	Pts with ≥5 courses (n=1036)
Total patient years of observation	979.46	9342.29	3386.04	3908.27
AE Rate per 100 pt-yr	353.05	309.43	285.11	327.69
95% CI	(341.5:365.0)	(305.9:313.0)	(279.5:290.9)	(322.1:333.4)
Serious AE Rate per 100 pt-yr	15.52	16.23	15.48	13.15
95% CI	(13.24:18.19)	(15.43:17.07)	(14.21:16.86)	(12.06:14.34)
Infection Rate per 100 pt-yr	100.77	94.30	83.19	101.71

95% CI	(94.67:107.26)	(92.35:96.29)	(80.18:86.32)	(98.59:104.92)
Serious Infection Rate per 100 pt-yr	4.29	4.35	3.19	3.40
95% CI	(3.17:5.80)	(3.94:4.79)	(2.64:3.85)	(2.87:4.03)
Malignancy Rate per 100 pt-yr	1.33	1.49	1.42	1.05
95% CI	(0.77:2.29)	(1.26:1.76)	(1.07:1.88)	(0.77;1.42)
Myocardial Infarction Rate per 100 pt-yr	0.31	0.49	0.32	0.38
95% CI	(0.10:0.95)	(0.37:0.66)	(0.18:0.59)	(0.23:0.64)

The incidence and nature of serious adverse events is presented in the table 32 below:

Table 32: Summary of all Serious Adverse Events Reported in ≥ 10 Patients Comparison of All Exposure Populations from September 2008 and September 2009

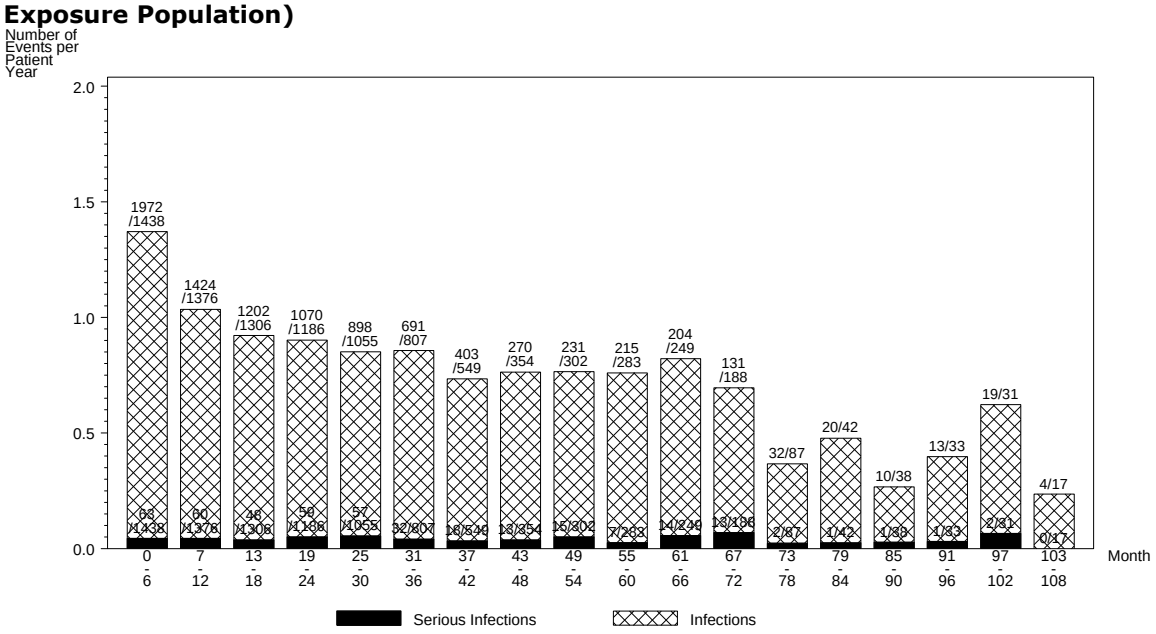
BODY SYSTEM/ Adverse Event	All Exposure Population (September 2008) N = 3095 No. (%)	All Exposure Population (September 2009) N = 3189 No. (%)
ALL BODY SYSTEMS		
Total Pts with at Least one SAE	700 (23)	855 (27)
Total Number of SAEs	1132	1438
Rheumatoid arthritis	52 (2)	66 (2)
Pneumonia	41 (1)	52 (2)
Osteoarthritis	37 (1)	49 (2)
Fall	35 (1)	47 (1)
Myocardial infarction	29 (<1)	33 (1)
Cellulitis	16 (<1)	22 (<1)
Coronary artery disease	16 (<1)	19 (<1)
Infusion related reactions	14 (<1)	17 (<1)
Gastroenteritis	13 (<1)	19 (<1)
Chest pain	12 (<1)	16 (<1)
Urinary tract infection	11 (<1)	15 (<1)
Breast cancer	10 (<1)	13 (<1)
Road traffic accident	11 (<1)	12 (<1)
Cerebrovascular Accident	9 (<1)	12 (<1)
Cholecystitis	7 (<1)	12 (<1)
Pyrexia	11 (<1)	11 (<1)
Deep vein thrombosis	11 (<1)	11 (<1)
Atrial fibrillation	10 (<1)	11 (<1)
Bronchitis	9 (<1)	11 (<1)
Lower respiratory tract Infection	9 (<1)	11 (<1)
Pulmonary Embolism	9 (<1)	11 (<1)
Diverticulitis	7 (<1)	11 (<1)
Bronchopneumonia	9 (<1)	10 (<1)
Uterine Leiomyma	9 (<1)	10 (<1)
Interstitial Lung Disease	9 (<1)	10 (<1)
Syncope	8 (<1)	10 (<1)
Cholelithiasis	8 (<1)	10 (<1)

Sources: stae11ser_a (15Dec2009); stae11ser_a (12Jan2009). Investigator text for Adverse Events encoded using MedDRA version 12.1.Percentages are based on N. Multiple occurrences of the same adverse event in one individual counted only once. The individual symptoms of an infusion related reaction are reported as a single IRR event. Imputed start dates were used to identify whether the adverse event was treatment emergent. Includes placebo data from patients treated with Rituximab who then received placebo as Retreatment

Infections (serious)
Two cases of pulmonary tuberculosis (TB) were reported in 2 patients, providing a rate of 0.02 events/100 pt-yr. No cases of extra-pulmonary TB, atypical mycobacterial infection or multidrug resistant TB were reported.
There were 4 cases (4 patients) of serious opportunistic infection identified in the all exposure population, including atypical pneumonia (treated as presumed Pneumocystis jiroveci, but no organism was isolated), Pneumocystis jiroveci pneumonia, progressive multifocal leukoencephalopathy and Candida septicaemia, providing an estimated rate of 0.04 events/100 pt-yrs. In contrast there was a single case of Pneumocystis jiroveci pneumonia observed in the pooled placebo population providing an estimated rate of 0.1/100pt-yrs.

Rates of all infections and serious infections are shown in figure 12.

Figure 12: Plot of Rate of all infections and serious infections by 6-monthly Time Intervals (All Exposure Population)



The numbers above the bars are the numbers of SAEs/patient-years exposed during the 6-month period (1 month = 28 days). The display of data ends when the number of patient-years exposed is ≤ 10. Includes placebo data from patients treated with rituximab who then received placebo as retreatment. Imputed start dates were used to identify whether the adverse event was treatment emergent and to assign an adverse event to a time period. Terms were identified using the infections AEGT and the identifying tick box on the adverse event page for studies U3374G, U3384g, WA17044, WA17045 and WA17047.

From the frequency table that was submitted, it could be concluded that the incidence ranged between 3-4.5 % per course (13 courses), and that the incidence per course did not increase in due time.

Long-term safety was specifically investigated by considering the long-term patient population and identifying all new adverse events that occurred after 5 years. Overall 372/587 (63%) of long-term patients reported an adverse event that occurred after 5 years with 79/587 (13%) reporting a serious adverse event. The nature of these events was consistent with the overall safety profile, with the most commonly reported events being those of infection (37%), musculoskeletal (27%), gastrointestinal (13%) and injury/poisoning/procedural complications (10%) MedDRA system organ classes. Adverse events occurring beyond 5 years in 5% or more of patients are presented in table 33, with serious adverse events occurring in 2 or more patients presented in table 34.

Table 33: Adverse Events Occurring Beyond 5 Years Exposure ≥ 2% of Patients

Adverse Event	Patients with >60 mth exposure (all doses) (N=587) No (%)
ALL BODY SYSTEMS	
Total patients with at least 1 adverse event	372 (63)
Number of adverse events	1192
Rheumatoid Arthritis	83 (14)
Upper respiratory tract infection	46 (8)
Nasopharyngitis	43 (7)
Bronchitis	33 (6)
Urinary Tract Infection	32 (5)
Fall	23 (4)
Infusion Related Reaction	18 (3)
Hypertension	18 (3)
Bursitis	17 (3)
Diarrhoea	15 (3)
Back Pain	16 (3)
Osteoarthritis	12 (2)
Anaemia	10 (2)
Musculoskeletal Pain	10 (2)
Rash	12 (2)
Sinusitis	12 (2)
Gastroenteritis	11 (2)
Lower respiratory Tract Infection	9 (2)
Vulvovaginal Mycotic Infection	9 (2)
Cateract	9 (2)

Table 34: Serious Adverse Events Occurring Beyond 5 Years Exposure in ≥ 2 patients

Serious Adverse Event	Patients with >60 mth exposure (all doses) (N=587) No (%)
ALL BODY SYSTEMS	
Total patients with at least 1 SAE	79 (13)
Number of Serious Adverse Events	110
Rheumatoid Arthritis	7 (1)
Fall	6 (1)
Myocardial Infarction	3 (<1)
Myocardial Ischaemia	3 (<1)
Osteoarthritis	3 (<1)
Abortion spontaneous	2 (<1)
Accident	3 (<1)
Cellulitis	2 (<1)
Infusion Related Reaction	2 (<1)
Large Intestine Perforation	2 (<1)
Lower respiratory Tract Infection	2 (<1)
Road Traffic Accident	2 (<1)
Surgical failure	2 (<1)

PML (progressive multifocal leucoencephalopathy)
One fatal case of PML was reported in All Exposure population. This case occurred in an earlier trial in TNF-IR patients, and was reported earlier to the authorities. This case describes a 46 year old female diagnosed with RA with Sjögren's syndrome 9 years prior to entry of study. The patient received previous treatment with hydroxy-chloroquine and infliximab. The patient developed PML approximately 4 years and 9 months after receiving her first course of rituximab and 1 year and 5 months since the last infusion, and 7 months after the end of chemotherapy for treatment of oropharyngeal cancer. The investigator considered the event of PML to be related to study medication as well as to tonsillar carcinoma, chemotherapy (specifically carboplatin and erbitux) and methyl-prednisolone.

One case of PML was reported within the post-marketing surveillance. A 73-year-old female patient with a 30 year history of RA had received five treatment courses with RITUXIMAB between 2006 to 2008 with other concomitant medications including MTX, etanercept (2002-2003) and adalumimab (2005). In November 2008 a diagnosis of PML was made based on positive PCR finding of JC virus DNA in the CSF. Clinical symptoms and imaging were atypical with MRI showing microvascular changes consistent with age. There were no visual disturbances, or cognitive changes noted although the patient had progressive right hemiataxia. As of March 2009 the patient, although wheelchair bound, remains stable with a right hemiataxia and no cognitive impairment. It is of note that this patient had a known risk factor for PML of sustained lymphopenia that was present pre-rituximab treatment.
A further 4 confirmed cases of PML have been reported in RA patients treated with rituximab from the post-marketing experience. All the cases reported within the post-marketing surveillance are summarized below (table 35):

Table 35: Rituximab-Treated RA Patients with PML

Characteristic	Case 1 (MCN262153)	Case 2 (MCN272265)	Case 3 (MCN289875)	Case 4 (MCN 293692)	Case 5 (MCN295138)
Age (Sex)	51 (F)	72 (F)	73 (F)	62 (F)	67 (F)
RA duration	14	30	3	10	3
Rituximab exposure	4 Courses	5 Courses	1 Course	4 Courses	1 Course
HIV	Negative	Negative	Negative	Negative	Negative
Malignancy	Yes	No	No	No	Yes
Possible contributory risk factors	Chemo/radio therapy, undetectable complement	Sustained lymphopenia Advanced Age	Advanced Age	None	Radiotherapy. Lymphopenia,
Prior Biologics	Infliximab	Adalimumab Infliximab	None	Adalimumab Etanercept Anakinra	None

Two new PML cases (spontaneous reports) were recently identified (in 2010), raising the latest count of PML cases in RA patients to seven. In three out of 6 cases, only rituximab but no other biologicals were given, and no other risk factor such as malignancy or HIV was present. In one case report, the use of co-medication was not clear.

Malignancies
Based on the updated safety analysis, a total of 139 events were identified as malignancies defined using the Wide Malignant or Unspecified Tumours standard MedDRA query (SMQ), providing an overall rate of 1.49 events/100 pt-yr. This rate is essentially unchanged from previous data (1.47 events/100 pt-yr) and also consistent with that observed in the pooled placebo population (1.33 events/100 pt-yr). The rate and standardized incidence ratio (SIR) estimates for any malignancy (excluding, non melanoma skin cancers and the non-malignant events) are presented in table 23 below. The SIR for any malignancy (excluding non-melanoma skin cancers) is 1.06 (95%CI 0.81-1.37). The most frequently reported malignancy (excluding non-melanoma skin cancers) was breast cancer with a SIR of 0.63 (0.34, 1.24), compared with the US general population (SEER database).
The Clinical Summary of Safety identified that the rate and SIR of thyroid malignancies was potentially elevated, although with wide confidence intervals and with point estimates that were within the range

reported in other RA cohorts. Since that analysis, no further cases of thyroid malignancies have been reported in clinical trials. The revised SIR of thyroid malignancies is 2.51 (95% CI: 0.81-5.88).
A cumulative search of the global safety database using the high level group term "Thyroid neoplasm malignant" identified 3 spontaneous cases (2 papillary carcinoma of thyroid gland and 1 Thyroid cancer).
Patients with RA have a known increased risk of lymphoma of approximately 2-fold compared to the general population. As of 30 September 2009, there were a total of 4 cases of lymphoma reported in clinical trials with rituximab (2 Non-Hodgkin's lymphoma [NHL] and 2 Hodgkin's disease) providing an overall rate of 0.04 events/100 pt-yr and a SIR of 1.49 (95%CI 0.40-3.81).

Table 36: Overview of Standardized Incidence Ratio (SIR) estimates for Malignancy

	SIR (95% CI)	Published SIRs for RA
Overall Malignancy	1.06 (0.83-1.32)	1.0, 1.1, 1.2, 1.5, 1.23
Breast cancer	0.63 (95% CI: 0.34, 1.08).	0.7; 0.97, 0.4 – 1.68 (range across 11 separate studies), 0.8*
Thyroid malignancy	2.51 (0.81-5.88)	1.43, 8.1*
Lymphoma	1.49 (0.40-3.81)	1.98, 2.0
NHL	0.82 (0.09-2.97)	2.34. 2.4
Hodgkin's Disease	7.83 (0.88-28.27)	4.06

* Relative Risk. SIRs based on U.S. Surveillance, Epidemiology, and End Results (SEER 2008).

The rate of malignancy (defined using the SMQ) in patients with 5 years follow-up was 1.42 events/100 pt-yr and was similar to that in both the all exposure and placebo populations (table18). In the 587 patients with over 5 years follow-up, a total of 8 neoplasms (benign, malignant, and unspecified, including cysts and polyps) were reported beyond 5 years. Of these, 2 (<1%) were confirmed malignancies excluding non-melanoma skin cancers: bladder cancer (serious) and lung neoplasm malignant (serious). There were 2 events that were non melanoma skin cancers.

Discussion on clinical safety

IMAGE study
In general, the adverse event profile between the rituximab and placebo (+ MTX) was similar with respect to nature and incidences of AEs. The incidence of infections and malignancy was not enhanced in the rituximab treatment groups versus placebo (i.e. MTX alone).

The incidences of AEs that are thought to be associated with the use of immune-suppressive biological products (infections, cancer) were similar between rituximab add-on MTX and MTX alone study arms.

Infusion reactions were common, especially in the first course. Remarkably, infusion reactions were commonly reported after placebo as well. This might be due to 'over-reporting' of local reactions following manipulation of the infusion device. In the rituximab arms, the incidence of infusion reactions declined in due time with multiple courses. This might indicate the development of tolerance, or is a result of selection bias as some intolerant patients dropped out because of IRR. There was a trend of more serious infusion reactions with higher dose of rituximab compared to low dose.

Lower GI events consisted mainly of constipation and diverticulosis. Cardiac events were higher in the highest dose group. These events were not considered to be treatment related. Cardiac risks are included in the RMP, and in the SmPC it is mentioned that rituximab should not be used in cardiac patients due to lack of experience.

It is difficult to draw final conclusions regarding the safety of rituximab in early MTX-naïve RA patients based on such a small and short-term dataset. Follow-up data till maximal two year were only available for a small subset. A follow-up period of 1-2 years is anyway considered too short to detect slowly developing AEs like malignancies and some opportunistic infections like PML. The solid tumours that were reported during the IMAGE trial probably also existed before the trial, but were not detected at inclusion.

Small risks cannot be detected from a database of ± 500 subjects exposed to rituximab.

Safety data from the other rituximab trials in advanced RA patients are available. However data from patients primed by a broad range of immunosuppressant's including MTX and biologicals (TNF-blockers) could not just be extrapolated to the early RA population.

When rituximab will be applied as first line treatment, the exposure will be considerable longer and in less-treatment experienced patients compared to the accepted target population of TNF-IR patients.

There is no experience and information available about the possible consequences of long-term use of rituximab when it will be applied in early disease state.

SERENE study
The overall prevalence of adverse events during the 24-week placebo-controlled period was similar across all 3 treatment groups.
The incidence rates of AEs did not significantly increase after second course at Week 24.

All exposure population
The new emerging cases of PML preclude approval of early stage RA treatment at present state. The overall incidence of PML in RA patients treated with rituximab is so far low, and lower than reported for e.g. natalizumab. However, it is anticipated that the number of incidents will be increased when rituximab will be used at larger scale and in earlier treatment phase of RA. PML is not preventable, no treatment options exists, and is often fatal. Patients, who survived, remained brain-damaged. Alternative biologicals indicated for RA had similar efficacy rates as rituximab, and they are not associated with PML. When cases were reported for alternate biologicals in RA, other risk factors were also present.

Most PML cases reported for RTM occurred in patients with haematological malignancies. The causality in these oncology cases is less clear, as the disease itself and accompying therapy may cause PML. However, several cases have been reported in non-cancer patients who were treated before with other biologicals than rituximab. Therefore, there is a potential risk for a very severe and life-threatening neurological AE associated with rituximab.

The most common AEs were IRRs which occurred mostly in the high-dose rituximab group. Infections, although numerically more common in the rituximab groups, were similar when numbers were calculated per 100 pt years. There were several cases of potentially serious cardiovascular conditions (MI, stroke, TIA, angina, AV-conduction disturbances etc.) However, these AEs were not grouped together in the "all exposure group". Therefore, it is not possible to conclude about an overrepresentation among rituximab treated patients. Malignancy didn't seem to occur with increased rate in the rituximab groups, but the time perspective is too short to conclude definitively on this issue. Therefore, the estimate of cancer risk of rituximab should be interpreted very carefully, as only a few subjects (7% of the total safety database) were followed for more than 5 years, whereas solid tumours develop slowly.

Risk Management Plan
The MAA submitted a risk management plan. The RMP is summarized in Table 32:

Table 37: Summary of the EU Risk Management Plan

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
RA – Identified Risks		

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
Infections (including serious infections)	Routine Pharmacovigilance Activities Additional: In ongoing and planned clinical trials, prospective data collection and focused evaluation of all infections/symptoms of infection is conducted. Spontaneous reports of hepatitis B infection will be assessed using a standardized questionnaire to determine if the infection is de novo or a reactivation of a previous infection. All reports of Hepatitis B or reactivation of Hepatitis B are expedited for reporting to the agency, with regular data reviews. All reports of tuberculosis or reactivation of tuberculosis will be carefully analysed and reported to the agency. As part of its rituximab-specific protocol, the BSRBR, ARTIS and RABBIT will collect data regarding the incidence of serious infections and the administration of IV immunoglobulins.	Routine: The labelling for the RA indication cautions prescribers regarding the use of rituximab in patients with an active infection or other predispositions to serious infection, and regarding the prompt evaluation and treatment of infections that occur following rituximab therapy. Company representatives will be informed as part of their training to draw prescribers' attention to this information. Additional: In ongoing and planned clinical trials, prospective monitoring of laboratory markers of humoral immune status (eg, B cell counts, Ig counts/titres, complete blood counts) is performed. The clinical trials allow placebo comparisons of humoral immunity markers during the double blind period, as well as long term follow up for patients who continue with rituximab in open label extensions.
Acute Infusion-Related Reactions	Routine Pharmacovigilance Activities Additional: In ongoing and planned clinical trials, prospective data collection and evaluation of serious/severe infusion reactions will continue to be carried out in long term follow-up for patients in open-label extensions. As part of the proposed rituximab-specific protocols, the British Society of Rheumatology Biologics Register (BSRBR), the Swedish registry (ARTIS) and the German registry (RABBIT) will report serious infusion reactions. Additional: Spontaneous reports of possible infusion reactions will be assessed and evaluated using good pharmacovigilance practices	Routine: The decision for all patients to receive IV corticosteroid pre-medication was based on the reduced incidence and severity of acute infusion reactions in patients in study WA17043, who were pre-treated with IV corticosteroid. In study WA17043, medically-reviewed acute infusion reactions following the first infusion of the first course occurred in 18/65 (28%) patients who received rituximab (1 g dose) without IV corticosteroid pre-medication compared to 24/127 (19%) patients who received rituximab with IV corticosteroid premedication. The addition of oral corticosteroid between rituximab infusions did not appear to provide any additional benefit over use of IV corticosteroid alone for the prevention of acute infusion reactions. Therefore the sponsor considers the use of IV corticosteroid as pre-medication to be advisable prior to all rituximab infusions. This advice is reflected in the SmPC. .

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
Impaired immunization Response	Routine Pharmacovigilance Activities	Routine: The current SmPC advises the following: *Data on the ability to generate a primary or anamnestic humoral response to any vaccine are not yet available.* *Physicians should review the vaccination status of patients being considered for treatment with MabThera and follow local/national guidance for adult vaccination against infectious disease.* *Vaccination should be completed at least four weeks prior to first administration of MabThera. Live vaccines are not recommended in patients while B-cell depleted".* Additional: For all ongoing and planned trials the investigator reviews the patient's immunization history and status. Patients who require immunization should be immunized 4 weeks prior to commencing rituximab treatment.
RA – Potential Risks		
De Novo HBV, HBV reactivation and Opportunistic Infections	Routine Pharmacovigilance Activities Additional: In ongoing and planned clinical trials, prospective data collection and evaluation of the occurrence of any infection is undertaken. Comparison of incidence and rates between rituximab and placebo are made using pooled analyses from long term follow up of patients who continue with rituximab in open label studies is conducted. As part of the core protocol, the BSRBR, ARTIS and RABBIT collect data regarding infections and outcomes.	Routine: See recommendations for infections (including serious infections) above. The MAH plans to update the SPC Section 4.4. informing that reactivation of hepatitis B infection can occur in Rheumatoid Arthritis patients receiving MabThera. Additionally, a cross reference will be added between this language in section 4.4 and related text in section 4.8 of the SPC.
PML	The occurrence of PML is being monitored through the sponsor's enhanced pharmacovigilance system. For events reported to the sponsor's pharmacovigilance system as spontaneous reports, additional data will be collected by means of a Guided Questionnaire. Continued collection of reports from spontaneous reporting and clinical trial sources. The MAH aggressively pursues additional information from reporters for a number of pre defined terms that could potentially be representative of PML, in the form of a guided questionnaire [7296].	Additional: Patient alert card was implemented.

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
Malignant events	Routine Pharmacovigilance Activities Additional: In ongoing and planned clinical trials, prospective data collection and evaluation of the occurrence of any neoplasm is carried out. Comparisons of incidence and rates between rituximab and placebo are made using pooled analyses from long-term follow-up of patients who continue with rituximab in open-label studies is conducted Standardized Incidence Ratios (SIRs) compared to the US general population are made using the SEER database, together with comparison of SIRs to those from other RA cohorts. As part of the core protocol, the BSRBR, ARTIS and RABBIT collect data regarding malignant events and outcomes.	Routine: There are no options above and beyond standard cancer screening methods for malignant neoplasms.
Use in Pregnancy/lactation	Routine Pharmacovigilance Activities Additional: In ongoing and planned clinical trials, prospective data collection and evaluation of pregnancies that occur and their outcomes is carried out. The BSRBR, ARTIS and RABBIT register the occurrence of pregnancies in enrolled patients and follows outcome of the pregnancy by asking the patients.	Routine: The SmPC currently advises the following; Due to the long retention time of rituximab in B-cell depleted patients, women of childbearing potential should use effective contraceptive methods during treatment and for 12 months following MabThera therapy. *Whether rituximab is excreted in human milk is not known. However, because maternal IgG is excreted in human milk, and rituximab was detectable in milk from lactating monkeys, women should not breastfeed while treated with MabThera and for 12 months following MabThera treatment.*
Impact on cardiovascular disease	Routine Pharmacovigilance Activities Additional: Good pharmacovigilance practices will be utilized to identify any signals of impact on cardiovascular disease. Cardiac events will be monitored as part of the RMP as follows: Data regarding serious cardiac events will be monitored in the PSURs. As part of the respective core protocols, the BSRBR, ARTIS and RABBIT collect data regarding the incidence of any serious co-morbidity leading to hospitalization, including serious cardiac events.	Routine: The SmPC currently advises the following; "*There are no data on the safety of MabThera in patients with moderate heart failure (NYHA class III) or severe, uncontrolled cardiovascular disease. In patients treated with MabThera, the occurrence of pre-existing ischemic cardiac conditions becoming symptomatic, such as angina pectoris, has been observed, as well as atrial fibrillation and flutter. Therefore, in patients with a known cardiac history, the risk of cardiovascular complications resulting from infusion reactions should be considered before treatment with MabThera and patients closely monitored during administration. Since hypotension may occur during MabThera infusion,*

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
		consideration should be given to withholding anti-hypertensive medications 12h prior to the MabThera infusion"
Gastrointestinal perforation	Routine: GI perforation events in patients treated in autoimmune indications will continue to be monitored by the MAH Additional: In ongoing and planned clinical trials, prospective data collection and evaluation of the occurrence of gastrointestinal perforation is carried out. Data regarding gastrointestinal perforation will be monitored in the PSURs. BSRBR, ARTIS and RABBIT collect data regarding the incidence of any serious co-morbidity leading to hospitalization, including gastrointestinal perforation. This information will be included in 6-monthly reports to be provided by the registries to the company.	.
RA – Missing Information		
Immunogenicity and autoimmune disease	Routine Additional: As part of their rituximab-specific protocols, the BSRBR, ARTIS and RABBIT will document the occurrence of serious immunological reactions. Data accrued from all clinical trials, spontaneous reports, and planned observational studies will be evaluated regularly for overall trends, new signals, and consistencies and/or inconsistencies across the various data sources. Spontaneous reports will continue to be analysed using event report frequencies. Data from ongoing and planned trials will be reported in Annual Safety Reports and from spontaneous reports and literature sources within Periodic Safety Update Reports.	Routine: N/A Additional: In ongoing and planned clinical trials, evaluation of serology data for HACA is carried out prospectively under open-label conditions. Focused evaluation of symptoms of immune complex disorder (eg, serum sickness) is also carried out.
NHL/CLL – Identified Risks		
Acute infusion related reactions	Routine	Routine: Infusion-related reactions cannot be reliably predicted or prevented. However, the incidence and severity may be reduced by premedication and appropriate monitoring and treatment.
Infections	Routine	Routine: Prophylaxis for Pneumocystis Pneumonia (PCP) and viral infections may be indicated according to the concomitant chemotherapy given (eg, PCP and

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
		antiviral prophylaxis for patients treated with fludarabine-based regimens). Patients reporting signs and symptoms of infection following rituximab therapy should be promptly evaluated and treated appropriately. Before giving a subsequent course of rituximab treatment, patients should be re-evaluated for any potential risk for infections.
Neutropenia	Routine + planned analysis of prolonged neutropenia in ML17102/CLL-8 study	Routine: Neutropenia due to concomitant cytotoxic therapy is not generally preventable without dose modification and there are no known methods of preventing rituximab-associated neutropenia. However, complications (infection) may be prevented by monitoring counts and promptly administering antibiotic and/or granulocyte-colony stimulating factor (G-CSF) treatment. Prophylactic antibiotics and/or G-CSF may also be appropriate for some situations. Physicians should exercise caution when considering the use of rituximab in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection.
HBV reactivation	Routine	Routine: The following SPC text is proposed: *Cases of hepatitis B reactivation, including reports of fulminant hepatitis, some of which were fatal, have been reported in subjects receiving MabThera, although the majority of these subjects were also exposed to cytotoxic chemotherapy. The reports are confounded by both the underlying disease state and the cytotoxic chemotherapy. Hepatitis B virus (HBV) screening should be considered for high risk patients before initiation of treatment with MabThera. Carriers of hepatitis B and patients with history of hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection during and for several months following MabThera therapy.*
NHL/CLL – Identified Risks (continued)		
Tumour lysis syndrome	Routine	Routine: Maintenance of adequate hydration and urine output are crucial in preventing TLS. Allopurinol and/or rasburicase are also recommended depending on the risk group. Patients at low-risk of TLS may require no additional treatment

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
		other than hydration. Those with intermediate risk require allopurinol with the addition of rasburicase if hyperuricaemia still develops. Vigorous hydration is recommended for all patients in the middle-to-high risk groups and for those with diagnosed TLS. Rasburicase is recommended for patients with hyperuricaemia associated with a diagnosis of TLS or in the initial management of high risk paediatric patients.
PML	Routine + continued expedited reporting of new cases/questionnaire used to better characterise all such reports (all indications).	Routine: There are no treatments available to prevent, retard, stop, or reverse the disease once established in patients.
Serious viral infection	Routine	Routine: See Infections
GI perforation	Routine	Routine: There are no known ways of preventing GI perforation in patients receiving rituximab for haematological malignancies.
Impaired immunization response	Routine	Routine: an update to the SmPC has been proposed based on results of a study in patients with NHL.
NHL/CLL – Potential Risks		
Prolonged B-cell depletion	Routine + results of PRIMA (MO18264) study (expected 2010 or 2011)	Routine: B-Cell depletion is the expected therapeutic outcome with rituximab. Prolonged B-cell depletion/delayed B-cell recovery is currently not listed as a potential risk in the rituximab SmPC but detailed information on B-cell and immunoglobulin changes is provided.
Grade 3/4 and serious blood and lymphatic AEs in patients > 70 years with CLL	Routine	Routine. The SmPC already includes information on blood and bone marrow system disorders (without reference to age categories). The following new text is also proposed for the SmPC *Elderly patients (≥ 65 years)* The incidence of Grade 3/4 blood and lymphatic adverse events was higher in elderly patients (≥ 65 years of age) compared to younger patients, with previously untreated or relapsed/refractory CLL.
Opportunistic infections	Routine	Routine: See Infections
AML/MDS	Routine	Routine: There are no known ways of reducing the risk of treatment-related secondary AML/MDS, other than by reducing exposure to chemotherapy and radiotherapy and/or by substituting a less DNA-damaging agent, if possible (eg, substitution of ABVD for MOPP chemotherapy in Hodgkin's lymphoma).

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
NHL/CLL – Missing Information		
Prolonged neutropenia	See neutropenia above	See neutropenia above
Prolonged B-cell depletion	See under potential risk above	See under potential risk above

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2. Benefit-Risk Balance

The benefit for the 1st line indication has not been demonstrated. The effect of high-dose rituximab add-on treatment on the prevention of radiographic progression was minor (10.6%) and not considered clinically relevant compared to MTX monotherapy (63.5 vs 53.4%: 95% CI difference 1.5-18.6). The effect of rituximab on prevention of radiographic progression seems less than reported for TNF-alpha blockers.
The attributive effect of add-on rituximab therapy on clinical outcomes was however more convincing: About twice as much subjects achieved remission (according DAS28-ESR criteria) after one year of rituximab add-on treatment compared to MTX alone (30.5 vs 12.6, 95% CI diff 11-25%). Major clinical response, defined as a high ACR70 response for 6 months or more, was also achieved in significantly more subjects in the rituximab arm (21.1 vs 8.4%, 95% CI 7-19%). Maintenance of efficacy was demonstrated for three treatment courses (± 1.5 year).
One of the major objections of CHMP is the safety profile of rituximab. Immune-suppressive biologicals, including rituximab, are associated with an increased risk of serious infections and malignancies. RA is a chronic disorder and use of rituximab as first line treatment option will implicate a more prolonged use in clinical practice than the approved third line indication.
The available safety database of early RA patients is small (about 500 subjects) and mainly consists of short-term follow-up data till maximal 2 years. The risk on more slowly developing AEs like malignancies and PML could thus not be evaluated. More safety data are available from other studies with TNF and MTX experienced patients and post-marketing database. However, this information is derived from patients primed with immune-suppressant drugs cannot be extrapolated to first-line therapy.
MTX is the overall established first-line treatment in active RA and since MTX response was also considerable and persistent (e.g. ACR50 responder rate was 39.8 and 41.8% after 24 and 52 weeks, respectively), it is doubtful whether the benefits of add-on rituximab outweighs the risks on development of malignancies and PML.

Regarding the 2nd line indication the CHMP concluded that safety database is very limited. A major concern was raised as long-term safety data in the sought indications were lacking, and the consequences of long-term B-cell suppression in the RA population were unclear. Moreover, the risk of malignancies was unclear.
The new emerging cases of PML preclude approval of early stage RA treatment at present state. For RA patients with insufficient response to conventional DMARDs the benefit-risk balance of switching directly to rituximab is at present not settled. There is considerable more clinical experience with the use of anti-TNF agents. Therefore, a second line indication for rituximab is not acceptable.

Based on the above findings, the CHMP considered that the benefit-risk balance for rituximab in MTX-naïve patients (1st line treatment) and in MTX-IR patients (2nd line treatment) was not favourable and that the therapeutic efficacy has not been properly and sufficiently demonstrated. However, the CHMP considered acceptable the update of section 4.1 of the SmPC with information of improvement in physical function and reduction in the rate of joint damage as measured by x-ray, when given in combination with methotrexate and sections 4.2, 4.4, 4.5, 4.8 and 5.1 have been updated as a consequence. The Package Leaflet has been updated accordingly.
In addition to this, sections 5.1 and 5.2 of the SmPC have been updated with additional information from studies in patients with early arthritis.
Furthermore changes were made to the SmPC, labelling and Package Leaflet to bring them in line with the current QRD template.
Finally Annex II has been updated in order to reflect the latest version of the RMP.