Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Rituximab

Proprietary Product Name: MabThera

Sponsor: Roche Products Pty Ltd

September 2010

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	Extension of indications/Broaden patient population
Decision:	Approved
Date of Decision:	6 May 2010
Active ingredient(s):	Rituximab
Product Name(s):	Mabthera
Sponsor's Name and Address:	Roche Products Pty Ltd, PO Box 255, Dee Why, NSW 2099.
Dose form(s):	Concentrated solution
Strength(s):	10 mg of antibody/mL: 100mg/10mL and 500mg/50mL
Container(s):	vial
Approved Therapeutic use:	***Non-Hodgkin's Lymphoma*** Mabthera is indicated for treatment of patients with: · CD20 positive, previously untreated, stage III/IV follicular, B-cell non-Hodgkin's lymphoma, · CD20 positive, relapsed or refractory low grade or follicular, B-cell non-Hodgkin's lymphoma, · CD20 positive, diffuse large B-cell non-Hodgkin's lymphoma, in combination with chemotherapy. ***Chronic Lymphocytic Leukaemia*** Mabthera is indicated for the treatment of patients with CD20 positive chronic lymphocytic leukaemia (CLL) in combination with chemotherapy. ***Rheumatoid arthritis*** Mabthera (rituximab) in combination with methotrexate is indicated for the treatment of adult patients with severe, active rheumatoid arthritis who have had an inadequate response or intolerance to at least one tumour necrosis factor (TNF) inhibitor therapy. Mabthera has been shown to reduce the rate of progression of joint damage as measured by x-ray when given in combination with methotrexate.
Route(s) of administration:	Intravenous (IV) infusion
Dosage:	Two 1000 mg IV infusions, two weeks apart.
ARTG number(s):	60318 and 60319

Product Background

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterized by progressive inflammatory synovitis manifested by polyarticular joint swelling. B-lymphocytes (B-cells) are an important mediator in the pathogenesis of RA via production of

auto-antibodies, their role as antigen-presenting cells, and in activation of T-lymphocytes. Rituximab is a chimeric mouse/human monoclonal antibody that binds with high affinity to the transmembrane antigen CD20 located on pre-B and mature B-cells. Rituximab is believed to exert its therapeutic effect by promoting B-cell lysis via several possible mechanisms including complement-mediated cytotoxicity, antibody-dependent cellular cytotoxicity and induction of apoptosis.

Rituximab is currently registered for use in rheumatoid arthritis, non-Hodgkin's lymphoma and chronic lymphocytic leukaemia. This submission is only related to the rheumatoid arthritis indication.

Current indication for Rheumatoid Arthritis:

> Mabthera (rituximab) in combination with methotrexate is indicated to reduce the signs and symptoms in adult patients with severe, active rheumatoid arthritis who have had an inadequate response or intolerance to at least one tumour necrosis factor (TNF) antagonist therapy.

Proposed indication for Rheumatoid Arthritis:

> Mabthera (rituximab) in combination with methotrexate is indicated in adult patients for:
>
> § the treatment of moderate to severe, active rheumatoid arthritis when the response to disease modifying anti-rheumatic drugs including methotrexate has been inadequate,
> § treatment of moderate to severe, active rheumatoid arthritis in patients who have had an inadequate response or intolerance to at least one tumour necrosis factor (TNF) antagonist therapy.
> Mabthera has been shown to reduce the rate of progression of joint damage as measured by x-ray, to improve physical function and to induce major clinical response, when given in combination with methotrexate.

The sponsor initially requested an additional indication for use in methotrexate (MTX) naïve patients based on the IMAGE study. The IMAGE study was designed to assess use of rituximab in early, active RA patients who were naïve to methotrexate use and considered candidates for methotrexate treatment. However following a report of progressive multifocal leukoencephalopathy (PML) within the postmarketing setting in a patient on rituximab who was MTX naïve, the IMAGE study was terminated worldwide and the sponsor withdrew this indication from the TGA submission during the evaluation process. The sponsor decided to withdraw this indication based on an unfavourable risk/benefit profile in MTX naïve patients given the availability of many treatment options in early RA and the seriousness of PML.

Rituximab has been considered by the Australian Drug Evaluation Committee (ADEC; now called Advisory Committee of Prescription Medicines, ACPM) previously for oncology indications, however not for RA. The RA indication was considered by the TGA Peer Review panel in October 2006 and it recommended approval of the RA indication.

Regulatory Status

The status of the current submission in various countries and regions around the world is shown in Table 1.

Table 1. International regulatory status.

Country	Status
Canada	Under evaluation (submitted 25 May 2009).
European Union (EU)	Under evaluation (submitted 9 June 2009).

New Zealand	Not yet submitted.
Switzerland	Under evaluation (submitted 28 May 2009).
USA	Complete response letter received 16 October 2009.

In the USA, the sponsor submitted an application to extend the indication to "disease modifying anti-rheumatic drugs (DMARD) inadequate responders", to seek a claim for improvement in physical function, and to modify a current US claim on structural damage from "slowing" to "inhibition". On 16 October 2009, the FDA decided to reject the "DMARD inadequate responders" indication, reject the inhibition of structural damage claim but approve the physical function claim in the clinical trials section only and not the indications. The reasons cited for rejection of the DMARD inadequate responders indication are safety concerns from prolonged rituximab mediated B-cell depletion and the risk of PML making the risk/benefit profile unfavourable in less refractory RA populations. The FDA was satisfied with the efficacy of rituximab in less refractory RA populations based on the SERENE and IMAGE studies, but was concerned about the safety of rituximab in this indication and did not believe the risk of PML could be mitigated, therefore the only practical solution was to limit the indication to the currently approved "TNF inhibitor inadequate responder" population. For the radiographic claim, the US currently includes a claim for "slowing" progression of the disease based on one year data from the REFLEX study. To extend this to an "inhibiting" claim, two year data were required that showed at least a 75% inhibition of progression of structural damage compared to placebo. The two year data in the submission did not meet the FDA's requirements however it was added to the US product information to further support the "slowing" claim.
The following are the approved indications in

- the USA:
  Rituxan (rituximab) in combination with methotrexate is indicated for the treatment of adult patients with moderately- to severely- active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.
- the EU:
  MabThera in combination with methotrexate is indicated for the treatment of 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.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

There were no new quality data submitted with this application.

III. Nonclinical Findings

There were no new nonclinical data submitted with this application.

IV. Clinical Findings

Introduction

The submission was presented in a clear manner. Ethics certification was included in the submission for the relevant studies. All phases of the clinical investigation were conducted in

accordance with Good Clinical Practice guidelines, and in compliance with principles of the Declaration of Helsinki.

Dataset Overview

The original RA treatment indication in Australia was based on a single pivotal Phase III study (REFLEX) that investigated the efficacy and safety of rituximab (2 x 1g infusions) in combination with methotrexate (MTX) in patients with RA who had an inadequate response to one or more anti-tumour necrosis factor (anti-TNF) agents, and who were not controlled on MTX. The study demonstrated that in this treatment refractory population of RA patients that rituximab in combination with MTX reduced the signs and symptoms of RA compared to MTX alone. The original application was supported with data from two double-blind, Phase II studies (WA16291, and DANCER/WA17043) in patients with RA who had responded inadequately to disease-modifying anti-rheumatic drugs (DMARDs), including biologic agents, and who were not controlled on MTX. The WA16291 study was a Phase IIa trial that investigated the efficacy and safety of rituximab monotherapy (2 x 1g infusions) and two different combination treatment regimens (cyclophosphamide 2 x 750mg IV, or oral MTX 10-25mg/week). The DANCER trial was a dose-ranging Phase IIb study that investigated the effect of two differing dose regimens of rituximab (either 2 x 1g or 2 x 0.5g infusions) in combination with MTX (oral or parenteral at a dose of 10-25 mg/week) and different regimens of adjunctive corticosteroids (IV and/or oral to a total dose of 0, 250 mg, or 820 mg prednisone equivalent). Repeat courses of rituximab were provided in the extension periods of all three studies (Protocol WA16855 for WA16291 and DANCER, and WA17531 for REFLEX). Data from the extended follow-up periods of the REFLEX and DANCER studies, in particular the two year radiographic outcomes from the REFLEX Study, are provided in this submission in support of the long term efficacy and safety of rituximab.

In addition to the above, four new phase III have been conducted to support the proposed extension of indications. The new clinical studies included in this submission are two pivotal Phase III studies (IMAGE and SERENE) and two supportive studies (MIRROR and SUNRISE). The key differentiating features of these studies with regard to treatment populations and primary efficacy objective can be summarized by the following:-

§ IMAGE (WA17047) – examined MTX naïve patients early in the disease course (typically < 6 months duration) with a primary efficacy objective of radiographic progression at Week 52,
§ SERENE (WA17045) – assessed MTX-IR (Inadequate Response) patients with a mean disease duration of 6-7 years with a primary efficacy objective of ACR20 (American College of Rheumatology's index of 20% improvement of RA) response rate at Week 24,
§ MIRROR (WA17044) – examined MTX and anti-TNF-IR patients using a dose escalation design for the primary efficacy objective of ACR 20 response rate at Week 48, and
§ SUNRISE (U3384g) – evaluated anti-TNF-IR patients receiving repeat rituximab treatment for the primary efficacy objective of ACR 20 response rate at Week 48.

Although the SUNRISE study is completed, the other three new Phase III studies listed above are on-going with patients eligible to receive re-treatment. The data from the extension periods were not included as part of this submission. A further study (U3374g or SIERRA) was included in the submission and provides information on the effect of rituximab treatment on the immune response, particularly in response to vaccinations.

The results of the REFLEX Study and the other 5 Phase III clinical trials have been published in peer reviewed journals. In nearly all of the controlled studies in the dataset, the primary efficacy comparison for clinical endpoints was made following 24-52 weeks of observation.

However, patients continued to be followed-up in open-label extension protocols, in which some patients received additional doses of rituximab. The designs of the two new pivotal studies, IMAGE and SERENE, were discussed with regulatory authorities in Europe prior to study commencement and were considered to adequately address the proposed variations in indication for rituximab. The endpoints used in the studies were consistent with those recommended by European League against Rheumatism (EULAR), ACR and various regulatory agencies at the time of their conduct.

In the RA clinical trial program, a total of 3095 subjects have received at least part of one infusion of rituximab (0.5 or 1g) in a controlled or open-label setting as of the data cut-off dates (30 September 2008 for IMAGE, and 29 August 2008 for all other studies including those with on-going follow-up periods). Patients received rituximab or matching placebo as two IV infusions, the first on Day 1 and the second on Day 15. With the exception of patients who received rituximab monotherapy or rituximab + cyclophosphamide in one of the earlier studies (WA16291) which was part of the original submission, all patients continued to receive concurrent MTX.

With respect to repeat dose exposure, 2365 of the 3095 (76.4%) patients received two courses of rituximab, 1581 (51.1%) patients received three courses, 1038 (33.5%) patients received 4 courses, and 497 (16%) have received a fifth course. A course of rituximab is defined as two infusions given 14 days apart (for example, at study entry, first infusion is given on Day 1 and the second infusion given on Day 15).

Regarding duration of follow-up following drug exposure, at the time of the data cut-off, 1669 patients had been followed for more than two years, and 225 patients had been followed for at least 5 years after their first infusion of rituximab. This represents a total duration of exposure of 7198.49 patient-years.

Pharmacokinetics

The pharmacokinetics (PK) of different rituximab dosing regimens (2 x 1g and 2 x 0.5g) used for the treatment of RA patients were examined in the 4 controlled studies (IMAGE, SERENE, MIRROR and SUNRISE) involving blood samples from 1446 patients. Samples for PK analysis were collected following up to two courses of two IV doses at 0.5g and 1g, given 14 days apart (n=653 for first course of 2 x 0.5g; n=793 for first course of 2 x 1g; n=329 for second course of 2 x 0.5g; n=663 for second course of 2 x 1g).

Table 2 provides a summary of the mean PK parameters for rituximab in the 4 controlled studies.

Table 2.

Mean PK Parameters for Rituximab from all Four Studies

	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 (32)	198 ± 58 (29)	1.16			14.83 ± 5.78 (39)
SERENE	157 ± 45.9 (29)	183 ± 54.7 (30)	1.17			15.65 ± 5.12 (33)
MIRROR	164 ± 41 (25)	193 ± 61 (32)	1.18			16.38 ± 6.06 (37)
2 x 0.5 g in Course 2						
IMAGE	170 ± 38 (22)	ND	ND	0.99	ND	ND
SERENE	ND	ND	ND	ND	ND	ND
MIRROR	175 ± 41 (24)	207 ± 69 (33)	1.18	1.1	1.1	19.37 ± 5.97 (31)
2 x 1 g in Course 1						
IMAGE	341 ± 84 (25)	404 ± 102 (25)	1.18			16.89 ± 5.36 (32)
SERENE	318 ± 85.8 (27)	381 ± 98.3 (26)	1.20			18.50 ± 5.82 (31)
MIRROR	312 ± 103 (33)	365 ± 126 (34)	1.14			17.95 ± 6.21 (35)
SUNRISE	298 ± 91.2 (30.6)	355 ± 112 (31.4)	1.19			21.2 ± 8.2 (38.7)
2 x 1 g in Course 2						
IMAGE	370 ± 101 (27%)	ND	ND	1.1	ND	ND
SERENE	ND	ND	ND	ND	ND	ND
MIRROR	348 ± 89 (26)	386 ± 132(34)	1.11	1.1	1.1	21.82 ± 6.39 (29)
SUNRISE	317 ± 107 (33.8)	377 ± 120 (31.8)	1.19	1.1	1.1	20.9 ± 5.77 (27.6)

C_{first} = post-infusion concentration after first infusion; C_{second} = post-infusion concentration after second infusion
Values are mean ± SD (CV%)
ND = not determined

The maximum plasma concentration of rituximab (C_{max}) was observed following the second infusion in any course at a magnitude of 11-20% higher for the second versus first infusion. The C_{max} values increased in proportion to the increase in dose, suggesting that rituximab PK were linear over the limited dose range investigated. The mean (coefficient of variation, CV, %) C_{max} value for serum rituximab following first infusion was 164 (29%) µg/mL for the 2 x 0.5g dose, and 317 (29%) µg/mL for the 2 x 1g dose. The mean terminal elimination half-life after the first infusion ranged from 15-16.5 days for the 2 x 0.5g dose group and 17-21 days for the 2 x 1g dose group. Following the second infusion, the mean (CV %) C_{max} value for serum rituximab was 172 (23%) µg/mL for the 2 x 0.5g dose, and 345 (28%) µg/mL for the 2 x 1g dose. The mean terminal elimination half-life after the second infusion course was 19 days for rituximab 2 x 0.5g dose and ranged from 21-22 days for the 2 x 1g dose. Thus, the PK parameters of C_{max} and elimination half-life were comparable over the two treatment courses.

A population PK analysis using a 2-compartment model with first order elimination was also undertaken using data from 6 clinical studies in patients with RA (2 Phase II studies [WA16291 and DANCER] and 4 Phase III studies [REFLEX, SERENE, MIRROR and SUNRISE]. A total of 24,165 samples from 2005 patients who received two doses of rituximab (either 2 x 1g or 2 x 0.5g) 14 days apart showed that the inter-individual variability for clearance (29.3%) and the volume of the central compartment (Vc; 14%) were not large. The mean terminal half-life of rituximab was 18.0 days (range: 5.17-77.5 days). Weight, gender and C-reactive protein (CRP) were the most significant covariates to explain inter-individual variability for the above PK parameters, but still only managed to describe a small proportion of the variation. Other variables such as Human Anti-Chimeric Antibody (HACA) status, erythrocyte sedimentation rate (ESR), age, rheumatoid factor (RF) status (positive or negative) and previous or concurrent therapies (MTX, cyclophosphamide, corticosteroids and anti-TNF medications) failed to be significant covariates. Based on this population PK model, dosing with rituximab should not be adjusted according to the above disease related or

physiologic variables. The population PK analysis also indicated that the apparent mean volume of distribution at steady state was 6.49 L and mean systemic serum clearance was 0.335 L/day.

The elimination of rituximab is mediated by both the specific CD20-receptor mediated pathway and the non-specific immunoglobulin (Ig) G clearance pathways. Thus, rituximab would not be expected to interact with other drugs based on the lack of competition for protein binding, effects on cytochrome P450 activity, renal excretion and/or competition for common drug transporter proteins. Although no specific drug interaction studies have been performed, based on the population PK analysis from data collected in the Phase II/III studies, corticosteroids (both peri-infusional and on-going maintenance oral therapy), MTX and cyclophosphamide seemed to have no clinically important effect on rituximab PK.

The population PK analysis also failed to show a correlation between rituximab PK and efficacy, as examined by the specific parameters of ACRn (index of improvement of RA) and the change from baseline in DAS28 (disease activity score using 28 joint counts) and erythrocyte sedimentation rate (ESR) over 48 weeks of follow-up. In addition, a relationship between rituximab PK and safety was explored. Rituximab concentrations are known to be dose proportional over the limited dose range studied. With the exception of a higher rate of infusion related reactions with the first infusion of Course 1 for rituximab 1g versus 0.5g, the two doses had similar safety profiles over repeated infusions.

Using a pooled analysis of data from the SERENE, MIRROR and SUNRISE studies, no significant difference was observed in the post-infusion serum concentrations of rituximab for HACA positive and negative patients. Following the first course of rituximab, mean (CV %) C_{max} values for serum rituximab in HACA positive subjects (n=34) was 358 (33.2%) µg/mL compared with 370 (28.6%) µg/mL for HACA negative patients (n=528). Following the second course of rituximab, mean (CV %) C_{max} values for serum rituximab in HACA positive subjects (n=28) was 386 (23.2%) µg/mL compared with 387 (30.1%) µg/mL for HACA negative patients (n=357). Two HACA positive patients (1 case each in SERENE and IMAGE) had significantly lower (by approximately 30%) serum rituximab concentrations after their second infusion in Course 1 compared to the first infusion.

Drug Interactions

There were no drug interaction studies submitted with this application.

Pharmacodynamics

(a) Effects on Lymphocytes

Treatment with rituximab results in a rapid, profound, and often sustained depletion of circulating peripheral B-lymphocytes. Because rituximab can confound assays of CD20 cells, CD19 is used to measure the levels of peripheral B-cells after rituximab therapy. CD19 is expressed on B-cells from the earliest recognizable B-lineage cells during development to B-cell blasts but is lost on maturation to plasma cells. From a pooled analysis of data from patients involved in the IMAGE, SERENE, MIRROR and SUNRISE studies, 4 patient populations were defined to examine the effect of rituximab on B-cell depletion and repletion: treatment to remission with rituximab 2 x 1g (n=464), treatment to remission with rituximab 2 x 0.5g (n=487), treatment as needed with rituximab or a "prn treatment group" (n=257) and patients treated with placebo infusions + MTX (n=422). Treatment with either dose of rituximab + MTX resulted in a rapid and near complete depletion (median post-infusion B-cell count was 1 cell/µL) of peripheral CD19 B-cells with >95% of patients in all studies having counts below 10 cells/µL by the end of the second infusion. Furthermore, the depletion of peripheral B-cells was maintained over the initial 24 weeks after a course of

rituximab (2 infusions) in the majority of patients (94.7%, 1064/1123). There was no difference in the magnitude of the initial peripheral B-cell depletion, and also rates of repletion by 24 weeks, between the two rituximab dose regimens. In contrast, patients receiving placebo infusions + MTX consistently showed a slight decrease in peripheral CD19 B-cell count following their first infusion and an increase at Week 2 prior to the second infusion. These fluctuations were probably due to high dose corticosteroid treatment given over the first two weeks in most of the studies. After the second placebo infusion (with ongoing MTX), B-cell numbers returned to baseline and remained constant thereafter.

The extent and duration of B-cell depletion was similar for each treatment course with repeat rituximab treatment. This was investigated in patients who had received between two and five courses of rituximab. Again, no clear difference in the extent of B-cell depletion and recovery characteristics were observed on the basis of rituximab dose (2 x 1g or 2 x 0.5g) with repeat treatment courses. However, for patients who received rituximab via the prn dosing strategy a significantly higher proportion of subjects (40.2%, 167/415) had B-cell counts above the lower limit of normal at the time of each repeat treatment compared with patients receiving rituximab by the treatment to remission approach (9.5% [98/1035] for rituximab 2 x 0.5g and 8.4% [53/628] for rituximab 2 x 1g).

No correlation was found between the extent of B-cell depletion and proportionate decrease in disease activity measurements. However, recrudescence of clinical disease after initial improvement was usually associated with evidence of increasing numbers of B-cells in the peripheral blood. Likewise, patients with long term clinical responses frequently maintain B-cell depletion.

There was no difference over one year of follow-up between any of the treatment groups in overall T-cell counts (CD3), or any of T-cell subsets including T-helper cells (CD4), cytotoxic T-cells (CD8), CD3 or CD4 memory cells. Mean peripheral T-lymphocyte cell counts transiently decreased after each infusion (for example, on Days 1 and 15 of their first course) but recovered to baseline within two weeks, and then remained stable. The transient decreases in T-cell numbers post-infusion are likely to be related to the use of corticosteroids.

(b) Effects on Serum Immunoglobulins

Following the first course of study infusions (rituximab or placebo) in SERENE, mean concentrations of immunoglobulins (IgA, IgG and IgM) decreased from baseline in all treatment groups and then tended to stabilize between Weeks 8 and 24. Larger decreases in mean concentrations up to Week 24 were observed in both rituximab dose groups compared to placebo infusions + MTX, where in contrast there was a negligible mean change in serum concentrations. Following the second treatment course of rituximab, mean Ig concentrations declined further from baseline. The largest relative decreases from baseline were seen for IgM (approximate mean decrease of 20% at Week 24 and 30% at Week 48 for rituximab 2 x 1g and 2 x 0.5g). Mean decreases in IgA and IgG levels in both rituximab dose groups were approximately 7% at Week 24 and 9-15% at Week 48. With respect to the proportion of subjects with an IgM concentration below the lower limit of normal in SERENE, at baseline it was low for all three treatment groups (0.6-1.8%) but increased significantly after Week 8 for patients who received treatment with rituximab. At Week 24, 6.4% (10/156) patients in the rituximab 2 x 0.5g + MTX group and 6.6% (10/153) patients in the rituximab 2 x 1g + MTX arm had low IgM concentrations compared to 0 patients in the placebo infusion + MTX group. At Week 48, these proportions increased further to 9.3% (14/151) patients in the rituximab 2 x 0.5g + MTX group and 14.3% (21/148) patients in the rituximab 2 x 1g + MTX group. In the same study, patients who initially received placebo infusions could be switched to re-treatment with rituximab (2 x 0.5g) and the proportion of patients developing low IgM

concentrations also increased by Week 48 in this group (6.6%, 9/137). However, only one patient with a low Ig concentration developed a serious infection in the SERENE Study.

For the other pivotal study (IMAGE) in this submission, a similar relationship between rituximab treatment (regardless of dose) and decreasing mean serum Ig levels with time after therapy was observed. Following the first treatment course in IMAGE, mean IgA, IgG and total Ig levels all similarly declined from baseline in the three treatment groups by 12-17% by Week 24 and 16-23% by week 52. However, from week 32 onwards, Ig levels rose slightly in the group allocated to placebo infusions + MTX but remained unchanged for the two rituximab + MTX treatment groups. Again, changes in IgM were more pronounced with the mean decline from baseline higher in the rituximab treatment groups (31-32% by Week 24 and 40-44% by Week 52) compared with placebo + MTX (16% by week 52). With respect to the proportion of subjects with an IgM concentration below the lower limit of normal in IMAGE, at baseline it was low for all three treatment groups (0-0.8%) but increased significantly for patients who received treatment with rituximab. At Week 24, 8.3% (19/233) patients in the rituximab 2 x 0.5g + MTX group and 9.4% (22/235) patients in the rituximab 2 x 1g + MTX arm had low IgM concentrations compared to 2.3% (5/220) patients in the placebo infusion + MTX group. At Week 52, these proportions increased further to 12.9% (27/210) patients in the rituximab 2 x 0.5g + MTX group and 17.1% (37/218) patients in the rituximab 2 x 1g + MTX group. Two patients in IMAGE with a low Ig concentration developed serious infections (1 case of low IgG and tonsillitis, and one case of low IgM and concurrent infections with pneumonia, urinary tract infection and appendicitis). Both of these patients had their infections resolved without sequelae.

Treatment with rituximab does not appear to have an effect on specific humoral immunity to several common bacterial and viral antigens over 48-52 weeks of observation in the SERENE and IMAGE studies. In all the rituximab treatment groups, the proportion of patients with positive antibody titres at baseline to mumps, rubella, varicella, tetanus toxoid, influenza, and *S. pneumoniae* remained stable during (for example, at Week 24) and at the conclusion of the respective studies. This indicates that specific protective antibody responses developed before B-cell depletion tend to be maintained for at least one year in individual patients after they receive rituximab.

(c) Effects on Biomarkers

Within both the SERENE and IMAGE studies, mean Rheumatoid Factor (RF) concentrations decreased by approximately 40% at Week 24 from baseline with rituximab (either dose regimen) + MTX treatment compared to patients receiving MTX alone where RF levels remained relatively constant. Within the IMAGE, SERENE and MIRROR studies, anti-Cyclic Citrullinated Peptide (CCP) antibody titres (a significant disease associated autoantibody) decreased from baseline with rituximab treatment (equivalent effects between the different dosing regimens) – median percentage decrease from baseline was 65% in IMAGE at Week 52, 30% in SERENE by Week 40 and 45% in MIRROR at Week 48.

Other biochemical markers known to correlate with RA disease activity and progression show that rituximab treatment results in significant decreases in the mean concentrations of CRP and ESR, both markers of inflammation, relative to the declines observed in patients receiving placebo infusions + MTX. In addition, earlier development studies (such as WA16291) have shown that concentrations of interleukin-6 and serum amyloid A protein decrease over 24 weeks after a single course of rituximab supporting an effect on the markers of inflammation.

Efficacy

The data for the extended RA indication is based on two new pivotal Phase III studies (IMAGE and SERENE) which are supported by two new Phase III studies (MIRROR and SUNRISE). The submission also included efficacy reports from two open-label extension periods in the REFLEX and DANCER Studies as supportive data but the clinical endpoint analysis in these studies is limited by very low patient numbers. However, Study WA17042/17531 (the extension phase of REFLEX) provided two year radiographic outcome data that is important in the assessment of the sponsor's claim of rituximab improving radiographic outcome.

IMAGE STUDY

Study Design

The IMAGE study was a prospective, multicentre, randomized, double-blind, placebo-controlled, parallel-group study with three treatment groups: placebo + MTX or two different doses of rituximab (2 x 0.5 g [low dose group] or 2 x 1g [high dose group] + MTX. Approximately 250 subjects were to be randomly assigned to each treatment group. Randomization was administered by a central randomization centre, and stratified by RF status (positive or negative) and region of recruitment (USA or non-USA).

The dose of rituximab used in this study was based on the results from a previous Phase IIb trial (DANCER) where rituximab was administered intravenously at a dose of either 500 or 1000mg given on Days 1 and 15 with matching placebo infusions to maintain blinding. In IMAGE, all patients received a corticosteroid regimen consisting of methylprednisolone 100 mg IV administered 30 minutes prior to infusions of rituximab or placebo. Usual therapeutic doses of MTX were utilized with all patients receiving weekly oral MTX at a dose of 10-25 mg/week. In the IMAGE study protocol, MTX was commenced at 7.5 mg/week and escalated by 2.5 mg/week every 1-2 weeks to achieve 15 mg/week by Week 4 and up to 20 mg/week by Week 8. All subjects received concomitant oral folic acid at a dose of 5 mg/week. The use of intra-articular corticosteroids was discouraged within 4 weeks prior to baseline through to Week 52, but was permitted in a limited manner for severe RA flares (up to a maximum of one joint per 24 week period or two joints per 52 weeks). The primary efficacy endpoint evaluation occurred at Week 52 but patients were assessed for eligibility to receive a further course of rituximab after Week 24 depending on their disease activity. Subjects were eligible to receive further rituximab (2 x 1g or 2x0.5 g as per their randomised dose) if their DAS28-ESR score was equal to or greater than 2.6. The minimum period of 24 weeks between courses was derived from the known pharmacodynamics of rituximab, as well as the clinical outcome data from the preceding DANCER study in which 90% of patients treated with rituximab at Week 24 would have met the clinical re-treatment criteria.

The study report in the submission covered the patients initial 52 weeks of follow-up, but subjects were eligible to continue receiving repeat doses of rituximab up to three years. Patients who withdrew from the study at any point were followed to one year for safety assessments.

In the course of the IMAGE study, treatment allocation was unblinded for 12 patients across 10 study sites: 8 received placebo + MTX, three low dose rituximab + MTX and one high dose rituximab + MTX. These patients were excluded from the per protocol efficacy analysis but included in the safety evaluation. Reasons for breaking the blind were serious adverse events (5 cases), guidance for future therapy (5 cases) and locally determined CD19+ B-cell count (2 cases). Four amendments were made to the study protocol but none significantly affected the conduct, outcome or statistical analysis.

Radiographs of the hands, wrists (posterior/anterior) and feet (anterior/posterior) for the assessment of the primary endpoint were read by a central independent radiologist who was blinded to treatment allocation, chronological order of the radiographs and the patients' clinical response. All radiographs were scored by two radiologists according to the Sharp method, modified by Genant, and the average of the two scores was used for the analysis. Checks for consistency were made between the two readers and resolution of discrepancies was made through an independent third reader who derived an adjudicated score. Radiographs were performed at baseline (screening), Week 24 and Week 52.

Study Population Characteristics

The IMAGE Study was conducted in 169 study sites (27 countries) in North, Central and South America, as well as Europe, Asia and Australia between January 2006 and September 2008. Subjects were required to be >18 years of age with RA of at least 8 weeks but less than 4 years duration, who had not been previously treated with MTX. At study entry, patients were required to have active disease as defined by the 1987-revised ACR criteria which included >8 swollen joints out of 66 joints assessed, >8 tender joints out of 68 joints assessed, raised serum inflammatory markers (CRP>10 mg/L), and at least one joint erosion attributable to RA on plain x-ray if they were RF negative patients. Corticosteroids (oral prednisone <10mg/day or equivalent doses) were permitted if stable for at least 4 weeks prior to baseline. The use of non-steroidal anti-inflammatory drugs (NSAID) was permitted if stable for at least two weeks prior to baseline.

The studied population was clearly delineated and the three treatment groups were well matched with respect to demographic characteristics. Subjects had a mean age of 48 years (range: 18-79 years) and were predominantly female (77-85% across the treatment groups). Caucasians (64-66% across the treatment arms) accounted for the major racial background followed by patients of Hispanic ethnicity (31-33%) and Oriental background (11-14%). A quarter of the patients were recruited from the USA.

The patients involved in the IMAGE Study had short disease duration (median < 6 months) and a modest quantity of pre-existing joint damage (mean Genant-modified Total Sharp Score (mTSS)[1] of 7.3 [range: 0-94]). Over 85% of patients in each group were seropositive for rheumatoid factor (RF>20 IU/mL) which is a significantly higher ratio compared to most RA patient cohorts where approximately 70% of patients are RF positive.

The baseline disease parameters reflect severely active disease and were comparable among the three treatment groups. The baseline median tender joint count was 29-32 (of a possible maximum of 68), and the median swollen joint count was 16-19 (of a possible maximum of 66). The overall activity score, as measured by the DAS28-ESR score, was 7.04-7.11, indicating high disease activity. As a validated marker of progressive disease, CRP values were high across the three treatment groups (mean 3.0-3.4 mg/dL). In addition, the mean Health Assessment Questionnaire – Disease Index (HAQ-DI) scores were high (1.73-1.83) which is consistent with a severely active disease state. The population in this study does not match the sponsor's claim of treating patients with moderately active RA.

The treatment groups were well-balanced with respect to previous and concomitant treatments for RA. All patients recruited into the study were MTX naïve and only 30% had received prior

[1] Total Modified Sharp Score (TMSS) is the sum of the erosion score (ES) and the joint space narrowing (JSN) score and has a range of 0 to 398. The ES is the sum of joint scores collected for 46 joints and has a range of 0 to 230. The JSN is the sum of joint scores collected for 42 joints and has a range of 0 to 168. A score of 0 would indicate no change.

DMARDs with the most common prior DMARDs being anti-malarial agents (16.3%) followed by sulfasalazine (13.6%). A small percentage of patients (3.6%) had received prior immunosuppressant treatment, mainly leflunomide. All patients were commenced on MTX at study entry with the mean weekly intake of MTX being similar for all three treatment groups at the various stages of the study. The dose of MTX remained stable from Week 8 through to Week 52, at a median dose of 20 mg/week. Oral corticosteroid therapy (mean dose 6.9 mg/day) was recorded by approximately 45% of patients at study entry and was similar between the treatment groups. In addition, over 60% of patients were taking anti-inflammatory medication at study entry.

Approximately 60% of the study population had at least one medical problem other than RA with the most common concurrent conditions being hypertension (22%), dyslipidaemia (8%), osteoporosis (6%), and gastro-oesophageal reflux disease (5%). Overall, the study population is externally valid but some limitations need to be considered. For example, patients with the following characteristics were excluded:- history of recurrent infection, positive serology for Hepatitis C virus, history of non-cutaneous malignancy, or significant underlying cardiac, pulmonary, or renal conditions. Thirty-three patients entered the study positive for antibodies to Hepatitis B core antigen with negative viral load and negative Hepatitis B surface antigen.

Primary Efficacy endpoint

The primary radiographic endpoint in the IMAGE Study was the mean change in the mTSS from screening to Week 52 between the three treatment groups.

The primary clinical endpoint was the proportion of patients in each treatment group achieving an ACR50 response at Week 52, and the primary functional endpoint was the mean change from baseline in the HAQ-DI for the three treatment arms.

Secondary Efficacy endpoints

Major secondary efficacy endpoints (all assessed at Week 52) included:

- Radiographic – mean change in the erosion score and Joint Space Narrowing (JSN) score, as well as the proportion of subjects with no x-ray progression (defined as a change in mTSS of zero or lower);
- Clinical signs and symptoms - proportion of subjects achieving American College of Rheumatology (ARC) improvement criteria of 70% improvement (ACR70), and 20% improvement (ACR20), the change from baseline in mean ACRn, the change from baseline in mean DAS28-ESR score, the proportion of subjects achieving DAS28-ESR remission, the proportion of subjects achieving EULAR clinical response (that is, a categorical DAS28 response), the proportion of subjects achieving major clinical response (as defined by an ACR70 response maintained for at least 6 consecutive months) and the change from baseline in the individual ACR core set parameters;
- Functional - proportion of patients achieving the Minimally Clinically Important Difference (MCID) in HAQ-DI (improvement defined as a decrease equal to or greater than 0.22);
- Quality of Life: the mean change in the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score from baseline, and the mean change (with minimal clinically relevant improvement standards) in the Physical and Mental Health Components of the SF-36.

Explanation and validity of the major efficacy variables

In general, the selected endpoints in the IMAGE Study use well-accepted, validated metrics that have served as the basis of previous published studies, prior regulatory approvals, and are consistent with published guidelines.

The **mTSS** (assessed using the Genant modification of the Total Sharp Scoring system) is the sum of the joint space narrowing (JSN) score plus the erosion score (ES) and has a range of 0-448. Plain x-rays of both hands and feet are obtained. A higher score represents greater structural damage. The JSN score has a range of 0-168 and is derived from evaluating 40 joints in the hands and feet which are scored from 0 (no damage) to 4. The ES has a range of 0-280 and is derived from assessing 44 hand and foot joints. Each joint is scored 0 (no damage) to 5, except the metatarsophalangeal joints of the feet which are scored 0-10. In addition, this study has evaluated the proportion of subjects with no radiographic deterioration (defined as change from baseline of equal to or less than 0 in the mTSS) over 52 weeks of therapy. This secondary radiographic endpoint is an important supporting analysis for the evaluation of the drug's ability to inhibit structural progression in RA.

Although the mTSS is the appropriate radiological scoring method, the minimum time point in which it is assessed is crucial to deciding the validity of a drug's claim to inhibition of the rate of structural progression of RA. The pertinent European Medicines Evaluation Agency (EMEA) document[2] states that for agents claiming to prevent structural joint damage, it is recommended to demonstrate radiological differences of the hands and forefeet on the basis of before and after treatment comparisons taken not less than one year apart, but ideally two years, using full randomization and pre-agreed criteria. Furthermore, the FDA has two levels of efficacy claim for structural damage in RA – either "slowing" or "inhibiting" the progression of structural damage. The criteria for the higher therapeutic claim of "inhibiting" requires at least 75% inhibition in the progression of structural damage compared to a placebo treated group over a 104 week period of follow-up. At present, the FDA has only approved the claim of "slowing" radiographic progression for rituximab based on the two year data from REFLEX.

Assessments of disease activity were based on the criteria from the American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR). Both of these measures are based on a combination of a core set of clinical outcome measures, some assessed by the physician, and some by the patients themselves. Definitions of the ACR and EULAR score changes that represent clinically relevant improvements on disease activity have been developed and validated.

The **ACR response** criteria are a standard instrument used in RA trials. The ACR criteria of 20%, 50% or 70% improvement in clinical manifestations are an attempt to quantify response to therapy. Thus, a patient with an ACR 20 response to an intervention has demonstrated a 20% decrease in the combined number of swollen and tender joint counts, and a 20% improvement in any three of the 5 core-set measures which include Patient's Global Assessment, Physician's Global Assessment of Disease Activity (on 10 cm visual analogue scores, VAS), Patient's Assessment of Pain Score (on 10cm VAS), HAQ-DI, and acute phase reactants (ESR or CRP). The achievement of an ACR 20 response by an individual subject is considered to be the minimally achieved level of response that is of clinical relevance. The ACRn was defined as the minimum of the following three items: (i) the percentage change

[2] EMEA guideline: "Points to consider on clinical investigations of medical products other than NSAIDs for treatment of rheumatoid arthritis." CPMP/EWP/556/95rev1/final. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003414.pdf

from baseline in the number of tender joints, (ii) the percentage change from baseline in the number of swollen joints, and (iii) the median of the percentage change from baseline for the other 5 ACR response criteria: Patient's Global Assessment of Disease Activity, Physician's Global Assessment of Disease Activity, Patient's Assessment of Pain Score, HAQ-DI and CRP.

The **DAS 28** is a widely used and validated method used in research trials and clinical practice for measuring outcome in patients with RA. It is a composite disease activity index of 4 clinical variables involving the tender joint count (up to 28 joints), swollen joint count (up to 28 joints), ESR (used in this study) or CRP, and the patient's assessment of general health using a 10cm VAS. The final score is derived by a complex mathematical calculation of the individual elements. DAS 28 has a scale from 0 to 10, and most scores range from two to a maximum of 10. According to the EULAR guidelines, a DAS 28 >5.1 indicates high disease activity, >3.2 and up to 5.1 indicates moderate disease activity, 3.2 or less indicates low disease activity, and "clinical remission" is indicated by a DAS 28 score of <2.6. There are three categories of **EULAR response** (good, moderate and non-responders) which include not only the individual's amount of change in the DAS but also the attainment of a particular DAS value (low, moderate or high) at the endpoint. A change from baseline of at least -1.2 (that is, two times the potential measurement error) in a patient's DAS is considered indicative of a significant change in disease activity (compared with >-0.6 to -1.2 as moderate change in disease activity, and -0.6 or less as no change in disease activity). Hence, to be classified as a good EULAR response, the patient must demonstrate a significant change from baseline (that is, >-1.2) as well as reach low disease activity (that is, DAS 28 <3.2). Moderate EULAR response is a minimum change from baseline in the DAS 28 of >-0.6 to -1.2, as well as the endpoint achievement of a DAS 28 equal to or less than 5.1.

The measures that are most valuable in assessing **major clinical response** are the proportion of subjects who achieved DAS 28 responses to a score of <2.6, and/or the proportion of subjects achieving an ACR 70 response for a continuous period of 6 months. This study pre-specified the latter variable as its secondary endpoint for determining this claim.

The **HAQ-DI** is a patient reported questionnaire used to provide an assessment of the impact of the disease and its treatment on physical function. The tool assesses the degree of difficulty experienced by the individual in 8 domains of daily living activities using 20 questions. The domains include dressing and grooming, arising, eating, walking, hygiene, reach, grip and common daily activities, with each domain (activity) consisting of two or three items. For each question, the level of difficulty is scored from 0 to 3 with 0 = "without any difficulty", 1 = "with some difficulty", 2 = "with much difficulty" and 3 = "unable to do". If the maximum score equals 0 or 1, but a device related to that activity was used or help from another person was provided for the activity, then the activity score is increased to 2. However, if the activity score was already 2 and a device related to that activity was used or help from another person was provided, the score for that activity remains 2. A total score of between 0 and 3 is obtained from the mean of each activity. A change from baseline in the HAQ-DI of at least -0.22 units has been specifically defined for RA in peer-reviewed literature to be the smallest measurable reduction that is clinically significant.

Statistical methods

Sample Size: A total of 750 subjects were calculated (250 in each treatment arm) in order to detect a difference at a 2-sided significance level of 2.5% for a 1:1:1 randomization with 90% power. For the primary endpoint of change in mTSS endpoint at Week 52, it was predicted that the mean change from baseline would approximate 3.7 (SD=9.6) for the control group and 0.5 (SD=5.6) for each of the rituximab treatment groups. These calculations were based on the

mean changes in mTSS assumed from the ASPIRE study data which similarly assessed patients with early RA. The sample size calculations included both RF positive and negative patients who were to be equally distributed between treatment groups, but limited the inclusion of RF negative subjects to approximately 20% of the total sample size.

Methods: Radiographic endpoints were analysed on the modified intention-to-treat (mITT) principle which included all randomized patients with a screening and at least one post-baseline set of x-rays (either at 26 or 52 weeks). However, the clinical efficacy endpoints were analysed using the ITT population, defined as all patients randomized who received at least a part of the first of two study infusions.

As changes in radiographic outcomes are known to be skewed, non-parametric methods (Kruskal-Wallis [global test] and Van Elteren [confirmatory pair-wise tests against placebo]) were employed for the primary radiographic analysis stratifying by region (US/non-US) and rheumatoid factor (positive/negative) status. X-rays were taken at baseline, Week 26 and Week 52. Subjects who terminated early from the study were required to obtain an x-ray evaluation at the time of withdrawal. Missing values for the mTSS were imported by a pre-defined, linear progression method based on the slope between two non-missing assessments. Several sensitivity analyses were also performed, repeating these analyses in different populations (such as the per protocol population) and accounting for missing data using alternative imputation assumptions. The secondary radiographic endpoint of the proportion of patients without progression was evaluated using a Cochrane-Mantel-Haenszel (CMH) analysis, stratifying by RF and region.

A hierarchical approach was taken in testing the other (non-radiological) primary endpoints. The study protocol outlined that if the primary radiographic endpoint was achieved by the global test analysis, then the primary clinical endpoint (ACR50 response rate 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. Sub-hierarchies of secondary endpoints under each of the three main endpoints were assessed in a predefined manner.

Categorical efficacy endpoints such as the various levels of ACR response and EULAR response were evaluated using a CMH analysis, stratified by RF status and region. Continuous efficacy variables such as the change from baseline in DAS28 and ACRn were assessed using an Analysis of Variance (ANOVA) model with baseline parameter of interest, RF status and region as terms in the model. Imputation methods including the last observation carried forward (LOCF) and non-responder imputation (NRI) were used to handle missing data.

The numbers in the mITT population used in the radiographic endpoint analysis differed from the ITT population (n=748) and total number of randomized patients (n=755). In total, 7 subjects who were randomized failed to receive treatment (two for placebo + MTX, three for low dose rituximab and two for high dose rituximab). In addition, a further 33 patients (17 for placebo + MTX, 10 for low dose rituximab and 6 for high dose rituximab) did not have both a screening and subsequent radiographic assessment, and hence were excluded from the mITT. The final mITT population for radiographic analysis was 232 (of a possible 251) subjects for placebo + MTX, 239 (of a possible 252) patients for low dose rituximab and 244 (of a possible 252) for high dose rituximab.

Following the mITT analysis, a further 76 patients (30 for placebo + MTX, 20 for low dose rituximab and 26 for high dose rituximab) were excluded from the per protocol analysis because of significant protocol violations such as receiving study medication beyond temperature excursion (16 patients), commencement of oral corticosteroids (13 patients), receiving <80% of planned dose for each treatment course (13 patients), compromised blinding

(12 patients), and receiving incorrect study medication or incorrect randomization number (10 patients).

Completion status

Of the 755 patients randomized, 748 subjects received at least one dose of treatment in the IMAGE Study. A further 790 subjects underwent screening but failed to meet eligibility criteria. The most common reason for screening failure, affecting 55% of ineligible patients, was insufficient elevation in baseline CRP (>1.0mg/dL) followed by serological positive status to either Hepatitis B or C virus (18%). Of the 755 patients enrolled into the study, 252 were randomized to receive treatment with rituximab 2 x 0.5 g + MTX, 251 were assigned rituximab 2 x 1 g + MTX, and 252 to receive placebo + MTX. Three patients received a study medication other than that to which they were randomized for their first course of therapy.

In total, 670 (89.6%) of treated patients completed 52 weeks of study follow-up with a higher percentage of patients in the rituximab + MTX groups (90.1% [227/252] for low dose rituximab and 91.6% [230/251] for high dose rituximab) reaching this study endpoint compared with 84.5% (213/252) of patients in the placebo + MTX group.

Similar proportions of patients in each treatment group received a second course of therapy: 81% [205/252] for placebo + MTX, 80% [201/252] for low dose rituximab and 84% [211/251] for high dose rituximab. The majority (80%) of re-treated patients received their second course between Weeks 24 and 32 and this result was consistent for each of the treatment groups. More patients (43.7% [110/252]) in the placebo + MTX group received a third course of treatment than patients in the rituximab groups-37.3% [94/252] for low dose rituximab and 36.3% [91/251] for high dose rituximab.

In total, 14.8% (37/250) of patients assigned to placebo + MTX withdrew prior to Week 52 compared to 8.8% (22/249) of patients in the low dose rituximab group and 7.6% (19/249) in the high dose rituximab group. The most common reason for premature withdrawal was insufficient therapeutic response, which led to the discontinuation of 19 patients (7.6% of 250) in the placebo + MTX group, 9 patients (3.6% of 249) in the low dose rituximab group and 4 patients (1.6% of 249) in the high dose rituximab group. Other non-safety withdrawals included a small number of patients in each group who refused treatment or failed to return: 11 placebo + MTX patients, 9 low dose rituximab subjects and 8 high dose rituximab patients.

Result for primary efficacy variables

Treatment with high dose rituximab (2 x 1g) + MTX resulted in a reduction in the rate of progressive joint damage compared with MTX monotherapy as evaluated by the mean change in mTSS at Week 52 (mean change in mTSS of 0.359 for high dose rituximab versus 1.079 for MTX alone; $p<0.0004$). However, treatment with low dose rituximab (2 x 0.5g) did not result in a significant reduction in mean mTSS scores compared with MTX monotherapy (mean change in mTSS of 0.646 for low dose rituximab versus 1.079 for MTX alone; $p=0.0369$). Similar results were obtained for all sensitivity analyses (using different imputation rules) performed on differently defined patient populations (in particular, using the per protocol population) for the primary radiological efficacy outcome. In total, 6.3% of the data was imputed for the primary x-ray analysis: 13/232 (5.6%) for placebo + MTX, 13/239 (5.4%) for low dose rituximab and 19/244 (7.8%) for high dose rituximab. Furthermore, concordance between scoring of the two radiographic raters was high with regression coefficients ranging between 0.9360 and 1.0307 for all scores (Total, Erosion, and JSN). Readings from 93 patients were adjudicated by the third rater as part of the quality control process (that is, the top 10% of patients with the largest discrepancy in mTSS between readers, and the top 5% of subjects with the largest change from baseline for each reader were independently adjudicated).

The favourable radiological result for high dose rituximab was seen across all subgroups (with n >20 patients) including age (less than or greater than 65 years), gender, ethnicity, region,

body surface area, disease duration (< 6 months, 6 months-2 years, or > 2 years), and autoantibody status (RF and/or anti-CCP positive or negative). However, there are some caveats to this interpretation as some of the subgroups were small in number (for example, age > 65 years) or exhibited wide confidence intervals.

The primary clinical endpoint of ACR50 response at Week 52 was achieved by a significantly higher proportion of patients (ITT population) in both rituximab treatment groups compared with placebo + MTX (59.4% [148/249] for low dose rituximab and 64.8% [162/250] for high dose rituximab versus 41.8% [104/249] for MTX alone; p<0.0001 for both pair-wise comparisons; see Table 3).

Table 3. IMAGE Study

Summary of ACR Endpoints at Week 52 (ITT Population)

	Placebo + MTX (N=249)	Rituximab (2 × 0.5 g) +MTX (N=249)	Rituximab (2 x 1 g) +MTX (N=250)
ACR50	**104 (41.8%)**	**148 (59.4%)**	**162 (64.8%)**
p-value		**<0.0001**	**<0.0001**
Major clinical response	**21 (8.4%)**	**45 (18.1%)**	**53 (21.2%)**
p value		**0.0015**	<0.0001
ACR20	160 (64.3%)	191 (76.7%)	200 (80.0%)
p-value		0.0013	<0.0001
ACR70	62 (24.9%)	105 (42.2%)	117 (46.8%)
p-value		<0.0001	<0.0001
ACR90	23 (9.2%)	43 (17.3%)	41 (16.4%)
p-value		0.0091	0.0171
Complete clinical response	0	0	4 (1.6%)
p value			0.1470
ACRn (adjusted mean)	19.5	42.9	46.0
p-value		<0.0001	<0.0001
Standardised AUC of ACRn	28.3	38.7	39.7
p-value		0.0006	0.0002

All comparisons to Placebo + MTX
Cochran-Mantel-Haenszel analysis was used to calculate p-values for categorical response variables, ANOVA for continuous.
Analysis was stratified by RF status (positive >= 20 IU/mL, negative < 20 IU/mL) at baseline and region (US, Rest of World - ROW)
Response is set to 'Non Responder' when the ACRn score is missing. Patients are non-responder from the point of withdrawal or rescue use. Patients who receive non-permitted DMARDs prior to Week 52 were non-responders from the point of receiving medication
For ACRn,. LOCF used for tender and swollen joint counts, HAQ Score, CRP, ESR and VAS assessments. CRP is used primarily, however if the change in CRP is not calculable, the change in ESR is used if available.

For the primary functional endpoint, treatment with both doses of rituximab + MTX resulted in significantly greater mean changes in HAQ-DI score compared with placebo + MTX (-0.905 for low dose rituximab and – 0.916 for high dose rituximab versus -0.628 for MTX alone; p<0.0001 for both pair-wise comparisons; see Table 4).

Table 4. IMAGE study

Physical Function: Summary of HAQ-DI Endpoints at Week 52 (ITT)

	Placebo + MTX (N=249)	Rituximab (2 × 0.5 g) +MTX (N=249)	Rituximab (2 x 1 g) +MTX (N=250)
n assessable	248	247	249
Change in HAQ-DI	-0.628	-0.905	-0.916
p-value[a]		<0.0001	<0.0001
% with MCID (decrease ≥ 0.22)	192 (77.4%)	216 (87.4%)	218 (87.6%)
p-value[b]		0.0036	0.0018
% with improvement (decrease ≥ 0.3)	178 (71.8%)	199 (80.6%)	207 (83.1%)
p-value[b]		0.0185	0.0015
% with improvement (decrease ≥ 0.5)	156 (62.9%)	187 (75.7%)	195 (78.3%)
p-value[b]		0.0014	<0.0001

a based on ANOVA model containing baseline value, RF status at BL and region
b based on CMH test (% based on n assessable) stratified by RF status at BL and region. These p-values are exploratory as they fall below a non significant parameter in the hierarchy structure

Results for secondary efficacy variables

Further analysis of the **radiographic data at Week 52** using the components of the mTSS showed that the overall result in favour of treatment with high dose rituximab + MTX compared with MTX alone was driven principally by a statistically significant reduction in erosion score (mean change 0.233 versus 0.738 for rituximab 2 x 1g + MTX and placebo + MTX groups respectively; p<0.0001). The mean change in erosion score was not significant for low dose rituximab compared with MTX alone (0.453 versus 0.738 for rituximab 2 x 0.5g + MTX and placebo + MTX groups respectively; p=0.1194). The pair-wise comparison of mean change in erosion score between the high and low dose rituximab treatment groups was also statistically significant (p=0.0270). No statistically significant difference between any of the three treatment groups was recorded for the JSN score at Week 52.

Significantly more patients in the rituximab 2 x 1g group (63.5%, 155/244) showed no radiographic progression (that is, change in mTSS of equal to or less than 0) at 52 weeks compared to the placebo + MTX group (53.4%, 124/232; p=0.0309). This was mainly reflected by the significantly higher proportion of patients in the high dose rituximab group with no progression in erosion score (66.8% [163/244] versus 54.7% [127/232] for placebo + MTX; p=0.0081) and a higher number of patients with no newly eroded joints (77.5% [189/244] for high dose rituximab versus 67.7% [157/232] for placebo + MTX; p=0.0175). There were no statistically significant differences for these same erosion endpoints when the low dose rituximab group was compared to placebo + MTX. Furthermore, a high proportion of patients (82-84%) in all three treatment groups showed no progression in JSN. This result is expected given the patients had short duration disease and follow-up was limited to 52 weeks of observation.

A summary of the **ACR20, 70 and 90 response rates** at Week 52 is presented in Table 3. In particular, 46.8% (117/250) of subjects who received rituximab 2 x 1 g + MTX therapy and 42.2% (105/249) of patients who received rituximab 2 x 0.5 g + MTX therapy achieved an ACR70 response compared to 9.2% (23/249) of subjects who received placebo + MTX (p<0.0001 for both rituximab comparisons with placebo). Consistent with the ACR responses, the mean ACRn at Week 52 was higher for patients treated with rituximab + MTX (46.0 for high dose rituximab and 42.9 for low dose rituximab) than for patients who received placebo + MTX (19.5; p<0.0001 for both rituximab comparisons to placebo)-see Table 3.

The **changes from baseline in the individual ACR core set parameters** followed the same trend as the other ACR results with greater mean decreases consistently observed for patients in either rituximab + MTX group compared with the placebo + MTX group.

Major clinical response (as defined by an ACR70 response maintained for at least 6 consecutive months) was seen in a higher proportion of patients in both rituximab treatment groups (18.1%, 45/249; 95% confidence interval (CI) 0.13, 0.23 for low dose rituximab and 21.2%, 53/250; 95% CI 0.16, 0.26 for high dose rituximab) compared to placebo + MTX (8.4%, 21/249; 95% CI 0.05, 0.12). This was statistically significant for both rituximab treatment groups compared to placebo + MTX (p=0.0015 for low dose rituximab and p<0.0001 for high dose rituximab).

The mean **change from baseline in DAS28-ESR score** to Week 52 is presented in Table 5. A reduction in DAS28 is indicative of disease improvement. There was a statistical and clinically significant greater reduction in mean DAS28 in the two rituximab + MTX groups (low dose -3.05 and high dose -3.21) than the placebo + MTX group (-2.06; p<0.0001 for both rituximab comparisons to placebo).

Table 5.

Summary of EULAR (DAS28-ESR) Endpoints at Week 52 (ITT)

	Placebo + MTX (N=249)	Rituximab (2 × 0.5 g) +MTX (N=249)	Rituximab (2 x 1 g) +MTX (N=250)
DAS28 score			
n	244	247	248
Adjusted mean change from baseline	-2.06	-3.05	-3.21
p value[a]		<0.0001	<0.0001
EULAR Response (%)[c]			
n	249	249	250
None	72 (28.9%)	44 (17.7%)	35 (14.0%)
Moderate	132 (53.0%)	108 (43.4%)	111 (44.4%)
Good	45 (18.1%)	97 (39.0%)	104 (41.6%)
p value[b]		<0.0001	<0.0001
n	247	248	249
Low disease activity	49 (19.8%)	100 (40.3%)	107 (43.0%)
p-value[b]		<0.0001	<0.0001
DAS remission	31 (12.6%)	63 (25.4%)	76 (30.5%)
p-value[b]		0.0002	<0.0001

Source outputs: page 530, page 531, page 532, page 533
All comparisons to placebo + MTX
LOCF used for joint counts, ESR and Patient's Global Assessment of Disease Activity VAS.
EULAR response is set to 'No response' while low disease activity and remission is missing when the DAS28 score is still missing.
a p-value from ANOVA. Model contains the baseline value, region, RF status and treatment.
b p-value from Cochran-Mantel-Haenszel analysis stratified by region, and RF status

The **EULAR response** categorizes the change in DAS28 for individuals as good, moderate or no response, according to the DAS28 attained and the change in DAS28 from baseline. A significantly higher proportion of patients in both rituximab + MTX groups achieved a good or moderate EULAR response (82.4% [205/249] for low dose rituximab and 86% [215/250] for high dose rituximab) compared to treatment with placebo + MTX group (71.1% [177/249]; p<0.0001 for both comparisons; Table 5). Treatment with both doses of rituximab was similarly associated with a higher proportion of patients achieving low disease activity (DAS28-ESR score equal to less than 3.2) and clinical remission (DAS28-ESR score < 2.6; Table 5).

The proportion of patients achieving the minimal clinically important improvement (decrease of equal to or greater than 0.22) was statistically greater in both rituximab treatment groups: 87.4% (216/247) for low dose rituximab (p=0.0036) and 87.6% (218/250) for high dose rituximab (p=0.0018) versus 77.4% (192/249) for placebo + MTX therapy; Table 4).

Patients in the rituximab + MTX groups reported a statistically significant reduction in fatigue over 52 weeks of observation compared to patients who received placebo + MTX. An increase in the FACIT-Fatigue score reflects improvement and a change from baseline of >4 points has been defined as a clinically meaningful improvement in RA patients. The **mean change in FACIT-F (fatigue) score** for patients in the rituximab + MTX group was 9.362 for low dose rituximab (baseline score 34.5; n=239) and 10.282 for high dose rituximab (baseline score 29.2; n=245) compared to a mean change from baseline of 6.83 (baseline score 29.8; n=249) for the placebo + MTX group. The difference in the adjusted means was statistically significant as shown by the results of the ANOVA model (p=0.0034 for low dose rituximab and p<0.0001 for high dose rituximab). A higher proportion of patients in the rituximab treatment groups (72.8%, 174/249 for low dose rituximab and 75.1%, 184/245 for high dose rituximab) achieved the minimal clinically important difference in fatigue score than the placebo + MTX group (67.6%, 165/249).

Regarding the **SF-36 results**[3], only the high dose rituximab + MTX group (57%, 138/242; p=0.0392) showed a statistically significant improvement in the Mental Health Component (MHC) score from baseline (defined as a change of >6.33) compared with placebo + MTX patients (49% [117/249] and 51% [120/236] for MTX alone and low dose rituximab respectively, p=0.2433). The Physical Health component score was also only seen to significantly improve (defined as a change >5.42) in patients treated with high dose rituximab + MTX (76.4%, 185/250; p=0.0006) versus 63.2% (151/239) for placebo + MTX patients and 69.9% (165/236) for low dose rituximab (p=0.1604).

Efficacy conclusions

The efficacy data from the IMAGE Study indicates that rituximab 2 x 1 g + MTX is statistically superior in a clinically meaningful manner to MTX monotherapy in reducing the rate of radiographic progression over 52 weeks in patients with short duration RA who had high disease activity at baseline. However, the lower dose of rituximab (2 x 0.5 g) + MTX did not show a significant difference from placebo + MTX in reducing the rate of radiographic progression. Both doses of rituximab + MTX were superior to MTX alone in reducing the signs and symptoms of RA, as assessed by ACR and EULAR criteria, including the proportion of patients achieving a major clinical response. Clinically and statistically significant improvements in physical function, as evaluated by the mean change in HAQ-DI, were observed for both doses of rituximab + MTX compared with placebo + MTX.

SERENE STUDY

Study Design

The SERENE Study is a randomized, double-blind, parallel-group study involving patients with active RA who had an inadequate clinical response to MTX. There were three treatment groups: MTX alone (+ placebo infusions), rituximab 2 x 0.5 g + MTX and rituximab 2 x 1 g +

[3] The SF-36 is a multi-purpose, short-form health survey with only 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group.

MTX. Approximately 500 subjects were planned to be recruited with equal numbers in each treatment group. Randomization was administered by a central randomization centre, and stratified by RF titre at screening (negative or positive at a cut-off value of 20 IU/mL) and region (USA versus Rest-of-World [ROW]). The overall population of RF negative patients was limited to 20% of the total sample size. The target population was patients with severely active RA of at least 6 months duration who had an inadequate response to MTX 10-25 mg/week (oral or parenteral) for at least 12 weeks, of which the last 4 weeks prior to baseline must have been at a stable oral dose >10mg/week. Previous treatment with biologic drugs for RA was an exclusion criterion.

The dose of rituximab (2 x 0.5g or 2 x 1g administered on Days 1 and 15) used in this study was based on the results from the preceding DANCER study in which patients derived improvements in disease activity with an acceptable short term (up to 24 weeks) adverse event profile. All patients continued to receive concurrent MTX 10-25 mg/week (oral or parenteral) at a stable dose throughout the study, as well as folic acid 5 mg/week. Stable background doses of oral corticosteroids (equal or less than 10 mg/day of prednisolone or equivalent) and NSAID were allowed if the patient had already been on these therapies for at least 4 weeks prior to baseline visit. All patients received methylprednisolone 100 mg IV administered 30 minutes prior to infusions of rituximab or placebo on Days 1 and 15. Paracetamol 1g and diphenhydramine 50 mg or equivalent was also administered orally 30 minutes prior to the start of an infusion to minimize the risk of acute infusion reactions.

The primary efficacy evaluation occurred at 24 weeks (placebo-controlled comparison) with additional analysis being performed at 48 weeks (active dose comparison). Between weeks 16 and 23, patients who had less than a 20% improvement in both tender and swollen joints counts compared to baseline were allowed to initiate “rescue” therapy with one additional non-biological DMARD at the discretion of the treating physician. These patients could receive further courses of rituximab if eligible after 24 weeks but were considered non-responders for all categorical efficacy endpoints at Week 24. Rescue medication was to remain stable for the duration of the study and switching of or further additional DMARDs was not permitted. From Week 24 onwards, all patients were eligible for re-treatment every 24 weeks if they were not in clinical remission (defined as DAS28-ESR score equal to greater than 2.6). The re-treatment course(s) were the same as the original dose for those who received rituximab initially, and the original placebo + MTX group patients were eligible to receive rituximab 2 x 0.5g as their re-treatment course.

Two minor protocol amendments were recorded and neither of these had a significant effect on the outcome of the trial or statistical analysis.

Study Population Characteristics

The SERENE Study was conducted in 102 study sites in 11 countries: including USA, Canada, Europe (France, Germany and Poland), Mexico, Guatemala and United Kingdom between October 2005 and November 2007. Subjects were required to be 18-80 years of age with RA of at least 6 months duration. At study entry, patients were required to have active disease as defined by the 1987-revised ACR criteria (>8 swollen joints out of 66 joints assessed, and >8 tender joints out of 68 joints assessed). Patients must have received MTX 10-25 mg/week for at least 12 weeks prior to screening and have raised serum inflammatory markers (ESR>28mm/hr or CRP>0.6 mg/dl) at baseline.

The studied population was clearly delineated and the three treatment groups were well balanced with respect to demographic characteristics. Subjects had a median age of 54 years (range: 18-79 years) and were predominantly female (79.6-85.5% across treatment arms).

Most patients were Caucasian (80.2-82.6% across groups) and just over half of all the patients (54%) involved in the study were recruited from ROW sites.

The patients involved in the SERENE Study had established disease with a mean duration of RA since diagnosis of 7.1 years (range: 0.2-44 years). Rheumatoid factor was positive at baseline in 75% of patients at similar median levels across the three treatment groups (105-120 IU/mL).

The disease parameters at baseline were reflective of a population of patients with RA who had severely (not moderately) active disease. The baseline median tender joint count was 25-27 (of a possible maximum of 68), and the median swollen joint count was 16-18 (of a possible maximum of 66). Overall disease activity score as measured by the DAS28-ESR score was high at 6.4-6.54. In addition, the other individual components of the ACR criteria were consistent with a severely active disease state. Baseline disease parameters were comparable among the three treatment groups although there was a trend for higher disease activity in patients enrolled in the placebo + MTX arm.

The treatment groups were well-balanced with respect to previous and concomitant treatments for RA. The median weekly intake of MTX prior to and during the study was similar for the three treatment groups at a dose of 15mg/week and approximately 95% of subjects were taking weekly folic acid. In general, the majority of patients had taken one DMARD (other than MTX) with a range of 0-7 drugs. The most common previous DMARD used was sulfasalazine (38%) followed by antimalarials (36%). Immunosuppressants, predominantly leflunomide (14%), had been used by 17-20% of patients in each treatment group. Although the study protocol excluded patients who had received prior biologic treatment, three patients (1 in each treatment group) had this history. Prior (and ongoing) corticosteroid therapy was recorded by 47.7% (82/172) of placebo + MTX treated patients, 47.9% (80/167) of low dose rituximab subjects and 39.4% (67/170) of high dose rituximab patients. Similarly, the proportion of patients taking NSAIDs was slightly higher in the placebo + MTX (58.7%, 101/172) and low dose rituximab (58.1%, 97/167) compared with the high dose rituximab group (56.5%, 96/170). However, analgesic use (30% of patients) and opioid analgesic use (14% of patients) was similar between the three treatment groups.

A higher proportion of subjects received rescue therapy for RA (initiated between Weeks 16-23) in the placebo + MTX arm (9%, 16/172) compared with the rituximab treatment groups (low dose 4% [6/167] and high dose 2% [4/170]). Rescue treatments comprised leflunomide (7 patients), sulfasalazine (7 patients), hydroxychloroquine (6 patients), cyclosporin (5 patients), and cyclophosphamide (1 patient). However, concurrent treatment with rituximab and cyclophosphamide is contraindicated.

Nearly 90% of the study population had at least one concurrent medical problem with the most common concurrent conditions being hypertension (36%), osteoporosis (12%), depression (15%) and gastro-oesophageal disorders (16%) such as reflux disease. Overall, the study population is externally valid but some limitations need to be considered. For example, patients with the following characteristics were excluded: history of recurrent significant infection, history of non-cutaneous malignancy, or significant underlying cardiac, pulmonary, or renal conditions.

Primary Efficacy endpoint

The primary efficacy endpoint in the SERENE Study was the proportion of subjects in each treatment group who achieved an ACR20 response at Week 24.

Secondary Efficacy endpoints

Major secondary efficacy endpoints assessed at Week 24 included:

- Proportion of subjects who achieved an ACR50 response and ACR70 response,
- Mean change from baseline in DAS28-ESR,
- EULAR response rates,
- Mean changes from baseline in the individual ACR core set parameters,
- Mean change in SF-36 and FACIT-Fatigue scores from baseline,
- Proportion of patients achieving DAS28-ESR remission (that is, DAS28-ESR < 2.6) and DAS28-ESR low disease activity state (that is, DAS28-ESR equal to less than 3.2), and
- Proportion of patients with change from baseline in HAQ-DI equal to greater than the MCID (that is, a change of at least 0.22).

Additional secondary endpoints assessed at Week 48 comparing the two rituximab treatment groups:

- Proportion of subjects obtaining a good EULAR response,
- Proportion of patients achieving a DAS28-ESR low disease activity score or clinical remission state, and
- Proportion of subjects who achieved an ACR50 response and ACR70 response.

Statistical methods

All efficacy analyses (done at both Weeks 24 and 48) were performed on the ITT population, defined as all randomized patients who received at least a part of an infusion of study drug. The primary treatment period was 24 weeks and the main statistical analysis was performed on the data collected up to this time point. Part of the secondary study objective was to compare the two doses of rituximab (2 x 0.5g versus 2 x 1g) at Week 48.

The primary endpoint was the proportion of patients with an ACR20 response at Week 24. The primary analysis tested the difference in this endpoint between the placebo and each rituximab treatment group and was presented using the CMH statistic stratifying by RF status and region of treatment. The Non Responder Imputation (NRI) method was applied for missing data. In addition, other methods of analysis (such as logistic regression) were carried out on different populations (for example, per protocol cohort) to confirm the primary findings.

A hierarchical approach was taken in testing the second primary endpoints. Categorical efficacy endpoints such as the various levels of ACR response and EULAR response were evaluated using a CMH analysis, stratified by RF status and region of treatment. Continuous efficacy variables such as the change from baseline in DAS28, FACIT-Fatigue and SF-36 were assessed using an ANOVA model with baseline value of interest, RF status and region as terms in the model. The Last Observation Carried Forward (LOCF) imputation method was principally used to handle missing data for the secondary endpoints.

Sample Size: The sample size was determined to ensure adequate numbers for the safety database with approximately 500 patients (167 per treatment group) needed. However, based on prior study experience it was estimated that this sample size would provide 90% power (using Fisher's exact test, adjusting for multiplicity with a 0.025 two-sided significance level for each test) to demonstrate a difference between the proportions of patients achieving an ACR20 response at Week 24 for the placebo + MTX group versus the two rituximab treatment groups. The expected rate of ACR20 response was 40% for patients in the placebo + MTX group and 60% in either of the rituximab treatment groups.

Completion status

Of the 512 subjects randomized (168 were randomized to receive treatment with rituximab 2 x 0.5 g + MTX, 172 were assigned rituximab 2 x 1 g + MTX, and 172 were to receive placebo + MTX), 509 received at least one infusion of study medication (2 patients in the high dose rituximab didn't return for treatment and one patient was randomized twice). A further 220 subjects underwent screening but failed to meet eligibility criteria. The most common reason for screening failure, affecting 41% of ineligible patients, was insufficient elevation in baseline CRP (>6 mg/L) or ESR (>28mm/hr).

The completion rates for the initial 24 week treatment period were high: - 92.4% (159/172) for placebo + MTX, 96.4% (162/167) for low dose rituximab + MTX and 96.5% (166/170) for high dose rituximab + MTX. Similar proportions of patients in each treatment arm completed 48 weeks of study follow-up:- 89.5% (154/172) for placebo infusions + MTX, 93.5% (157/167) for low dose rituximab + MTX and 91.3% (157/170) for high dose rituximab + MTX.

Approximately 90% of patients in all three treatment group received re-treatment after Week 24. The majority (75%) of re-treated patients received their second course between Weeks 24 and 28, and this result was consistent for each of the treatment groups.

A higher proportion (7.6% [13/172]) of patients assigned to placebo infusions + MTX withdrew prior to Week 24 compared to 3.6% (6/167) of patients in the low dose rituximab group and 3.5% (6/170) in the high dose rituximab group. The most common reason for premature withdrawal was insufficient therapeutic response, which led to the discontinuation of 8 patients (7 in the placebo + MTX group and one patient in the low dose rituximab group). Other non-safety withdrawals included a small number of patients in each group who refused further treatment (n=3) or failed to return (n=5). The number of patients who withdrew between Weeks 24 and 48 was similar between the treatment arms: 5 patients for both the placebo/rituximab 2 x 0.5g + MTX and continued rituximab 2 x 0.5g groups, and 9 for the continued high dose rituximab + MTX cohort.

Result for primary efficacy variable

The regimens containing rituximab in combination with MTX (low dose rituximab 54.5%, 91/167; 95% CI 0.47, 0.62 and high dose rituximab 50.6%, 86/170; 95% CI 0.43, 0.58) resulted in levels of ACR20 response at Week 24 that were statistically significantly higher ($p<0.0001$) than that in the "control arm" of placebo infusions + MTX (23.3%, 40/172; 95% CI 0.17, 0.30; Table 6). A logistic regression analysis of the ACR20 responder rates demonstrated a statistically significant treatment effect with rituximab after adjusting for region of treatment and RF status at screening. A subgroup analysis was also made according to seropositivity to anti-CCP antibodies and no differential response to rituximab was observed. Similar confirmatory results were obtained for all sensitivity analyses (such as changing the method of imputation to LOCF, or no imputation) as well using the different defined populations (namely, the per protocol cohort).

Table 6. SERENE Study

Summary of Primary and Secondary Clinical Endpoints Comparing Placebo + MTX and Rituximab (2 x 0.5 g and 2 x 1.0 g) + MTX at Week 24 (ITT Population)

	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

Results for secondary efficacy variables

All secondary endpoints assessed at Week 24 resulted in a statistically significant improved observation seen with both regimens containing rituximab compared to MTX alone, except for the ACR70 response rates and the SF-36 Mental Health Component summary score (Table 6).

The **proportion of patients achieving ACR50 responses** at Week 24 was higher in the two rituximab treated arms than in the MTX alone group and this result achieved statistical significance (p<0.0001 for both pair-wise comparisons) – placebo + MTX (9.3%, 16/172; 95% CI 0.05, 0.14), low dose rituximab (26.3%, 44/167; 95% CI 0.20, 0.33) and high dose rituximab (25.9%, 44/170; 0.19, 0.32). However, the **proportion of patients reaching an ACR70 response** at Week 24 was not statistically significant between the treatment groups - placebo + MTX (5.2%, 9/172; 95% CI 0.02, 0.09), low dose rituximab (9.0%, 15/167; 95% CI 0.05, 0.13) and high dose rituximab (10.0%, 17/170; 95% CI 0.05, 0.15). In a post-hoc analysis, RF status did not affect the chance of response for either the ACR50 or ACR70 endpoint, however, patients treated in the USA (compared with ROW patients) had a higher rate of response for both.

For each of the **individual disease activity parameters** comprising the ACR criteria, a greater improvement from baseline to Week 24 was recorded in groups receiving rituximab compared to those patients who received MTX monotherapy (Table 7).

Table 7. SERENE Study

Analysis of Variance of Change from Baseline in the ACR Core Set Parameters at Week 24, LOCF Imputation (ITT Population)

	Swollen Joint Count (66 joint count)	Tender Joint Count (68 joint count)	Patient's Global VAS (mm)	Physician's Global VAS (mm)	Patient's Pain VAS (mm)	CRP (mg/dL)	ESR (mm/hr)	HAQ-DI
Placebo + MTX								
n	172	172	171	172	171	172	172	172
Adjusted Mean	-5.5	-6.1	-10.4	-16.4	-6.5	0.1293	-5.81	-0.189
Rituximab 2x0.5g + MTX								
n	166	166	166	166	166	166	166	165
Adjusted Mean	-10.4	-13.4	-22.0	-28.5	-18.4	-1.0323	-14.86	-0.435
Difference (a)	-4.9	-7.4	-11.6	-12.1	-11.9	-1.1616	-9.05	-0.246
95% CI for Difference	[-6.7;-3.1]	[-10.2;-4.5]	[-16.7;-6.6]	[-16.8;-7.4]	[-16.7;-7.0]	[-1.5305;-0.7927]	[-12.94;-5.16]	[-0.361;-0.132]
p-value	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001
Rituximab 2x1.0g + MTX								
n	170	170	169	170	169	170	170	170
Adjusted Mean	-10.3	-11.0	-23.4	-24.6	-20.4	-1.1076	-15.70	-0.415
Difference (a)	-4.8	-4.9	-13.0	-8.2	-13.9	-1.2369	-9.89	-0.227
95% CI for Difference	[-6.6;-3.0]	[-7.8;-2.1]	[-18.0;-7.9]	[-12.9;-3.6]	[-18.7;-9.0]	[-1.6037;-0.8701]	[-13.75;-6.02]	[-0.340;-0.113]
p-value	<.0001	0.0007	<.0001	0.0005	<.0001	<.0001	<.0001	<.0001

(a) Adjusted mean difference
All comparisons to Placebo + MTX
Model contains the baseline value, RF status (positive >= 20 IU/mL, negative < 20 IU/mL) at baseline, region (US, Rest of World - ROW) and treatment
Data after the point of rescue use is excluded and the last non-rescue value is carried forward

The **mean change in DAS28-ESR score** from baseline to Week 24 was better in either of the rituximab treatment arms compared to the placebo infusion + MTX group (Table 6). The mean DAS28-ESR score improved (numerically decreased) by 1.76 for the low dose

rituximab group and 1.69 for the high dose rituximab group versus 0.75 for MTX monotherapy. The difference between the control group and the two active treatment groups was -1.01 (95% CI -1.28, -0.73; p<0.001) for low dose rituximab and -0.94 (95% CI -1.22, -0.67; p<0.001) for high dose rituximab.

According to **EULAR response criteria**, a higher proportion of patients in the rituximab treatment groups had responded at Week 24 with 66.5% (111/167) of 2 x 0.5 g patients and 63.0% (107/170) 2 x 1 g patients achieving at least a moderate response (that is, decrease in DAS of at least 0.6 to a score below 5.1) compared to 33.8% (58/172) in the placebo + MTX group (Table 6). Similarly, a higher proportion of rituximab treated patients achieved DAS28-ESR scores indicating low disease activity or clinical remission at Week 24 (Table 6). Low disease activity was observed in 4.7% (8/172; 95% CI 0.02, 0.08) of patients who received placebo + MTX versus 17.5% (29/166; 95% CI 0.12, 0.23; p=0.003) of subjects who received rituximab 2 x 0.5 g and 12.4% (21/170; 95% CI 0.07, 0.17; p=0.0142) of patients who received rituximab 2 x 1 g. Clinical remission (defined as DAS28-ESR < 2.6) was achieved in 2.3% (4/172; 95% CI 0.00, 0.05) of patients who received placebo + MTX versus 9.6% (16/166; 95% CI 0.05, 0.14; p=0.0087) of subjects who received low dose rituximab and 9.4% (16/170; 95% CI 0.05, 0.14; p=0.0095) of patients who received high dose rituximab.

Treatment with either dose of rituximab + MTX resulted in a higher proportion of patients achieving the **MCID in their HAQ-DI** score compared to placebo + MTX (66.1% [109/165] for low dose rituximab and 58.2% [99/170] for high dose rituximab versus 47.7% [82/172] for MTX alone; p=0.0007 for the comparison between low dose rituximab and placebo; and p=0.0079 for the comparison between high dose rituximab and placebo; see Table 6).

Patients in the rituximab + MTX groups reported a statistically significant mean reduction in fatigue over 24 weeks compared to patients who received placebo + MTX. The **mean change in FACIT-Fatigue score** for patients in the rituximab + MTX group was 5.513 for low dose rituximab (baseline score 26.34; n=165) and 6.525 for high dose rituximab (baseline score 26.93; n=168) compared to a mean change from baseline of 2.119 (baseline score 25.12; n=170) for the placebo + MTX group. The difference in the adjusted means (3.394 [95% CI 1.462, 5.326] for low dose rituximab and 4.406 [95% CI 2.481, 6.332] for high dose rituximab) was statistically significant as shown by the results of the ANOVA model (p=0.0006 for low dose rituximab and p<0.0001 for high dose rituximab).

Regarding the **SF-36 results**, only the high dose rituximab + MTX group showed a statistically significant mean improvement in the Mental Health Component score from baseline compared with placebo + MTX patients (mean change 1.656, baseline score=40.34, n=147 for MTX alone versus 3.311, baseline score 41.63, n=152 for low dose rituximab and 4.576, baseline score 41.61, n=155 for high dose rituximab respectively; p=0.0973 for placebo versus low dose rituximab, and p=0.0034 for placebo versus high dose rituximab). The mean change in the Physical Health Component score was seen to significantly improve for patients treated with either dose of rituximab + MTX versus placebo + MTX (5.912, baseline score 31.35, n=152 for low dose rituximab and 5.704, baseline score 30.98, n=155 for high dose rituximab compared with 2.489, baseline score 31.12, n=147 for MTX + placebo (p < 0.0001 for both pair-wise comparisons).

There were no significant differences between the two **rituximab treatment groups at Week 48** for any of the additional secondary endpoints. In particular, the proportion of subjects who achieved an ACR50 response and ACR70 response were similar and did not reach statistical significance (p=0.7882 and p=0.7302 for the ACR50 and ACR70 endpoints, respectively). The ACR50 responders rates at Week 52 were 32.9% (55/167; 95% CI 0.26,

0.40) for low dose rituximab and 34.1% (58/170; 95% CI 0.27, 0.41) for high dose rituximab. The proportion of patients reaching an ACR70 response at Week 52 was also similar between the treatment groups; 12.6% (21/167; 95% CI 0.08, 0.18) for low dose rituximab and 13.5% (23/170; 95% CI 0.08, 0.19) for high dose rituximab. Considering only patients who received a second course of rituximab after Week 24, no dose difference in response rates was observed.

No difference in EULAR good response rates was seen between the two rituximab treatment groups; 19.8% (33/167) for rituximab 2 x 0.5 g and 20.6% (35/170) for rituximab 2 x 1 g (p=0.8123). Again, re-treated patients after Week 24 showed no differential response between the two treatment groups.

There was no statistical difference in the proportion of patients achieving DAS28-ESR low disease activity state or clinical remission between the two treatment groups. Low disease activity was recorded in 20.0% (33/165; 95% CI 0.14, 0.26) for low dose rituximab and 24.3% (41/169; 95% CI 0.18, 0.31) for high dose rituximab (p=0.3177). Clinical remission was observed in 9.1% (15/165; 95% CI 0.05, 0.13) for rituximab 2 x 0.5 g and 11.2% (19/169; 95% CI 0.06, 0.16) for high dose rituximab (p=0.4663). The same insignificant result for comparison between the two dose groups was obtained for patients who underwent a second course of rituximab after Week 24.

Efficacy conclusions

The efficacy data from the SERENE Study indicates that rituximab treatment when used in combination with MTX in patients with an inadequate response to MTX is statistically superior in a clinically meaningful manner to continued MTX monotherapy in reducing disease activity over 24 weeks in patients with established RA. There was no dose differentiation in efficacy when rituximab 2 x 0.5 g was compared 2 x 1 g. The efficacy of both doses of rituximab in treating the clinical signs and symptoms of RA was maintained over a 48 week period of observation.

MIRROR STUDY

Study Aim and Rationale

The aim of this study was to determine if a second course with an increased dose of rituximab is associated with an improved clinical response compared to re-treatment with the same dose. An earlier Phase IIb dose-ranging study (DANCER) had identified on post-hoc analysis that patients who initially received low dose rituximab (2 x 0.5g) and then received rescue treatment with rituximab 2 x 1g had a trend to improved rates of ACR response at all time points following the second course of higher dose therapy. In MIRROR, subjects could receive either rituximab 2 x 0.5g or 2 x 1g at study commencement (Days 1 and 15) and then a second course of rituximab at Week 24. All patients continued to receive stable concurrent MTX (oral or parenteral) at a dose of 10-25 mg/week with folic acid 5 mg/week throughout the study until Week 48. The rationale for re-treatment of all patients at Week 24 (unless a patient developed a contraindication to rituximab) was that earlier studies demonstrated no detectable serum rituximab levels and a return of peripheral $CD19^+$ cells at Week 24. Furthermore, best practice guidelines in recent years advising the care of patients with RA recommend that it is desirable to maintain patients in a clinically low or inactive disease state by limiting disease flares and hence, the potential progression of structural damage.

Study Design

This was a Phase III, randomized, double-blind trial evaluating the efficacy of various re-treatment regimens in patients with active RA who had an inadequate response to MTX.

Patients who had been previously treated with no more than one approved biological agent could also be included in the study (up to a maximum of 30% of the total sample size). Both RF positive and negative patients were eligible but the overall proportion of RF negative patients was to be limited to 20% of the total sample.

Prior to baseline, patients had to be discontinued from all DMARDs (except MTX) for at least 14 days, and at least 8 weeks for leflunomide and anti-TNF drugs.

Subjects were randomized to three rituximab treatment groups: low dose (2 x 0.5g for two courses), dose escalation (2 x 0.5g then 2 x 1g) or high dose (2 x 1g for two courses). Patients were to receive their first course of two infusions of study medication on Days 1 and 15, and between Weeks 24 and 26 received their second course of infusional therapy. Methylprednisolone (100mg IV) was given immediately prior to all infusions. Stratification variables for randomization included RF status (positive or negative), prior biologic use and treatment region (5 groupings – North America, two European zones, Asia, and then Australia, New Zealand and South Africa as a fifth regional grouping).

Evaluation of the primary endpoint (ACR20) occurred at Week 48 and the submission covers the period up until that point although patients could receive additional courses of rituximab for up to three years. One major amendment to the study protocol was made during the study that altered the study's design. Initially it was proposed that patients in the high dose rituximab group were to receive one single course of rituximab at study commencement followed by a course of placebo infusions at Week 24. The rationale for this original design was to determine if there was any difference in response rates if the total annual 2g dose of rituximab was given as a single upfront course or as divided doses 6 months apart. The majority of sites accepted the amendment apart from some centres in United Kingdom (UK). Thus some patients received the original defined regimen and had their results summarized separately. However, outside of any protocol defined regimen, some patients received a course of rituximab 2 x 1g followed by rituximab 2 x 0.5g. Hence, 5 different rituximab regimens were actually administered during the course of the study.

Study Population Characteristics

The MIRROR Study was conducted in 81 centres in 18 countries: including USA, Canada, Europe (France, Belgium, Netherlands, Spain, Italy and Hungary), Brazil, China, Taiwan, Thailand, South Africa, New Zealand and Australia between February 2006 and November 2007. Subjects were required to have had RA for at least 6 months. At study entry, patients were required to have active disease as defined by the 1987-revised ACR criteria (>8 swollen joints out of 66 joints assessed, >8 tender joints out of 68 joints assessed and raised serum inflammatory markers [ESR>28mm/hr or CRP>0.6 mg/dl]). Patients must have received MTX 10-25 mg/week for at least 12 weeks prior to screening, with the last 4 weeks prior to baseline at a stable dose.

The studied population was clearly delineated and the three treatment groups were reasonably well balanced with respect to demographic characteristics. Subjects had a mean age of 52 years (range: 21-78 years) and were predominantly female (75.6-82.8% across the three groups). Most patients were of Caucasian (85.7-87.3% across the three treatment arms) or Asian ethnicity (10.8-12.6%). The patients involved in the MIRROR Study had a wide range of disease duration with the median duration of RA since diagnosis of 6.5 years and the range being 0.5 to 50 years. Rheumatoid factor was positive at baseline in approximately 70% of patients at similar median levels of 79-103 IU/mL across the three treatment groups (range of RF positivity: 15-2970 IU/mL).

The disease parameters at baseline reflected patients with RA who had severely active disease. The baseline median tender joint count was 29-34 (of a possible maximum of 68), and the median swollen joint count was 15-18 (of a possible maximum of 66). Overall disease activity score as indicated by the median DAS28-ESR score was high at 6.7-6.8. Furthermore, the other individual components comprising the ACR criteria were consistent with a severely active disease state. Baseline disease parameters were similar among the three main treatment groups although there was a trend for higher disease activity in patients enrolled in the dose escalation rituximab group.

The treatment groups were well-balanced with respect to previous and concomitant treatments for RA. The median weekly intake of MTX prior to and during the study was similar for the three main treatment groups at a dose of 15 mg/week and approximately 95% of subjects were taking weekly folic acid.

The majority of patients had taken two non-biologic DMARDs (excluding MTX) with a range of 0-8 drugs. The most common previous DMARDs used at similar frequencies in patients of the three main treatment groups were antimalarials (52%), sulfasalazine (45%), leflunomide (34%), cyclosporin (9%) and azathioprine (7%). Prior biologic DMARD treatment (almost exclusively TNF inhibitors) had been received by 25-28% of patients across the three main treatment arms. Prior (and ongoing) corticosteroid therapy at a dose of less than 10 mg/day prednisolone was similar between the groups: - 63.4% (85/134) of rituximab 2 x 0.5g, 2 x 0.5g + MTX treated patients, 65.5% (78/119) of rituximab 2 x 0.5g, 2 x 1g + MTX subjects and 67.7% (63/93) of rituximab 2 x 1g, 2 x 1g + MTX patients. However, the proportion of patients taking NSAIDs was slightly lower in the continued low dose rituximab group (45.5%, 61/134) and dose escalation rituximab arm (47.9%, 57/119) compared with the continued high dose rituximab group (55.9%, 52/93).

Just over 80% of the study population had at least one concurrent medical problem with the most notable concurrent conditions being hypertension (29%), osteoporosis (15%), depression (8%), gastro-oesophageal disorders (12%) and diabetes mellitus (4%). Similar to the other studies in the rituximab clinical development program, patients with a history of recurrent significant infection (n=6, 3.6% of 167 for screening failures), non-cutaneous malignancy (n=2), or significant underlying cardiac (n=3), pulmonary, or renal conditions were excluded which limited the population's external validity.

Efficacy Parameters

Primary: The primary endpoint was the proportion of patients who achieved an ACR20 response at Week 48. Subgroup analyses based on the ACR20 response at Week 24 were made to explore the impact of various doses of rituximab.

Secondary: The secondary endpoints were evaluated at Week 48 and included:

1. Proportion of patients with ACR50 and 70 responses,
2. Change from baseline in Disease Activity (DAS28-ESR) score,
3. EULAR response rates,
4. Change from baseline in SF-36 Mental and Physical health summary scores, and
5. Change from baseline in FACIT-Fatigue assessment.

Statistical Analysis

The primary efficacy analysis of ACR20 response was based on the ITT (as randomized) patient population. However, prior to database lock it was evident that a significant proportion of patients received the incorrect rituximab dose regimen and hence sensitivity analyses using two different definitions of the mITT population were performed. The ITT-M1 population excluded patients who received incorrect treatment and the ITT-M2

population included patients as treated. The secondary endpoints were presented using the ITT-M2 population.

The primary comparison of ACR20 response at Week 48 was between low dose rituximab group and the dose escalation rituximab arm analysed using the CMH test stratifying by RF status, treatment region and prior biologic use. For patients with missing data during the treatment period, the primary imputation method was the Non-Responder Imputation (NRI) method, that is, patients with missing ACR responses were treated as non-responders. Patients who prematurely withdrew were also treated as non-responders. In addition, other methods of analysis (such as logistic regression) were carried out on different populations (for example, ITT-M2 population) to confirm the primary findings.

For testing of the secondary efficacy endpoints, categorical endpoints such as the various levels of ACR response and EULAR response were evaluated using the CMH test (stratified by RF status, region and prior biologic use) with the NRI method used to handle missing data. Continuous efficacy variables such as the change from baseline in DAS28, FACIT-Fatigue and SF-36 were assessed using an ANOVA model (with baseline parameter of interest, RF status, region and prior biologic use as terms in the model) and the LOCF imputation method was used to handle missing data.

A sample size of 125 patients per treatment arm (that is, 375 subjects in total) was to provide at least 80% power to detect differences in the proportions of patients achieving an ACR20 response between the low dose and dose escalation rituximab groups with a two-sided 5% significance level (using Fisher's exact test). No adjustment was made for patient drop-outs as patients who withdrew prior to Week 48 were considered to be non-responders for all categorical efficacy endpoints.

Patient Disposition/Completion

In total, 378 patients (n=123 for rituximab 2 x 0.5g, 2 x 0.5g; n=128 for rituximab 2 x 0.5g, 2 x 1g; n=113 for rituximab 2 x 1g, 2 x 1g and n=14 for rituximab 2 x 1g, placebo + MTX) were enrolled into the study and 377 patients were included in the ITT population for the primary efficacy analysis (1 patient in the rituximab dose escalation group did not receive any infusion of study medication and was excluded from the ITT analysis). A further 167 patients were screened but failed to meet eligibility criteria with the two most common reasons for screening failure being positive Hepatitis B status (37.1%, 62/167) and insufficient elevation in baseline CRP or ESR (26.3%, 44/167).

Due to study treatment errors, mainly caused by a failure to synchronize the updating of the approved study medication list with the randomization schedule, a total of 60 (16% of 377) patients were excluded from the ITT-M1 analysis resulting in n=113 (92% of 123 received correct treatment) for rituximab 2 x 0.5g, 2 x 0.5g; n=108 (85% of 128 got correct therapy) for rituximab 2 x 0.5g, 2 x 1g; n=90 (80% of 113 received assigned treatment) for rituximab 2 x 1g, 2 x 1g and n=6 for rituximab 2 x 1g, placebo + MTX. A further 25 patients received a non-protocol defined treatment regimen of rituximab 2 x 1g followed by rituximab 2 x 0.5g (that is, a dose descalation regimen). Hence, the ITT-M2 population (that is, all treated patients as they were treated) which was used for the analysis of secondary efficacy endpoints comprised 5 separate groups: n=134 for rituximab 2 x 0.5g, 2 x 0.5g; n=119 for rituximab 2 x 0.5g, 2 x 1g; n=93 for rituximab 2 x 1g, 2 x 1g; n=6 for rituximab 2 x 1g, placebo + MTX; and n=25 for rituximab 2 x 1g, 2 x 0.5g.

In total, 90.2% (340/377) patients completed the planned 48 week study period. More patients in the continued low dose rituximab treatment group completed the 48 weeks of follow-up (96.7%, 119/124) compared to 82.8% (106/128) in the dose escalation group and

70.0% (89/127) in the continued high dose rituximab. The majority of patients (93.3%, 352/377) received a second course of treatment after Week 24: 100% (123/123) for continued low dose rituximab, 85.9% (110/128) for dose escalation therapy and 93.7% (119/127) for high dose rituximab. This last treatment group of intended continued rituximab 2 x 1g can be sub-divided into n=88 for a further 2 x 1g dose of rituximab (as per the protocol), n=6 for placebo infusion at the re-treatment stage and n=25 for a subsequent 2 x 0.5g dose of rituximab.

Over the 48 week study period, withdrawal rates in the ITT-M2 population were higher in the low dose (11.2%, 15/134) and dose escalation groups (10.8%, 13/120) compared to the high dose rituximab arm (4.3%, 4/93). The most common reasons for study withdrawal were insufficient therapeutic response (12 patients in total, 4 from each of the three main treatment groups and this typically occurred before week 24), Adverse Events (AEs) (13 patients) and consent withdrawal (11 patients, all but one subject did so after study week 24).

Primary Efficacy Result

Approximately two-thirds of all patients across the three main treatment groups achieved an ACR20 response at Week 48. There was no significant difference in efficacy between the continued low dose and other dosing regimens of rituximab in either the ITT or ITT-M2 analyses. A lack of a differential treatment effect between the doses was also seen in the analyses using the ITT-M1 and per protocol populations, as well as the logistic regression model.

The proportion of ACR20 responders increased over time with the response to re-treatment being similar across the dose regimens. In particular, 41.5% (59/142) of non-responding patients at Week 24 subsequently achieved an ACR20 response at Week 48, which appeared to be irrespective of the rituximab re-treatment dose. Furthermore, 83.3% (170/204) of ACR20 responders at Week 24 maintained this response to Week 48, irrespective of the rituximab re-treatment dose.

For the subgroup analyses, the proportion of ACR20 responders was similar in patients with prior biologic use compared to those without (60.7%, 68/112 versus 64.5%, 171/265 respectively). The responses were slightly lower in RF negative patients compared to RF positive subjects (59.4%, 63/106 versus 64.9%, 176/271 respectively). However, the logistic regression analysis showed no statistically significant impact of these factors (prior biologic use or RF status) on ACR20 response at 48 weeks. In addition, the secondary outcome measures evaluated at Week 48 confirmed that improvements in disease activity and patient reported outcomes were similar between the prior and no prior biologic DMARD patient subsets. However, within the prior biologic treatment subpopulation there was a trend to higher responses with the high dose compared to the low dose rituximab (for example, ACR50 52.0% [13/25] versus 32.5% [13/40]; good or moderate EULAR responses 88.0% [22/25] versus 72.5% [29/40] for the high and low dose rituximab groups respectively) but the overall patient numbers are small and these did not reach statistical significance.

Results for Secondary Efficacy Endpoints

At Week 48, the proportions of patients who were **ACR50 responders** were numerically higher in the high dose rituximab group (48.4%, 45/93) compared to the low dose (38.8%, 52/134) and dose escalation rituximab groups (38.7, 46/119) but this did not reach statistical significance in any of the pair-wise rituximab dose comparisons.

Similar proportions of subjects across the three main treatment groups were **ACR70 responders** at Week 48: 20.1% (27/134) for low dose rituximab, 19.3% (23/119) for the dose escalation rituximab group and 22.6% (21/93) for high dose rituximab.

By Week 48, **mean DAS28** had improved (reduced) for all three main treatment groups at a similar magnitude of improvement (-2.3 to -2.6 for all rituximab treatment groups from a baseline value of 6.67 to 6.83; see Table 8 for the mean changes in DAS28 over 48 weeks). The result between the rituximab groups is not statistically significant for any of the pair-wise comparisons (p=0.7127 for low dose versus dose escalation rituximab; p=0.1018 for low versus high dose rituximab). The mean DAS28 decreased further with the second treatment course in the three main treatment arms with mean decreases of similar magnitude between the treatment groups between Weeks 24 and 48 (Table 9).

Table 8. MIRROR Study

Summary of EULAR (DAS28-ESR) Endpoints at Week 48 (ITT-M2)

	Rituximab (2 x 0.5g, 2x 0.5 g) + MTX (N=134)	Rituximab (2 × 0.5 g, 2 x 1g) +MTX (N=119)	Rituximab (2 x 1g, 2 x 1g) +MTX (N=93)
DAS28 score			
n	132	118	93
Adjusted mean change from baseline	-2.13	-2.19	-2.42
p value[a]		0.7127	0.1018
EULAR Response (%)[b]			
n	134	119	93
None	36 (26.9%)	33 (27.7%)	10 (10.8%)
Moderate	68 (50.7%)	66 (55.5%)	58 (62.4%)
Good	30 (22.4%)	20 (16.8%)	25 (26.9%)
p value[b]		0.5029	0.0495
n	133	118	93
Low disease activity	31 (23.3%)	20 (16.9%)	25 (26.9%)
p-value		0.2178	0.7545
DAS remission	12 (9.0%)	15 (12.7%)	18 (19.4%)
p-value		0.4234	0.0871

All comparisons to RTX (2x0.5g, 2x0.5g) + MTX
LOCF used for joint counts, ESR and Patient's Global Assessment of Disease Activity VAS. EULAR response is set to 'No response' while low disease activity and remission is missing when the DAS28 score is still missing.
a p-value from ANOVA. Model contains the baseline value, region, prior biologic use, RF status and treatment.
b p-value from Cochran-Mantel-Haenszel analysis stratified by region, prior biologic use, RF status and treatment

Table 9. MIRROR Study

Response to Second Course of Treatment (Week 48) According to Response to First Course (Week 24) (ITT-M2)

	ACR20 nonresponders at Week 24			ACR20 responders at Week 24		
	Low dose (N=65)	Dose escalation (N=46)	High dose (N=31)	Low dose (N=69)	Dose escalation (N=73)	High dose (N=62)
Primary endpoint ACR20 (%)	**27 (41.5)**	**17 (37.0)**	**15 (48.4)**	**59 (85.5)**	**59 (80.8)**	**52 (83.9)**
Secondary endpoints						
ACR50 (%)	10 (15.4)	3 (6.5)	7 (22.6)	42 (60.9)	43 (58.9)	38 (61.3)
ACR70 (%)	5 (7.7)	2 (4.3)	2 (6.5)	22 (31.9)	21 (28.8)	19 (30.6)
Change in DAS28 from Week 24 to Week 48 (adjusted mean)	-0.69	-0.89	-0.96	-0.05	-0.19	-0.23

Low dose= rituximab (2x0.5g,2x0.5g)+MTX, dose escalation = rituximab (2x0.5g, 2 x 1g) +MTX, high dose = rituximab (2x1g,2x1g) +MTX
Imputation for missing data: Nonresponder imputation for categorical variables, LOCF for continuous
Adjusted means from ANOVA model containing Week 24 value, region, prior biologic use, RF status

The **EULAR response** categorizes the change in DAS28 for individuals as good, moderate or no response, according to the DAS28 attained and the change in DAS28 from baseline. A higher proportion of patients in the high dose compared to low dose rituximab group achieved a good or moderate EULAR response (89.2% [83/93] for high dose rituximab versus 73.1% [98/134] for low dose rituximab; p<0.0495; Table 8). However, the comparison between low dose 73.1% [98/134] and dose escalation rituximab (72.2% [86/119]) was not statistically significant (p=0.5029). Treatment with any dose regimen of rituximab had similar effects on the proportion of patients achieving low disease activity (DAS28-ESR score equal to less than 3.2) and clinical remission (DAS28-ESR score < 2.6; Table 8).

The **mean changes from baseline in the SF-36** Mental and Physical health summary scores showed similar (not statistically significant) improvements at Week 24 in all treatment groups that were sustained or slightly higher at 48 Weeks. The mean baselines scores for all three main treatment groups were uniform: 39 for the Mental and 30 for the Physical health summary. The mean improvements at Week 48 for the Physical health summary score were 7.17-8.99 and 4.72-5.60 for the Mental health summary score.

The **mean change in FACIT-Fatigue score** from baseline to Week 48 for patients in the low dose rituximab group was 6.605 (baseline score 31.2; n=125), 8.109 for the dose escalation rituximab arm (baseline score 30.4; n=115) and 8.364 (baseline score 32.8; n=91) for the high dose rituximab group. The difference in the adjusted means was not statistically significant as shown by the results of the ANOVA model (p=0.4758 for low dose versus dose escalation and p=0.2932 for low versus high dose rituximab). An increase in the FACIT-Fatigue score of >4 points from baseline is considered the minimum clinically meaningful improvement. Although a higher proportion of patients in the high dose (69.2%, 63/91) and dose escalation (64.3%, 74/115) rituximab group achieved this standard compared to low dose rituximab (57.6%, 72/125), the result was not statistically significant in both pair-wise comparisons with the low dose rituximab arm.

Efficacy conclusions

The MIRROR Study demonstrated that rituximab in various dosing regimens significantly improves disease activity in patients with severely active RA refractory to previous DMARDs including recent MTX therapy and a subset (approximately 25% of patients) who failed to benefit from anti-TNF medications. There was a lack of improved clinical response with rituximab dose escalation (2 x 0.5 g followed by 2 x 1 g compared to two courses of 2 x 0.5 g given 24 weeks apart) although the power of the study to detect dose differences was diminished by the large number of treatment administration errors that occurred. Likewise, lower dose (2 courses of 2 x 0.5 g) and continued high dose rituximab (two courses of 2 x 1 g given 24 weeks apart) cannot be clearly differentiated in terms of efficacy after 48 weeks of follow-up although there was a trend to improvement in some outcomes (for example, EULAR responses) for patients receiving the high dose. Empiric re-treatment at 24 weeks appeared to maintain the clinical response to the first course of rituximab and may elicit a response in a subset of patients non-responsive to their initial treatment.

SUNRISE STUDY

Study Aim and Rationale

The aim of this study was to determine if a second course of rituximab (2 x 1g) given in those who did not achieve DAS remission by Week 24 is associated with an improved clinical response at Week 48 compared to patients who received a single upfront treatment with rituximab 2 x 1g. In addition, the patients in this study had a previous inadequate response or toxicity to at least one anti-TNF drug. The results of this study were to inform about the

efficacy and safety of re-treatment with rituximab in patients with RA in a controlled setting compared against continued background MTX. A previous re-treatment study (WA16855) was open-label, and showed that re-treated patients achieved sustained improvements in ACR20, 50 and 70 responses. The purpose of re-treatment with rituximab was to prevent flare, promote sustained control of disease and potentially prevent disease progression. The chosen re-treatment interval after Week 24 was based on the results of another Phase III study (REFLEX) in which 91% of subjects treated with rituximab at study commencement would have met the re-treatment criterion (DAS28-ESR score >2.6) at Week 24.

Study Design

This was a Phase III multicentre study conducted in 143 sites in the USA. An initial (first course) open-label rituximab treatment period was followed by a randomized, double-blind re-treatment period for eligible participants. In SUNRISE, all subjects received a course of rituximab (2 x 1g) at study commencement (Days 1 and 15) with 100 mg of IV methylprednisolone as a pre-medication 30-60 minutes prior to each infusion. Pre-medication with 1000 mg of paracetamol and 50 mg of oral diphenhydramine was also recommended for all subjects. In addition, all patients continued to receive a stable dose of MTX 10-25 mg/week in conjunction with folic acid at a minimum of 5 mg/week, and any background corticosteroids (<10mg/day prednisolone or equivalent) or oral NSAID at a stable dose. Appropriate wash-outs periods were recommended for patients on anti-TNF drugs at screening.

During Weeks 24-40, patients with active disease (defined as DAS28-ESR equal to greater than 2.6) were considered eligible for re-treatment with rituximab and were randomized in a 2:1 ratio to receive a further course of rituximab (2 x 1g) or placebo infusions. Background non-biological DMARD therapy was continued for all patients. Efficacy endpoints were assessed at Week 48. Patients were excluded from re-treatment if they had active infection of any kind (excluding fungal nail infections) or any significant cardiac, pulmonary or other systemic disease that was not controlled. Subjects who did not meet the criteria for re-treatment at Weeks 24-40 continued to be followed for both efficacy and safety until study conclusion. Those patients that refused re-treatment at Weeks 24-40 were withdrawn from the treatment period and only entered the safety follow-up. At or after 16 weeks after re-treatment, subjects who had not achieved at least a 20% reduction in both their tender and swollen joint count compared to baseline could initiate rescue treatment with an additional non-biologic DMARD at the discretion of their treating rheumatologist.

Two protocol amendments occurred after study commencement but these did not appear to significantly affect the outcomes. The first was to tighten the exclusion criterion (for example, no subjects were to receive prior abatacept therapy). The second was to clarify the minimum safety laboratory criterion before re-treatment (for example, neutrophil count > 1.5 x 10^9/L).

Study Population

Subjects were required to be 18-80 years of age with RA of at least 6 months duration. At study entry, patients were required to have active disease as defined by the 1987-revised ACR criteria which included >8 swollen joints out of 66 joints assessed, >8 tender joints out of 68 joints assessed, raised serum inflammatory markers (CRP>6 mg/L or ESR >28 mm/hr). Inadequate response to previous anti-TNF treatment included etanercept (at least three months of 50 mg/week), adalimumab (at least three months of 40 mg/fortnight) or infliximab (at least 4 infusions at a minimum dose of three mg/kg). Patients were required to have taken MTX 10-25 mg/week for at least 12 weeks prior to study commencement (stable for at least

the preceding 4 weeks). Corticosteroids (oral prednisone equivalent <10mg/day) were permitted if stable for at least 4 weeks prior to baseline. The use of an NSAID was permitted if stable for at least two weeks prior to baseline. In total, 43 patients were involved in the study but did not meet the inclusion or exclusion criterion: 7 (8.3% of 84) patients not randomized to re-treatment at Week 24, 9 (5.7% of 157) subjects in the placebo re-treatment group and 27 (8.5% of 318) patients in the rituximab re-treatment group. The main reasons for discordance were insufficient disease activity (3 and 7 patients for placebo and rituximab re-treatment, respectively) and insufficient wash-out of prior biologic agent (3 and 4 patients for placebo and rituximab re-treatment, respectively).

The studied population was clearly delineated and the two main treatment groups were well matched with respect to demographic characteristics. Subjects had a mean age of 54 years (range: 25-80 years) and 16% of subjects were older than 65 years. Female patients were predominately represented (80%). Caucasians (80%) accounted for the major racial background followed by patients of Hispanic ethnicity (9.5%) and Negro background (8%).

The patients involved in the SUNRISE Study had established disease with mean (standard deviation) duration of RA of 10.6 (8.5) years in the placebo re-treatment group and 11.9 (9.25) years in the rituximab re-treatment group. Approximately 75% of patients in each group were seropositive for rheumatoid factor (RF>15 IU/mL) and a similar percentage were anti-CCP antibody positive. The mean (standard deviation) RF titres in those positive were high at 523 IU/mL (715) and 628 IU/mL (1936) for the placebo and rituximab re-treatment groups, respectively.

Disease activity of the study participants at baseline and then Week 24 (that is, immediately prior to re-treatment) are presented in Table 10). The parameters at Week 24 reflect severely active disease and were comparable between the two re-treatment groups although it appears that the placebo re-treatment group had slightly higher ACR responses than the rituximab re-treatment group prior to re-treatment. The baseline mean tender joint count was 31.8-32.8 (of a possible maximum of 68) and the mean swollen joint count was 21.9-22.2 (of a possible maximum of 66). The overall (baseline) activity score, as measured by the DAS28-ESR, was 6.7, indicating high disease activity.

Table 10. SUNRISE Study

Disease Characteristics at Week 24:
Intent-to-Treat Population

Characteristic	Placebo Retreatment (n=157)	Rituximab Retreatment (n=318)
Tender joint count		
Mean (SD)	19.4 (17.50)	20.4 (16.58)
Swollen joint count		
Mean (SD)	11.6 (10.88)	12.8 (11.22)
ACR20, n (%)	76 (48.4%)	142 (44.7%)
ACR50, n (%)	42 (26.8%)	67 (21.1%)
ACR70, n (%)	17 (10.8%)	25 (7.9%)
C-reactive protein (mg/dL)		
Mean (SD)	1.2 (1.81)	1.1 (1.55)
Erythrocyte sedimentation rate (mm/hr)		
Mean (SD)	31.0 (22.69)	29.7 (21.49)
Health Assessment Questionnaire–Diagnostic Index		
Mean (SD)	1.2 (0.71)	1.2 (0.68)
DAS28–ESR		
Mean (SD)	5.1 (1.67)	5.2 (1.56)

The two main treatment groups were well-balanced with respect to previous and concomitant treatments for RA. All patients recruited into the re-treatment population were taking MTX at a median (mean) dose of 15 (16.4) mg/week. In addition, 68% had received prior non-biologic DMARDs (other than MTX) with the most common prior DMARDs being anti-malarial agents (45.5%) followed by leflunomide (27%) and sulfasalazine (26%). The mean number of prior non-biologic DMARDs (excluding MTX) taken by patients was 4.1 for both treatment groups and 19% of patients had taken 6 or more previous DMARDs. All but one patient (who subsequently received rituximab 2 x 1g, 2 x 1g) in the re-treatment population received a prior biologic DMARD with the most common prior treatment being etanercept (56%) followed by infliximab (53%) and adalimumab (46%). Oral corticosteroid therapy (mean dose of 7 mg/day) at study entry and continued through the study was recorded by two-thirds of patients (same rate in both treatment groups). In addition, 56% of patients were taking anti-inflammatory medication and 14% were taking strong analgesics.

Efficacy Parameters

Primary: The primary endpoint was the proportion of patients in each of the re-treatment groups who achieved an ACR20 response at Week 48 relative to baseline (Day 1).

Secondary: The secondary endpoints evaluated at Week 48 in the two re-treatment groups relative to baseline included:

1. Proportion of patients with ACR50 and 70 responses,

2. Change in DAS28-ESR score,
3. Proportion of re-treated patients achieving good or moderate EULAR responses,
4. Change in ACR core set variables,
5. The Area Under the Curve (AUC) of ACRn,
6. Change in SF-36 Mental and Physical health summary scores, and
7. Change in FACIT-Fatigue assessment.

Other secondary endpoints added after study commencement but prior to unblinding were the proportion of re-treated subjects with a change of at least 0.22 or 0.30 in HAQ-DI at Week 48, and the proportion of re-treated subjects achieving either DAS28 remission or low disease activity.

Statistical Analysis

The primary efficacy analysis of ACR20 response at Week 48 was between the rituximab and placebo re-treatment groups and was based on the ITT population which included all subjects who were randomized into the double-blind re-treatment phase at Week 24 and who received any amount of re-treatment study drug. Statistical analysis using CMH was undertaken, stratified by RF status at baseline and >20% improvement in both swollen and tender joint count at Week 24 from baseline (yes/no). Patients with missing data during the treatment period were analysed using both the LOCF and NRI imputation methods. In addition, subjects who received rescue therapy or withdrew were classed as non-responders. Sensitivity analysis using the per-protocol population was also performed.

For testing of the secondary efficacy endpoints, categorical endpoints such as the various levels of ACR and EULAR response were evaluated using the CMH test (that is, in the same manner as the primary endpoint). Continuous efficacy variables such as the change from baseline in DAS28, ACRn, FACIT-Fatigue and SF-36 were assessed using an ANOVA model with baseline parameter of interest, RF status (positive/negative), re-treatment group and >20% improvement in both swollen and tender joint count at Week 24 from baseline (yes/no) as explanatory terms in the model.

Patient Disposition/Completion

The planned enrolment for the study was 555 subjects and 561 patients were actually enrolled. Of these, 559 received an open-label infusion of rituximab at study commencement. Of the 559 subjects, 475 (85%; n=320 for rituximab and n=155 for placebo infusions + MTX) were randomized into the re-treatment phase of the study. As a major protocol deviation, two patients assigned to rituximab re-treatment actually were switched to the placebo re-treatment group.

In total, 85.3% (405/475) patients completed the planned 48 week study period. More patients in the rituximab re-treatment group completed the 48 weeks of follow-up (91.5%, 291/318) compared to 85.3% (134/157) in the placebo re-treatment group. Most of the discontinuations prior to Week 48 resulted from either the patient's (7.4%, 35/475) or physician's decision (1.3%, 6/475) to withdraw because of insufficient response rather than for AEs (2.9%, 14/475).

Between Weeks 24 and 28 (inclusive), 90% of subjects in both re-treatment groups had been re-treated. By Week 32, the re-treatment percentage exceeded 95% in both groups and by Week 40, >99% patients had received re-treatment.

Efficacy results

For the primary efficacy endpoint, the proportion of **ACR20 responders** at Week 48 was statistically significant higher for rituximab re-treatment subjects (170/318; 53.5%, 95% CI

48.0-58.9) than placebo re-treatment patients (70/157; 44.6%, 95% CI 36.8-52.4; p=0.0195). Consistent results were seen for the various sensitivity analyses.

However, the proportions of **ACR50 and 70 responders** at Week 48 were similar between the rituximab re-treatment (28.9% [92/318] and 13.8% [44/318] for ACR50 and 70, respectively) and placebo re-treatment groups (26.1% [41/157] and 13.4% [21/157] for ACR50 and 70, respectively). There was a slight imbalance in ACR responses at Week 24 with overall lower responses seen in the rituximab re-treatment group than placebo re-treatment group (see Table 11).

Table 11. SUNRISE Study

Proportion of Subjects with ACR20, ACR50, and ACR70 Responses at Week 24 and Week 48

	Week 24		Week 48	
Response	Placebo Retreatment n=157	Rituximab Retreatment n=318	Placebo Retreatment n=157	Rituximab Retreatment n=318
ACR20	48%	45%	45%	54%
ACR50	27%	21%	26%	29%
ACR70	11%	8%	13%	14%

Note: The LOCF was used to impute missing ACR components. Subjects with insufficient data to calculate an ACR20 response were classified as non-responders. Subjects who received rescue therapy, new DMARD or biologic therapy, or withdrew from the study were classified as non-responders.

The ACR subset analysis at Week 48 (according to responder or non-responder status at Week 24) showed that for subjects who had achieved an ACR20, 50 or 70 response at Week 24 re-treatment with rituximab was more likely to maintain the same level of response. For example, ACR50 response rates at Week 48 in the same level of responders at Week 24 were 64.2% (43/67) for rituximab re-treatment compared with 47.6% (20/42) for placebo re-treatment. However, for subjects who had not achieved an ACR response at Week 24, the rates of achieving a response did not differ between rituximab and placebo re-treatment. For example, the ACR50 response rate at Week 48 in non-responders at Week 24 was 19.5% (49/251) for rituximab re-treatment compared with 18.2% (21/115) for placebo re-treatment.

A significantly greater reduction in **mean DAS28-ESR score** at Week 48 was seen for rituximab re-treatment (n=312; mean change -1.9) compared with placebo re-treatment (n=157; mean change -1.5; difference in mean change -0.4 [95% CI -0.7, -0.1]; p=0.0058). Similar results were seen for the mean change in DAS28 when CRP was used instead of ESR. However, the proportion of patients at Week 48 achieving **low disease activity** (DAS28 equal to or less than 3.2) or **DAS remission** (DAS28<2.6) were similar between the rituximab re-treatment (21.1% [66/312] and 10.4% [32/312] for low disease activity and remission, respectively) and placebo re-treatment groups (18.5% [29/157] and 8.9% [14/157] for low disease activity and remission, respectively).

No statistically significant difference (p=0.09) in the rate of **EULAR good or moderate response** at Week 48 was seen between the rituximab and placebo re-treatment groups:

19.5% (59/302) and 18.3% (28/153) for good response, and 48.0% (145/302) and 42.5% (65/153) for moderate response for rituximab and placebo re-treatment groups, respectively.

Mean ACRn at Week 48 was significantly higher in the rituximab re-treatment group (n=317; mean 16.1) than the placebo re-treatment group (n=157; mean 2.6; difference in mean change 13.5 [95% CI 4.2, 22.8]; p=0.0046). However, for the pre-specified endpoint of the difference in **mean AUC of ACRn** at Week 48 between the two re-treatment groups this did not meet statistical significance (mean AUC of ACRn 3143 for placebo and 3834 for rituximab; difference in mean 691 [95% CI -1060, 2443]; p=0.4384).

The results of ANOVA of change from baseline in the **ACR core set components** showed a statistically significant difference in the adjusted means for all but two (tender joint count and HAQ) of the core set components in favour of rituximab re-treatment (see Table 12).

Table 12. SUNRISE Study

ANOVA of Change from Baseline in the Components of the ACR Core Set at Week 48: Intent-to-Treat Population

	ACR Core Set Components							
Group	SJC (66 Joint Count)	TJC (68 Joint Count)	HAQ	Subject's Global Assessment VAS (mm)	Physician's Global Assessment VAS (mm)	Subject's Assessment of Pain VAS (mm)	CRP (mg/dL)	ESR (mm/hr)
Placebo retreatment group								
n	157	157	157	157	157	157	157	157
Adjusted mean	–8.5	–12.0	–0.2	–19.3	–22.6	–15.8	–0.3	–9.5
Rituximab retreatment group								
n	318	318	316	316	318	317	318	315
Adjusted mean	–11.4	–13.7	–0.3	–24.3	–29.0	–21.4	–0.8	–15.1
Difference	–3.0	–1.8	–0.1	–5.0	–6.4	–5.6	–0.5	–5.5
95% CI for difference	(–4.9, –1.1)	(–4.3, 0.8)	(–0.2, 0.0)	(–9.8, –0.1)	(–11.0, –1.8)	(–10.5, –0.6)	(–0.8, –0.1)	(–9.2, –1.9)
p-value	0.0022	0.1818	0.1108	0.0456	0.0063	0.0286	0.0065	0.0030

ANOVA=analysis of variance; CRP=C-reactive protein; ESR=erthrocyte sedimentation rate; HAQ-DI=Health Assessment Questionnaire; LOCF=last observation carried forward; SJC=swollen joint count; TJC=tender joint count; VAS=visual analog score.

Notes: The mean was adjusted for retreatment, respective baseline ACR core set components, baseline rheumatoid factor status, and ≥20% improvement in both SJC and TJC at Week 24 from baseline (yes/no). The LOCF method was used to impute missing components.

Although numerically higher, the proportion of patients with a change from baseline of at least -0.22 in **HAQ-DI** at Week 48 was not statistically significant between the two treatment groups: 80/157 (51.0%; 95% CI 43.1, 58.8) for placebo versus 181/316 (57.3%; 95% CI 51.8, 62.7) for rituximab; weighted difference 7.72 (95% CI -1.48, 16.91); p=0.1000. A similar result was observed for the proportion of subjects achieving a change of at least -0.30 in their HAQ-DI: 62/157 (39.5%; 95% CI 31.8, 47.1) for placebo versus 145/316 (45.9%; 95% CI 40.4, 51.4) for rituximab; weighted difference 7.87 (95% CI -1.30, 17.04); p=0.0927.

No statistically significant mean change from baseline in the SF-36 Physical and Mental health summary scores was observed over 48 weeks in the two re-treatment groups. The placebo group (n=154) had a mean change of 4.0 and the rituximab arm (n=312) had a mean change of 5.4 in the Physical health summary score (difference 1.4 [95% CI -0.2, 3.0]; p=0.0852). For the Mental health summary score, the mean change from baseline was 3.5 for the placebo re-treatment group and 4.2 for the rituximab re-treatment group (difference 0.7 [95% CI -1.5, 2.8]; p=0.5452).

Both re-treatment groups recorded a mean reduction in FACIT-F score over 48 weeks and this was not statistically different between the two treatment groups. The placebo group

(n=157) had a mean change of -4.3 and the rituximab arm (n=318) had a mean change of -4.7 in the FACIT-F score (difference -0.4 [95% CI -2.1, 1.2]; p=0.6121).

The development of **HACA and its relationship with efficacy** was also explored. A total of 15 patients (9.6% of 157) in the placebo re-treatment group and 20 patients (6.3% of 318) in the rituximab re-treatment group had positive HACA at any time during the study. The presence of HACA did not appear to negatively correlate with efficacy upon re-treatment, as measured by the ACR or EULAR response criteria. However, with such small patient numbers, these data are difficult to interpret and therefore an effect of HACA on the efficacy of subsequent treatment courses cannot be excluded at this time.

Efficacy Conclusions

The SUNRISE Study examined the effect of one versus two courses (given 6 months apart) of rituximab over 48 weeks in subjects with active RA and a previous inadequate response to anti-TNF drugs. The re-treatment data suggests that rituximab offers improved efficacy over continued MTX alone at 48 weeks in some clinical measures of RA activity (such as the ACR20 response and mean change in DAS28 score) but the majority of efficacy endpoints showed no statistically significant enhanced efficacy. Patients most likely to benefit from re-treatment with rituximab were those who showed benefit from an initial course of therapy.

REFLEX STUDY and OPEN-LABEL EXTENSION (WA17531) ADDENDUM

An addendum to the 24 week Phase III controlled REFLEX study and its separate extension protocol (WA17531) was included in this submission mainly for the purpose of providing supportive data for the claim of improving radiographic outcome. Clinical endpoints at two years were also reported but only on the original ITT population (excluding the data of patients switched from placebo infusions to rituximab) and hence the overall number of patients remaining in this analysis made it difficult to draw any meaningful conclusions. Patients who completed 104 weeks of follow-up in the clinical endpoint analysis were 2.8% (6/208) for placebo + MTX and 9.4% (29/308) for rituximab + MTX. The radiographic ITT population was defined differently and included patients both in the original placebo + MTX group and the rituximab group who received further courses of rituximab in the open-label extension period. This analysis will be the focus of the efficacy evaluation in this report.

The REFLEX Study was pivotal in rituximab obtaining initial regulatory approval in Australia and overseas for use in patients with active RA. It was designed to assess the proportion of patients who achieved an ACR20 response at Week 24 (the primary efficacy endpoint). Following 24 weeks of treatment in the pivotal Phase III study (REFLEX), 51% (153/298) of subjects who received rituximab + MTX achieved an ACR20 response compared to 18% (36/201) of subjects who received MTX alone ($p<0.0001$). The clinical benefit of rituximab + MTX compared to MTX alone in reducing the signs and symptoms was further supported by statistically significant improvements in ACR50 and 70 responses, EULAR responses and mean change from baseline in DAS28 (ESR) scores. The treatment effect was similar in patients independent of other variables including rheumatoid factor status, age, gender, and number of prior treatments.

Assessment of the effect of rituximab on the progression of structural damage at Week 24 was an exploratory efficacy endpoint in REFLEX, and on the recommendation of the FDA it was suggested that radiographic follow-up be continued for up to two years. Exploratory analysis of the Week 24 radiographic data, using the modified Total Sharp Score on a total of 89% of the treatment cohort (445/499), showed a statistically significant reduction in joint space narrowing (p=0.0156) and a non-significant trend towards reductions in erosion score and Total Sharp Score following treatment with rituximab + MTX compared with MTX alone.

This current submission focused on the radiographic endpoints at two years (Week 104) but the study report did also summarize the main radiographic outcomes at one year (Week 56 analysis). These demonstrated:

- lower mean change in TSS in patients randomized to rituximab than patients randomized to placebo (rituximab versus placebo of 1.00 versus 2.31; p=0.0046),
- lower mean change in ES and JSN score in patients randomized to rituximab than patients randomized to placebo (rituximab 0.59 versus placebo 1.32 for ES with p=0.0114; and rituximab 1.00 versus placebo 2.31 for JSN score with p=0.0006),
- higher proportion of patients randomized to rituximab with no new erosions (61%, n=278) compared to patients randomized to placebo (52%, n=186; p=0.0494).

Study Design

The REFLEX Study was a prospective, multicentre, randomized, double-blind, parallel-group study with two treatment groups: placebo + MTX (n=209) and rituximab + MTX (n=308). Subjects were to have severely active RA and inadequate response to at least one anti-TNF drug. A minimum 4-8 week washout period was undertaken for subjects taking recent anti-TNF therapy to ensure the effects of the study regimens could be examined without the confounding effects of other medications active in RA. Randomization was administered by a central randomization centre, and stratified by RF status (positive or negative) and treatment region (USA or non-USA).

Rituximab was administered IV at a dose of 1000mg given on Days 1 and 15 (total dose 2000mg). Matching placebo infusions were administered on Days 1 and 15 to maintain blinding. All patients received a corticosteroid regimen consisting of methylprednisolone 100mg IV administered 30 minutes prior to infusions of rituximab/placebo, and prednisone 60mg orally (PO) on Days 2-7, 30 mg PO on Days 8-14, returning to baseline dose by Day 16. At the time of study initiation, the role of corticosteroids within rituximab treatment regimens was unclear. Originally, corticosteroids were considered to promote cytotoxicity but data to support a synergistic effect on B-cell killing was conflicting. However, an earlier Phase II study (DANCER) showed that combining rituximab with peri-infusional IV corticosteroids was effective at reducing the incidence and severity of acute infusion-related reactions, and this approach was continued in REFLEX. Most patients (94%) also received additional prophylactic treatment for infusion-related reactions in the form of paracetamol 1g and diphenhydramine 50mg (or equivalent anti-histamine) given orally 30 minutes prior to the start of an infusion.

In the protocol, usual therapeutic doses of MTX were utilized with all patients receiving weekly MTX (oral or parenteral) at a dose of 10-25 mg/week. All subjects received concomitant oral folic acid at a dose of 5 mg/week and continued to receive any background corticosteroid (<10 mg/day prednisone or equivalent) throughout the study, including Days 1-15.

Evaluation of the primary endpoints occurred at Week 24. After Week 24, patients entered the post-treatment period and were followed up every 8 weeks for 18 months, giving an overall study duration of 24 months. From Week 16 (and through to Week 24), patients withdrawn from the study due to lack of efficacy (defined as improvement from baseline of <20% in both the swollen joint count (SJC) and tender joint count (TJC)) were eligible to receive rescue therapy as follows:

1) Patients who received initial placebo treatment received rituximab (2 x 1g) preceded by methylprednisolone 100mg IV. Patients who responded to this rescue therapy

(>20% decrease in both SJC and TJC) were also eligible for further courses of rituximab under a separate open-label extension protocol (WA17531),

2) Patients who received initial rituximab treatment received standard of care treatments prescribed by the investigator and then entered the follow-up period. Such patients were not eligible to receive further courses of rituximab before week 24 but could receive other biologic therapies.

If patients discontinued from the study prior to Week 16 (for any reason), they were not eligible to receive rescue therapy. Rescue therapy was allowed only once during REFLEX. However, patients who completed the Week 24 visit, and who achieved at least a 20% reduction from baseline in both their SJC and TJC (at the same time) during any visit from Week 16 onwards, were eligible to receive further courses of open-label rituximab under a separate extension protocol (WA17531).

Patient Disposition and Exposure to Rituximab

A total of 520 subjects (and a further 231 screen failures) were recruited to REFLEX across 114 centres in 11 countries between July 2003 and July 2004. Of the 520 patients enrolled, 311 were randomized to receive treatment with rituximab + MTX, and 209 to receive placebo + MTX. The original ITT population on which the ACR20 response at Week 24 comprised 201 placebo treated patients and 298 rituximab treated subjects. Hence, 21 patients in total were excluded from the original ITT cohort due to three patients never being dosed, 7 due to unblinding, 5 at an Italian site with quality assurance (QA) irregularities and 6 who received study medication prior to randomization. All patients in the original ITT population had baseline x-rays.

At Week 104 (due to withdrawals from either the controlled or open-label extension study), 281 patients originally randomized to rituximab + MTX (197 with x-ray data at both time points [that is, observed cases] and 84 with imputed data) and 187 originally randomized to placebo infusions + MTX (135 observed cases and 52 with imputed data) comprised the radiographic ITT population for this analysis.

At Week 104, 31% (87/281) of patients in the original rituximab + MTX group had withdrawn following a single course of rituximab given within the REFLEX Study and 69% (194/281) of patients who responded to blinded rituximab enrolled into Study WA17351 to receive further courses of rituximab. A total of 116 patients (41.3% of 281) had received a single course of rituximab prior to their last observed x-ray and 165 subjects (58.7% of 281) had received two or more courses prior to their last observed x-ray. Specifically, 81 [29%] patients received two courses, 56 [20%] received three courses, 23 [8%] received 4 courses and 5 [2%] received 5 courses of rituximab.

Of the 187 patients originally randomized to placebo + MTX, 165 (88.2%) had received at least one dose of rituximab either through rescue therapy within the REFLEX Study (83 patients, 44.4% of 187) or through completing at least 24 weeks the REFLEX Study and then meeting the criteria for receipt of open-label rituximab in Study WA17351 (82 patients, 43.9% of 187). In total, 17.6% (33/187) patients originally randomized to placebo did not receive their first dose of rituximab prior to their last observed x-ray. Regarding rituximab exposure in this group, 32.1% (60/187) patients received a single of rituximab and 94 subjects (50.3% of 187) had received two or more courses prior to their last observed x-ray. For multiple rituximab treatment course exposure, 57 [30%] patients received two courses, 28 [15%] received three courses, 6 [3%] received 4 courses and three [2%] received 5 courses of rituximab.

Study Population

The REFLEX Study was conducted in 114 study sites in North America, Europe and Israel. Subjects were required to be >18 years of age with RA of at least 6 months duration. At study entry, patients were required to have active disease with >8 swollen joints, >8 tender joints and raised serum inflammatory markers (ESR>28mm/hr or CRP>15 mg/dl). In addition, subjects were required to have at least one joint erosion attributable to RA on plain x-ray at baseline. Patients must have received previous treatment with MTX at a dose of 10-25mg/week (oral or parenteral) for at least 12 weeks prior to screening, and had experienced an inadequate response to previous or current anti-TNF therapy of at least three months duration.

The two treatment groups were well matched with respect to demographic characteristics. Patients involved in this analysis had long-standing disease with a mean duration of RA since diagnosis of approximately 12 years (range: 0.6-48.3 years). Subjects had a mean age of 52 years (range: 20-81 years) and were predominantly female (81%). Caucasians (87%) accounted for the major racial background with Hispanics and Blacks each contributing approximately 5%. Seventy–nine percent of patients in both groups were seropositive for rheumatoid factor (RF>20IU/mL). In both treatment groups, 58% of patients in the ITT population were recruited in the USA.

The disease parameters at baseline were comparable between the two treatment groups and reflective of a population of patients with RA who had severely active disease. The baseline median tender joint count was 32 (of a possible maximum of 68), and the median swollen joint count was 23 (of a possible maximum of 66) for both groups. The mean DAS28 score at baseline was 6.9 consistent with high disease activity. The baseline mean (and median) TSS scores recorded by patients in each group were 32.48 (22.3) for placebo + MTX and 30.62 (24.0) for rituximab + MTX.

The two treatment groups were well-balanced with respect to previous and concomitant treatments for RA. All patients enrolled into the study had to have previously been treated with (and experienced an inadequate response to) one or more of the commercially available anti-TNF therapies: etanercept, infliximab and/or adalimumab. In both treatment groups, use of prior anti-TNF therapies was similar with 61% having taken one anti-TNF drug, 31% having taken two anti-TNF medications and 8% of patients in each treatment group having experienced an inadequate response to treatment with all three anti-TNF therapies. The most common prior anti-TNF therapy was infliximab (76%) followed by etanercept (52%). All patients had been exposed to MTX at study commencement. The mean weekly intake of MTX was similar for the two treatment groups and remained relatively stable at a median dose of 15 mg/week. The median number of non-biological DMARDs (other than MTX) previously taken by these patients was two in both treatment groups (range: 0-9 drugs) - predominantly leflunomide (57%).

Efficacy endpoints

The main radiographic endpoint in this analysis was the mean change in the Genant-modified Total Sharp Score (mTSS) from screening to Week 104 between the two treatment groups. Other radiographic efficacy endpoints (all assessed at Week 104) were the mean change in the erosion score and JSN score, as well as the proportion of subjects with no progression in mTSS (defined as a change in mTSS of zero or lower) and the proportion of patients with no erosive progression.

Statistical methods

Sample Size: This analysis was not prospectively sized or powered to detect a pre-specified treatment effect for structural damage progression. The original sample size and power

calculations were based on the proportions of patients in each treatment group expected to achieve the primary outcome measure of ACR20 response at Week 24.

Methods: Radiographic endpoints were analysed on the modified intention-to-treat (mITT) principle which included all randomized patients with a screening and at least one post-baseline set of x-rays (either at 24, 56 or 104 Weeks). The change in TSS was analysed using a Van Elteren test stratified by region (US/non-US) and rheumatoid factor (positive/negative) status. Missing values for the TSS were estimated by a pre-defined, linear progression method. Sensitivity analysis based on observed cases (rather than a combination of observed plus imputed data) was also performed. The endpoints examining the proportion of patients without x-ray progression were evaluated using a CMH analysis, stratifying by RF status and region of treatment.

Radiographs of the hands, wrists and feet were read by two independent radiologists who were blinded to treatment allocation, chronological order of the radiographs and the patient's clinical response. All radiographs were scored by two radiologists according to the Sharp method, modified by Genant, and the average of the two scores was used for the analysis.

Results

Treatment with rituximab + MTX resulted in a significant inhibition in the rate of progressive joint damage compared with MTX monotherapy as evaluated by the **mean change in mTSS** at Week 104 (Table 13). The mean change in mTSS was 1.14 for rituximab and 2.81 for MTX alone ($p<0.0001$). The results obtained from the observed case analysis were consistent with those obtained from the primary analysis; mean change in mTSS was 1.18 for rituximab (n=197) and 2.68 for placebo + MTX alone (n=135; p=0.0003). The favourable result for mean change in mTSS with rituximab therapy compared to placebo was seen across all subgroups containing >20 patients including age (less than or greater than 65 years), gender, region, autoantibody status (RF and/or anti-CCP positive or negative) and ACR20 responder status at Week 24.

Table 13. REFLEX Study

Summary of Sharp-Genant Total Score, Joint Space Narrowing Score, and Erosion Score from baseline to Week 104

	Sharp-Genant Total Score		Joint Space Narrowing Score		Erosion Score	
	Placebo (n=187)	Rituximab (n=281)	Placebo (n=187)	Rituximab (n=281)	Placebo (n=187)	Rituximab (n=281)
Baseline						
n	187	281	187	281	187	281
Mean	32.48	30.62	13.40	12.93	19.08	17.69
SD	31.476	26.718	15.593	13.911	16.876	14.024
Median	22.30	24.00	7.45	8.35	14.30	14.75
Min:Max	0.8:166.0	0.0:161.0	0.0:73.4	0.0:75.1	0.8:92.7	0.0:85.9
Week 104 (Day 728)						
n	187	281	187	281	187	281
Mean	35.29	31.76	14.40	13.35	20.89	18.41
SD	32.909	27.123	16.034	14.015	17.906	14.456
Median	24.30	25.35	9.60	9.04	15.50	15.40
Min:Max	1.1:166.0	0.0:161.0	0.0:73.4	0.0:75.1	1.1:99.6	0.0:85.9
Change from baseline at Week 104 (Day 728)						
n	187	281	187	281	187	281
Mean	2.81	1.14	1.00	0.42	1.80	0.72
SD	6.384	3.378	2.612	1.539	4.178	2.209
Median	0.55	0.00	0.00	0.00	0.30	0.00
Min:Max	-1.3:54.8	-6.7:34.0	-0.5:16.7	-4.5:12.5	-1.3:38.0	-3.6:23.2
p-value (a)	<0.0001		0.0009		<0.0001	

Missing values were imputed using linear extrapolation.
Rescue patients are reported under their original randomized treatment group.
(a) Comparison of rituximab versus placebo using van Elteren's test stratified for region and RF.

Both of the components (Erosion and JSN score) comprising the mTSS showed statistically significant lower mean changes from baseline to Week 104 for patients randomized to rituximab than for patients randomized to placebo (see Table 13). The **mean change in Erosion score** was 0.72 for patients randomized to rituximab and 1.80 for patients randomized to placebo ($p<0.0001$). For the **mean change in JSN score** over 104 weeks, the rituximab group result was 0.42 compared with 1.00 for the placebo arm ($p=0.0009$). Results for the mean change in Erosion and JSN score from baseline to Week 104 based on observed cases were consistent with the primary analysis result.

A statistically significant ($p<0.0001$) greater proportion of patients randomized to rituximab had **no worsening in mTSS** (56.9%, 160/281) compared to subjects randomized to placebo (38.5%, 72/187; 0.18 for the difference in proportions [95% CI 0.10, 0.27]). Two sensitivity analyses (using a higher definition of non-progression; 0.5 points or less, and 1.0 points or less) confirmed the above result was internally consistent. Furthermore, in the observed case population, 53% (104/197) of patients randomized to rituximab versus 34% (46/135) of subjects randomized to placebo had no worsening in their mTSS at two years (0.19 for the difference in proportions [95% CI 0.08, 0.29]; $p=0.0004$).

Erosive progression as defined as a worsening from baseline in erosion score (that is, any positive result). A statistically significant ($p=0.0003$) greater proportion of patients randomized to rituximab had **no worsening in Erosion score** (60%, 170/281) compared to subjects randomized to placebo (44%, 82/187; 0.17 for the difference in proportions [95% CI 0.08, 0.26]). Two sensitivity analyses (using a higher cut-off value defining non-progression – 0.5 points or less, and 1.0 points or less) confirmed the primary result, as did the analysis performed on the observed case population.

Study Conclusions

The two year x-ray data indicates that rituximab + MTX slows the expected rate of structural deterioration in patients with active RA at baseline who have had an inadequate response to anti-TNF therapy. The estimated yearly progression in mTSS for the study population was

2.79 points/year (that is, 5.58 points over two years) and treatment with rituximab + MTX reduced the rate of progression to 1.18 in the observed case analysis. In addition, a significant proportion of patients (57%) treated with rituximab + MTX had no evidence of radiographic progression over 104 weeks of follow-up. For the patients initially randomized to placebo infusions + continued MTX, the majority (88%) subsequently received at least one course of rituximab and more than half received two or more course of rituximab. Hence, the interpretation of this group's radiographic outcomes is confounded by the various administered treatments. Nonetheless, their radiographic outcomes were statistically inferior for all measures compared to the group who received rituximab + MTX at study commencement.

OPEN-LABEL EXTENSION for DANCER STUDY

The DANCER Study was a Phase IIb, randomized, double-blind, double-dummy, controlled multifactorial study of 9 different treatment regimens in a 3 x 3 configuration that comprised two different doses of rituximab (2 x 0.5 g and 2 x 1g) versus placebo infusions and three different corticosteroid regimens (including a placebo arm), along with continued weekly MTX (10-25 mg/week) and folate. For this analysis, the treatment regimens are pooled by rituximab dose/placebo arm, regardless of the corticosteroid regimen. The primary endpoint was conducted at Week 24 (double-blind period) and based on the proportion of patients in each treatment group that achieved an ACR20 response. No significant difference in efficacy outcomes was seen between the rituximab and different corticosteroid regimens. At any time after Week 24, patients who had achieved at least a 20% reduction in both their swollen and tender joint count from baseline at any visit from Week 16 onwards were eligible to receive further courses of rituximab under the extension protocol. In addition, patients who had an inadequate response to placebo infusions + MTX or the lower initial dose of rituximab (2 x 0.5g) were eligible to receive rescue therapy with the higher dose of rituximab (2 x 1g) between Weeks 16 and 24. All patients who remained in the DANCER Study beyond Week 24 were followed every 8 weeks in a post-treatment phase for up to 18 months (that is, up to 104 weeks post-infusion) to collect data on the duration of response to study medication following a single treatment course. This patient population formed the basis of this clinical study report.

Study Population and Disposition

The original recruited patient population consisted of subjects with severely active RA, who had previously failed 1-5 DMARDs (which may have included anti-TNF medications) in addition to recent or current MTX at screening. The three treatment groups were well matched with respect to baseline disease characteristics and demographics. In total, 465 patients were recruited from 95 centres in 14 countries and at baseline 380 (82%) were RF positive. Most subjects (81%, 375/465) completed the initial 24 week study period with a higher proportion in the pooled rituximab treatment groups achieving this time point (86% [165/192] for rituximab 2 x 1g, 91% [113/124] for rituximab 2 x 0.5g and 65% [97/149] for placebo + MTX). Overall, only a relatively small number and percentage (70/465, 15%) of patients remained in the study until the Week 104 visit and this significantly limits the interpretation of the clinical efficacy endpoint analysis. A higher proportion of subjects treated with rituximab 2 x 1g (20.8%, 40/192) remained in follow-up to 104 weeks compared with 12.1% (15/124) for rituximab 2 x 0.5g and 9.4% (14/149) for placebo infusions + MTX. Fifty-seven patients received rescue therapy with rituximab 2 x 1g – 48 subjects (32.2% of 149) in the original placebo infusion group and 9 patients (7.3% of 124) in the original low dose rituximab (2 x 0.5g) arm. The primary efficacy evaluation at Week 104 was done on the original ITT RF-positive population and this further reduced the subject numbers available for analysis to 122

patients for rituximab 2 x 1g, 123 subjects for rituximab 2 x 0.5g and 122 patients for placebo + MTX. Due to the small patient numbers involved in the analysis, no formal statistical testing was performed.

Results

The proportion of ACR20 responders at Week 104 (using NRI) was numerically highest in the rituximab 2 x 1g group (14.8%, 18/122) compared with 7.3% (9/123) for rituximab 2 x 0.5g arm and 4.1% (5/122) for the placebo + MTX group. A similar result was obtained using the observed data population as well as the complete ITT population (regardless of RF status). For the ACR50 and ACR70 response rates at Week 104, similar proportions of patients in both rituximab groups achieved these outcomes which was numerically higher than the placebo group: ACR 50 response rates were 7.3% (9/123) for low dose rituximab and 5.7% (7/122) for high dose rituximab versus 1.6% (2/122) for placebo; ACR 70 response rates were 3.3% (4/123) for low dose rituximab and 4.1% (5/122) for high dose rituximab versus 0.8% (1/122) for placebo.

In terms of major clinical response, a numerically higher proportion of subjects who received rituximab maintained an ACR70 response for greater than 6 months; 5.7% (7/123) for low dose rituximab and 6.6% (8/122) for high dose rituximab versus 0.8% (1/122) for placebo. In addition, a consistent result was seen for the proportion of patients achieving DAS28 clinical remission; 4.1% (5/123) for rituximab 2 x 0.5g and 3.3% (4/122) for rituximab 2 x 1g versus 0 for placebo + MTX.

Study Conclusions

Clinical Endpoints evaluated at Week 104 in the DANCER Study suggest that a single course of rituximab (in either dose regimen) may result in sustained responses in a subset of patients but this interpretation is limited by the very low overall number of patients completing such an extended period of follow-up.

Safety

The safety analysis included all patients who received at least part of one dose of study medication during the clinical trial program. In total, 3095 patients received at least part of one infusion of rituximab (0.5 or 1g) as of the data cut-off dates. Of these, half (1581 patients) received at least three courses of rituximab. The total duration of exposure is 7198.49 patient-years with 1669 patients followed for more than two years and 225 for more than 5 years after their first infusion of rituximab. The majority of patients received rituximab in combination with MTX.

IMAGE Study

Methods

The analysis of safety was performed on the ITT population (n=748): 250 subjects for placebo + MTX, 249 patients for rituximab 2 x 0.5g and 249 patients for rituximab 2 x 1g. For the IMAGE Study, safety information was recorded on Days 1, 15 and 28, and then every 4 weeks thereafter until Week 56 (that is, 4 weeks post-study). Adverse Events (AE) were classified using the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTC[4]-AE, version 3) which grades events as mild, moderate, severe, or life-

[4] Common Toxicity Criteria (CTC), is a standardised classification of side effects used in assessing drugs for cancer therapy, in particular. Specific conditions and symptoms may have values or descriptive comment for each level, but the general guideline is 1 – Mild, 2 – Moderate, 3 – Severe, 4 - Life threatening, 5 - Death.

threatening. The dates of onset and resolution of the AE were recorded, and the relationship of the AE to treatment was also assessed.

Overview of Adverse Events

The overall incidence of AEs in MTX naïve patients with RA was similar between the three treatment groups (81.2% [203/250] for placebo + MTX, 75.9% [189/249] for low dose rituximab + MTX and 79.1% [197/249] for high dose rituximab + MTX). Furthermore, the pattern of AEs was similar between the three treatment groups apart from a small increase in Infusion Related Reactions (IRRs) with rituximab during the first course of treatment. The majority of AEs were mild or moderate (grade 1 or 2) but 12.0% (30/250) of patients in the placebo + MTX group, 8.6% (22/249) of subjects in the low dose rituximab arm and 8.8% (22/249) in the high dose rituximab group experiencing severe or life-threatening (grade 3 or 4) adverse events. Approximately 20% of all AEs (other than IRRs) were considered to be related to study drug (rituximab and/or MTX).

The extent of exposure to study medication and follow-up was similar between the three treatment groups. All but 12 patients (5 in placebo + MTX group, one in low dose and 6 in high dose rituximab) received both infusions in their first course of treatment. Over 80% of patients in each treatment group received a second course of treatment with all but 14 (2 in placebo + MTX group, 10 in low dose and two in high dose rituximab) receiving both infusions. More patients received a third course of treatment in the placebo + MTX group (44%, 110/250) than the rituximab treatment groups (38%, 94/249 for low dose and 37%, 91/249 for high dose) suggesting that patients in the placebo + MTX group become eligible for re-treatment sooner than those receiving a rituximab containing regimen. In addition, a slightly higher proportion of patients were followed for the planned 52 weeks in the rituximab treatment groups (approximately 90%) than in the placebo + MTX group, and as such the patient-years observation was slightly higher in the rituximab groups (approximately 240 versus 230 patient-years).

Adverse events leading to withdrawal

A total of 16 patients withdrew from the study due to AEs: 7 patients treated with placebo + MTX, 4 patients treated with rituximab 2 x 0.5g and 5 patients treated with rituximab 2 x 1g. Four patients treated with rituximab + MTX (one in the low dose group and threein the high dose group) withdrew due to infusion-related reactions. Withdrawals due to malignancy occurred in 4 patients: three treated with placebo + MTX (1 case of colon cancer, metastatic melanoma and B-cell lymphoma) and one treated with rituximab 2 x 0.5g (metastatic endometrial cancer). Three patients withdrew due to infections: one patient developed pneumonia with placebo + MTX and two patients in the low dose rituximab + MTX group (1 case of septic shock and *Pneumocystis jiroveci* pneumonia). The other 5 withdrawals were as a result of single events: pulmonary embolus, asthma and perforated diverticular disease (placebo + MTX group); and dyspnoea and nausea (high dose rituximab group).

Most Frequent Adverse Events (>5% of patients)

The most common AE was IRR which occurred in a similar percentage of patients in the placebo + MTX group 18% (45/250) and rituximab 2 x 0.5g + MTX 17% (43/249), but at a higher rate in the rituximab 2 x 1g + MTX arm 23% (58/249). Other common AEs (> 5% incidence) had a similar incidence across the three treatment groups with the exception of headache which had a higher incidence in the high dose rituximab arm (10% [24/249] versus 6% [16/250] for placebo and 5% [12/249] for low dose rituximab). Common events occurring

at a similar incidence in all groups included upper respiratory tract infection (12-14%), nasopharyngitis (12%), nausea (12-14%), abnormal liver function tests (10-12%), hypertension (4-6%), urinary tract infection (6-10%) and diarrhoea (3-6%). A summary of adverse events with an incidence rate of at least 5% in the IMAGE Study is summarised in Table 14.

Table 14. IMAGE Study

Summary of All Adverse Events with an Incidence Rate of at Least 5% over 52 Weeks (Safety Population)

Adverse Event	Placebo + MTX N = 250 No. (%)	Rituximab 2x0.5g + MTX N = 249 No. (%)	Rituximab 2x1.0g + MTX N = 249 No. (%)
INFUSION RELATED REACTION	45 (18)	43 (17)	58 (23)
NAUSEA	29 (12)	33 (13)	36 (14)
UPPER RESPIRATORY TRACT INFECTION	32 (13)	29 (12)	35 (14)
NASOPHARYNGITIS	31 (12)	31 (12)	29 (12)
HEPATOTOXICITY	27 (11)	30 (12)	24 (10)
RHEUMATOID ARTHRITIS	37 (15)	21 (8)	18 (7)
URINARY TRACT INFECTION	21 (8)	16 (6)	25 (10)
HEADACHE	16 (6)	12 (5)	24 (10)
ANAEMIA	20 (8)	9 (4)	14 (6)
HYPERTENSION	12 (5)	10 (4)	14 (6)
DIARRHOEA	8 (3)	11 (4)	16 (6)
BRONCHITIS	8 (3)	13 (5)	12 (5)
DIZZINESS	11 (4)	7 (3)	14 (6)

Infusion Related Reactions

Adverse events occurring during or within 24 hours of each infusion were recorded and may be linked to cytokine release and/or acute Infusion Related Reactions (IRRs). Symptoms or signs suggesting an acute infusion reaction include pruritus, fever, urticaria/rash, pyrexia, chills, rigors, angioedema, throat irritation, cough, bronchospasm, with or without associated hypotension or hypertension.

A higher proportion of rituximab-treated patients with either dose (20.0% [50/249] for high dose rituximab and 17.7% [44/249] for low dose rituximab) experienced adverse events during or following the first infusion compared to placebo infusion (14.5%, 36/249). The majority of IRRs (>80%) in the rituximab treatment groups had an onset during the infusion consistent with previous knowledge of the drug, whereas the placebo infusion + MTX group had just over half of their IRRs recorded post-discharge from the infusion centre. Despite this, the pattern of IRRs was similar between the placebo and rituximab groups with the most common AEs being headache and flushing (affecting 4-6% of patients in any treatment group). However, some AEs occurred at a higher incidence in both of the rituximab + MTX groups compared to placebo + MTX and these include throat irritation (8-13% versus 2%), pruritus (3-10% versus 2%), and pyrexia (4-5% versus 2%). In addition, the high dose rituximab infusion had a higher incidence of rash (6% versus 2%), hypertension (4% versus 1%) and wheezing (3% versus 0) compared to both placebo infusions and low dose rituximab.

Nearly all of the IRRs were either grade 1 or 2 severity, but two patients in the rituximab 2 x 0.5g + MTX group and three patients in the rituximab 2 x 1g + MTX arm experienced severe (grade 3) AEs. Of note, one patient suffered a serious adverse event (anaphylactic reaction) during the fourth infusion of rituximab 2 x 1g (treatment day 15 of course 2). The presentation

consisted of angioedema, laryngeal oedema, throat irritation, and hypotension. The infusion was ceased after administration of 160mg of rituximab and the patient was given adrenaline and IV corticosteroids. The patient subsequently received further doses of rituximab without complications but was identified as being positive to HACA. Two patients in each of the rituximab + MTX treatment groups also experienced severe (grade 3) AEs during or within 24 hours of infusion including one case each of severe headache, bronchospasm, throat irritation and hypertension with tachycardia.

In total, three rituximab 2 x 1g + MTX patients (two patients during the first infusion of their first course and one patient on the infusion at Day 15 of a third course) and one rituximab 2 x 0.5g patient (Day 1 of second course) withdrew as a result of IRRs. All of the patients received recommended pre-medication (in particular, IV methylprednisolone) and displayed features consistent with anaphylactic or anaphylactoid reactions (such as airway oedema/irritation and/or bronchospasm, and cardiovascular changes – tachycardia with either hyper- or hypotension). Two patients required adrenaline as part of their rescue treatment and of note, one of the patients had HACA antibodies detected at Week 24. No placebo + MTX patients withdrew because of an IRR.

In addition to the patient withdrawals, another 68 patients had their infusions modified (that is, reduced amount infused, slowing or interruption) as a result of AEs. There was an observed rituximab dose relationship to this with more patients in the rituximab 2 x 1g group (14%, 34/249) experiencing this event compared to 9% (22/249) for rituximab 2 x 0.5g and 5% (12/250) for placebo + MTX. Most of these patients with dose interruptions had minor degrees of urticaria, flushing, or oropharyngeal pain or swelling. Infections was the second commonest reason for "dose modification" in all groups (affecting 4-5% of patients) since the protocol required that infusions be delayed in individuals with concurrent infection.

The vast majority of patients (80.5%, 603/748) received two complete infusions of either rituximab or placebo, as intended by the protocol design. Fewer adverse events were recorded during or within 24 hours after the second and third infusions. The pattern of adverse events observed was similar to that seen for the first infusion with no specific AE increased relative to placebo except throat irritation (2% for both doses of rituximab versus 0 for placebo infusions + MTX).

Serious Adverse Events (SAEs)

The overall incidence of SAEs was comparable between the three treatment groups and reported in a total of 73 subjects: - 26 of 250 (10%) of patients in the placebo + MTX group, 23 of 249 (9%) of subjects in the low dose rituximab + MTX arm and 24 of 249 (10%) of subjects in the high dose rituximab + MTX group. The most common type of SAEs was infections (2% for both rituximab groups versus 4% for placebo) and gastrointestinal disorders (2% in each group) with no increased rate seen in patients treated with rituximab compared with placebo + MTX treated patients. The majority of other serious adverse events (SAEs; non-infectious and non-IRR) were singular occurrences experienced by different patients, and no conclusions of comparative incidence between the treatment groups can be drawn.

Infectious Adverse Events

(a) Overall

The overall infection rate was similar in subjects treated with rituximab + MTX (51% [127/249] for low dose rituximab and 52% [129/249] for high dose rituximab) to those who received placebo + MTX (50%, 124/250). The most frequently (>5%) infections reported in a similar proportion of patients in all treatment groups affected the upper respiratory tract (12-14%), urinary tract infection (8-10%) and gastrointestinal system (6-8%). The majority of infections were suspected viral (46%, 295/636) or bacterial (47%, 302/636) with no discernible type of infection evident between the treatment groups.

With immunosuppression, herpetic infections are of special interest. A total of 11 subjects (2 in the placebo, 4 in low dose rituximab and 5 in high dose rituximab treatment group) developed oral herpes, and another 7 subjects (2 each for placebo and low dose rituximab; and three for high dose rituximab) experienced herpes zoster infection observed in the IMAGE Study. Each of these episodes resolved with appropriate anti-viral treatment. None of these herpes infections were considered to be serious AEs and no subject withdrew from the study for this reason.

(b) Serious infectious AEs

Twenty-seven patients experienced 34 serious infections (defined as those reported as SAEs and/or treated with IV antibiotics): - 5% (13/250) patients in the placebo + MTX group (14 infections), 2% (6/249) subjects in the rituximab 2 x 0.5g arm (11 infections) and 3% (8/249) patients in the rituximab 2 x 1g group (9 infections). Fifteen patients (~2.5% per group) experienced common terminology criteria (CTC) grade 3 infections which involved the respiratory tract (7 cases), gastrointestinal system (3 cases) and urinary tract (2 cases) with no distinguishing pattern between the treatment arms. Four patients, all the rituximab 2 x 0.5g + MTX group developed CTC grade 4 infections: two cases of appendicitis, one patient with pneumococcal pneumonia and septic shock, and a subject who developed *Pneumocystis jiroveci* pneumonia. The serious infections in the rituximab-treated patients were successfully treated with 5-14 days of IV antibiotics. However, one patient treated with placebo + MTX developed a fatal opportunistic infection, pneumonia due to *Pneumocystis jiroveci* and *Pseudomonas aeruginosa*.

All patients who developed serious infection were peripherally B-cell depleted at the time of onset of the infection and the majority (24 of 27 patients) had normal serum concentrations of immunoglobulin (Ig). Three patients (1 in each treatment group) had either low IgG or IgM levels at the time of infection. There was no established pattern regarding latency of infection with time to infection from initial infusion varying from 57 to 225 days (mean 115 days). The overall incidence rate (approximately 4-6 per 100 patient-years) of serious infections within the IMAGE Study is comparable to the expected rates seen in subjects with long-standing RA.

Lower Gastrointestinal (GI) Events

Analysis of lower GI events was an AE of special interest, particularly in relation to identifying GI perforation. The overall incidence of lower GI events was higher in the rituximab 2 x 1g + MTX group (13.3%, 33/249) compared with rituximab 2 x 0.5g + MTX (10.5%, 26/249) and placebo + MTX (8.8%, 22/250). The most common lower GI events were diarrhoea and gastroenteritis, both of which had a higher incidence in the high dose rituximab group 6.4% [16/249] for diarrhoea and 3.6% [9/249] for gastroenteritis for rituximab 2 x 1g versus 4.4% [11/249] and 2.0% [5/249] for low dose rituximab and 3.2% [8/250] and 1.2% [3/250] for placebo + MTX, respectively. The estimated rate of any lower GI event was higher in the rituximab 2 x 1g treatment group (18.67 [95%CI 13.94, 25.00] events per 100 patient-

years compared with 12.56 [95% CI 8.78, 17.97] in the low dose rituximab group and 12.19 (95% CI 8.41, 17.65) in the placebo + MTX group. The majority of lower GI events were CTC grade 1 or 2.

The incidence of serious lower GI events was lower in the rituximab treatment groups (1 [0.4%] patient in the rituximab 2 x 0.5g group, and two patients [0.8%] in the rituximab 2 x 1g cohort) compared to placebo + MTX (1.6%, 4/250). Two patients experienced lower GI perforations, both of whom received placebo + MTX. The estimated rate of serious lower GI events was also lower in the rituximab treatment groups (0.42 [95% CI 0.06, 2.97] and 0.83 [95% CI 0.21, 3.32] events per 100 patient-years in the low and high dose groups respectively) compared with 1.74 (95% CI 0.65, 4.64) in the placebo + MTX arm.

Cardiovascular (CVS) Events

Patients with long-standing active RA have an increased risk of CVS morbidity and mortality. The overall incidence of CVS events was higher in the rituximab 2 x 1g group (11.6%, 29/249) than in the placebo + MTX (8.0%, 20/250) and rituximab 2 x 0.5g groups (8.8%, 22/249). There was no single or collective group of events which clearly explained this difference. The most common event was hypertension (not including that associated with infusions) but this occurred at a similar frequency between the three treatment groups (approximately 5%).

Serious cardiovascular AEs appeared to have occurred at a higher frequency (albeit small total numbers) in the rituximab treatment groups (4 patients in each rituximab group versus two in the placebo). Two patients (1 in each of the rituximab arms) experienced myocardial infarction, and another two patients in the rituximab 2 x 1g group had angina. One patient in the high dose rituximab group suffered hypertensive crisis. One patient in the placebo group and one patient in the low dose rituximab group developed a deep vein thrombosis. The other two cardiovascular SAEs were “angiopathy” (described as a patient in the placebo group who underwent carotid endarterectomy for possible atherosclerosis) and complete atrioventicular block affecting a patient in the low dose rituximab group with established coronary artery disease and on-going CVS risk factors for atherosclerosis (smoking and hypertension).

Malignancy

Seven patients (3 in placebo + MTX group, two in the low dose rituximab arm and one in the high dose rituximab group) developed treatment-emergent malignancies during the IMAGE Study. In the patients who received placebo + MTX there was a case of primary mediastinal large B-cell lymphoma (onset Day 225), myelodysplastic syndrome (onset Day 58), colon cancer (onset Day 80) and metastatic malignant melanoma (Day 314). For the subjects allocated rituximab 2 x 0.5g + MTX, the patients developed metastatic endometrial cancer (onset Day 229) and carcinoma of the skin in situ (onset Day 229). The latter patient had a history of SCC of the skin. Another patient who received rituximab 2 x 1 g + MTX experienced cervical carcinoma with onset on Day 218.

Deaths

Three patients, all of whom in the placebo + MTX group, died during the 52 week study period + 4 week safety follow-up period. One patient, a 69 year old male, died on Day 345 after withdrawing from the study on Day 339 when he developed pneumonia on a background of worsening interstitial lung disease. The pneumonia was due to *Pneumocystis jiroveci* and *Pseudomonas aeruginosa*. Another patient, 57 year old female, died on Day 29 after developing pneumonia on Day 22. She had withdrawn from the study on Day 17 due to status asthmaticus which occurred two days earlier. The third death involved a 63 year old male who died on Day 183 of cerebral infarction after withdrawing from the study on Day 2 with a perforated colonic diverticulum.

Use in Pregnancy

The effect of study medication on pregnancy and lactation was not specifically examined in the IMAGE Study. Female subjects were to have a negative pregnancy test at screening, and patients of either gender were requested to use a reliable method on contraception during the study. Two subjects (both in the rituximab 2 x 1g + MTX group) were recorded as either becoming pregnant or fathering a pregnancy during the study. A 25 year old female was identified as pregnant on Day 208 and was considering a termination but became lost to follow-up. The other patient, a 34 year old male, fathered a female child 7 months after receiving a rituximab course (+ continued MTX) and regular residronate, paracetamol and hydrocodone. The patient's partner delivered a healthy baby at 33 weeks gestation following a caesarean section for pregnancy related hypertension.

Laboratory Test Evaluations

The most common newly occurring laboratory abnormality of CTC grade 3 or higher during the IMAGE Study was lymphopenia, which occurred at a higher incidence in patients treated with rituximab (65.6% [164/249] for low dose and 69.6% [173/249] for high dose) than in those received placebo infusions + MTX (25.2%, 63/250). In the majority of patients, the new significant lymphopenia was only recorded immediately following the infusion(s) and cell numbers subsequently recovered. In addition to rituximab depleting peripheral B-cells, corticosteroid treatment with infusions may reduce T-cell counts in the short-term. Grade 4 lymphopenia was not associated with any serious or severe infections in any patient.

Seven patients (4 treated with rituximab 2 x 1g, one treated with rituximab 2 x 0.5g and 2 treated with placebo infusions) experienced grade 3-4 neutropenia during the study period but without clinical sequelae.

Surprisingly, a very low incidence of three-fold or greater elevations in hepatic transaminases (aspartate aminotransferase, AST and/or alanine aminotransferase, ALT) was recorded in any treatment group: - 8 patients (3.2% of 249) in the rituximab 2 x 0.5 g + MTX group, 6 patients (2.4% of 249) in the rituximab 2 x 1g + MTX group and 4 patients (1.6% of 250) in the placebo + MTX group.

Human anti-chimeric antibodies (HACA)

In total, 73 (15% of 485) rituximab-treated patients with post-dose samples developed positive HACA titers [defined as >5 RU/mL] over the 52 week study period compared with 10/250 (4%) of placebo + MTX treated patients. At Week 24, a higher proportion of patients in the rituximab 2 x 0.5g + MTX group (11.9%, 28/235) were HACA positive compared to the rituximab 2 x 1g + MTX group (7.8%, 18/230) and placebo arm (1.4%, 3/222). However, by subsequent assessments at Week 40 and 52, the percentage of HACA positive in both rituximab treatment groups fell to a similar rate (4.6-5.7%), but still greater than that with placebo infusions + MTX (2-3%). The later rates of HACA detection should be cautiously interpreted as the process becomes technically more difficult with repeat courses of rituximab.

Of the 64 (out of a possible 73) rituximab-treated HACA positive patients who received a further course of therapy, 10 patients (5/29 [17.2%] with rituximab 2 x 1g and 5/35 [14.3%] with rituximab 2 x 0.5g) developed an IRR with re-treatment. This frequency of IRR is higher compared to an 11.4% incidence of IRR with either dose of rituximab in the overall safety population re-treated with rituximab. Two of the 10 patients who were HACA-positive patients and recorded IRRs developed clinically significant AEs upon re-dosing. Both patients had a significant loss of efficacy (leading one patient to withdrawal from the study) and the other patient reported recurrent (x 3 repeat infusions) moderate severity IRRs characterized by dyspnoea, chest symptoms (pain, cough, and bronchospasm), hypertension and tachycardia.

Although the overall numbers of HACA-positive patients are small, the safety profile (particularly involving infusion related events) in these patients is concerning.

Vital Signs

No treatment-based trend of change in vital signs was observed apart from a greater incidence of hypertension as an IRR (observed with first infusion of course 1) in the rituximab 2 x 1g treatment group (1.6%, 4/249) compared to 0.4% (1/250) for the placebo + MTX group and 0.4% (1/249) for rituximab 2 x 0.5g + MTX patients.

Safety conclusions

In the IMAGE Study, rituximab was generally well tolerated in MTX naïve patients with a relatively low incidence of serious adverse events. No new safety signals were observed. A higher proportion of patients receiving rituximab 2 x 1g experienced non-serious lower GI events (mainly, gastroenteritis and diarrhoea) and adverse cardiovascular events of unclear explanation. In addition, acute infusion related reactions with any dose of rituximab therapy, particularly during the first course of therapy or subsequently in those who develop HACA, are evident and require continued vigilance.

SERENE Study

Methods

The analysis of safety was performed on the ITT population and two treatment periods (that is, the initial 24 weeks of placebo-controlled comparison and then the active dose comparison period up to 48 weeks) were considered separately. For the 24 week safety period, a total of 509 patients (172 subjects for placebo + MTX, 167 patients for rituximab 2 x 0.5g and 170 patients for rituximab 2 x 1g) were evaluated. The 48 week rituximab dose comparison involved 337 subjects: 167 for low dose and 170 for high dose rituximab. During the SERENE Study, safety information was recorded on Days 1, 15 and 28, and then every 4 weeks thereafter until Week 56 (that is, 4 weeks post-study). Adverse Events (AE) were classified using the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE, version 3) which grades events as mild, moderate, severe, or life-threatening. The dates of onset and resolution of the AE were recorded, and the relationship of the AE to treatment was also assessed.

Overview of Adverse Events

The overall incidence of AEs during the 24 week period was similar in the three treatment groups (74.4% [128/172] for placebo + MTX, 76.6% [128/167] for low dose rituximab + MTX and 76.5% [130/170] for high dose rituximab + MTX). The pattern of AEs was similar between the three treatment groups, but a higher frequency of IRRs (particularly with rituximab 2 x 1g, and during the first course of treatment) was evident. The majority of AEs were grade 1 or 2, but 8.7% (15/172) of patients in the placebo + MTX group, 3.6% (6/167) of subjects in the low dose rituximab arm and 8.8% (15/170) in the high dose rituximab group experienced grade 3 or higher AEs. Approximately 15% of all AEs (other than IRRs) were considered to be related to study drug (rituximab and/or MTX).

The extent of exposure to study medication and follow-up was similar between the three treatment groups up until Week 24. Only 5 patients (three in placebo + MTX and three in the high dose rituximab group) did not receive both infusions in their first course of treatment. At Week 24, the number of years of patient data after first exposure was 79.24 for the placebo + MTX group, 79.63 for rituximab 2 x 0.5g + MTX and 81.36 for rituximab 2 x 1g + MTX.

Approximately 90% of patients in each treatment group received a second course of treatment, usually given between Weeks 28 and 32. Between Weeks 24 and 48, a further 145.12 years of patient exposure to rituximab were obtained in the two rituximab treatment arms, making for a total exposure of 152.43 and 153.36 patient-years for low and high dose rituximab, respectively. The overall safety profile remained similar in the two rituximab dose groups over the 48 week period of observation. Of note, the incidence of IRRs to a second course was comparable for both doses of rituximab (approximately 10%) and lower than that seen with the first course of therapy (19-25%).

Adverse events leading to withdrawal

In total, 7 patients withdrew prior to Week 24 because of AEs: two patients in the placebo + MTX group (1 due to a fall and another patient experienced cholelithiasis), two patients in the rituximab 2 x 0.5g + MTX group (a case each of myocardial infarction and stress fracture) and three patients in the rituximab 2 x 1g + MTX arm (1 due to an IRR with the first infusion, a case of pneumonia, and another subject who experienced pancreatic cancer).

At Week 48, withdrawals due to AEs were slightly higher in the high dose rituximab group (4.7% [8/170] versus 1.8% [3/167] for low dose rituximab). The three events in the rituximab 2 x 0.5g group were all different in nature: myocardial infarction, stress fracture and infection of a venous leg ulcer that was present at screening. In contrast, the rituximab 2 x 1g + MTX group had three withdrawals due to IRRs (1 was HACA positive) and two patients who developed malignancy (pancreatic and oesophageal adenocarcinoma). The other three cases who withdrew from the high dose rituximab group involved singular events of pneumonia, hypoglycaemia and a fall resulting in a fractured femur.

Most Frequent Adverse Events (>2% of patients)

The most common AE during the 24 week placebo-controlled period was IRR which occurred in a similar percentage of patients in the placebo + MTX group 18.0% (31/172) and rituximab 2 x 0.5g + MTX 20.4% (34/167), but at a higher rate in the rituximab 2 x 1g + MTX arm 27.1% (46/170). Other AEs with an incidence >2% had no consistently increased incidence in both rituximab treatment groups compared to placebo infusions + MTX (see Table 15). Common safety related AEs included upper respiratory tract infection (6-9%), nasopharyngitis (5-10%), nausea (2-4%), hypertension (2-3%), urinary tract infection (2-7%) and diarrhoea (4-5%).

Table 15. SERENE Study

Summary of All Adverse Events with an Incidence Rate of at least 2% over 24 Weeks (Safety Population)

Adverse Event	Placebo + MTX N = 172 No. (%)	Rituximab 2x0.5g + MTX N = 167 No. (%)	Rituximab 2x1g + MTX N = 170 No. (%)
ALL BODY SYSTEMS			
Total Pts with ≥ 1 AE	128 (74)	128 (77)	130 (76)
Total Number of AE	392	329	362
INFUSION RELATED REACTION	31 (18)	34 (20)	46 (27)
RHEUMATOID ARTHRITIS	30 (17)	17 (10)	15 (9)
NASOPHARYNGITIS	17 (10)	9 (5)	17 (10)
UPPER RESPIRATORY TRACT INFECTION	13 (8)	15 (9)	11 (6)
URINARY TRACT INFECTION	11 (6)	11 (7)	4 (2)
DIARRHOEA	7 (4)	9 (5)	7 (4)
NAUSEA	4 (2)	7 (4)	7 (4)
SINUSITIS	6 (3)	6 (4)	6 (4)
PHARYNGITIS	10 (6)	4 (2)	3 (2)
ARTHRALGIA	4 (2)	5 (3)	7 (4)
GASTROENTERITIS	10 (6)	1 (<1)	5 (3)
HEADACHE	6 (3)	3 (2)	7 (4)
COUGH	8 (5)	-	7 (4)
HYPERTENSION	3 (2)	5 (3)	5 (3)
DIZZINESS	4 (2)	4 (2)	3 (2)
ANAEMIA	5 (3)	3 (2)	1 (<1)
DIABETES MELLITUS	4 (2)	3 (2)	2 (1)
FATIGUE	2 (1)	3 (2)	4 (2)
BACK PAIN	3 (2)	4 (2)	1 (<1)
CONSTIPATION	1 (<1)	3 (2)	4 (2)
FALL	4 (2)	3 (2)	1 (<1)
OEDEMA PERIPHERAL	1 (<1)	2 (1)	5 (3)
PAIN IN EXTREMITY	1 (<1)	6 (4)	1 (<1)
SKIN ULCER	3 (2)	4 (2)	1 (<1)
GASTROOESOPHAGEAL REFLUX DISEASE	2 (1)	-	5 (3)
INSOMNIA	6 (3)	-	1 (<1)
RASH	1 (<1)	4 (2)	2 (1)
RESPIRATORY TRACT INFECTION	4 (2)	1 (<1)	1 (<1)
CONTUSION	1 (<1)	-	4 (2)
TINEA PEDIS	-	-	4 (2)

Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
All data is included regardless of rescue use
Infusion related reactions are AEs occurring within 24 hours of an infusion and considered by the investigator to be related to the rituximb/placebo infusion and to be an infusion related reaction

The overall incidence and profile of treatment related AEs was similar in each of the rituximab treatment arms over the 48 week study period apart from a slightly higher incidence of IRRs for rituximab 2 x 1g (31.2% [53/170]) compared with rituximab 2 x 0.5g (25.7% [43/167]). This result is accounted for by the difference in incidence of IRRs seen with the first infusion of Course 1. The recorded AE profile with either dose of rituximab in this part of the study is consistent with the known safety profile of the drug. Individual events with an apparent

increased incidence in either rituximab dose group included all infections (53.3% [89/167] versus 47.1% [80/170] for low and high dose, respectively), hypertension (6.0% [10/167] for low dose versus 2.9% [5/170] for high dose) and cough (1.8% [3/167] versus 5.3% [9/170] for low and high dose respectively).

In the placebo-switch population after Week 24, treatment with rituximab 2 x 0.5g resulted in a lower overall incidence in AEs (59.1% [91/154] versus 74.0% [114/154]) which was primarily accounted for by a lower incidence of all infections (25.3% [39/154] versus 41.6% [64/154]) and RA flares (5.8% [9/154] versus 15.6% [24/154]). Surprisingly, IRRs occurred at a similar incidence in the placebo-switch patients with placebo infusions + MTX or rituximab 2 x 0.5g + MTX (both 17.5% [27/154]).

Infusion-related events

A higher proportion of rituximab patients (27.1% [46/170] for high dose rituximab and 19.8% [33/167] for low dose rituximab) experienced adverse events during their first treatment course compared to placebo infusion (18.0%, 31/172). More than 60% of IRRs in the rituximab treatment groups had an onset during or immediately following the infusion whereas the placebo + MTX group had less than half of their IRRs recorded during this time period (that is, most occurred post-discharge from the infusion centre). The same type of IRRs was recorded between the placebo and rituximab groups but some AEs occurred at a higher incidence in the rituximab groups. These AEs include headache (5.3-6% versus 3.5%), throat irritation (3.0-8.8% versus 1.2%), pruritus (4.8-8.2% versus 0), and rash (3-7% versus 0; see Table 16). Of these, the high dose rituximab infusion had a higher incidence of throat irritation, pruritus and rash compared to low dose rituximab.

During the first 24 weeks of the study 8 patients had grade 3 IRRs (1 in the placebo group, 4 in the rituximab 2 x 0.5g + MTX group and three patients in the rituximab 2 x 1g + MTX arm) and no patients experienced grade 4 AEs. All of the grade 3 IRRs in the rituximab 2 x 0.5g arm were experienced by a single patient who suffered headaches and arthralgias after repeat infusions. Two patients had grade 3 IRRs in the rituximab 2 x 1g arm. Of note, one patient suffered an anaphylactoid reaction during the fourth infusion of rituximab 2 x 1g (treatment day 15 of course 2). This patient had a mild IRR with their first study infusion but had a severe IRR later in their treatment resulting in withdrawal from the study. This patient became HACA positive at Week 24. One additional patient who received rituximab 2 x 0.5g + MTX had a severe IRR that resulted in withdrawal after Week 48 due had a myocardial infarction in the evening following an infusion.

In addition to patient withdrawals, more patients had their infusions modified or interrupted in the rituximab 2 x 1g group (16.5%, 28/170) compared to 7.8% (13/167) for rituximab 2 x 0.5g and 5.2% (9/172) for placebo + MTX. Most of the patients (>90% for both rituximab groups) with dose modifications or interruptions had minor grades of IRRs. Infections were the second commonest reason for “dose modification” affecting a total of 6 patients (3 placebo + MTX patients, one patient in the low dose and two subjects in the high dose rituximab group). A dose related relationship was observed for infusion modifications or interruptions seen with patients treated with rituximab after their second course of therapy (between 24 and 48 weeks of study): incidence approximately 2-fold higher in the rituximab 2 x 1g group (19.4%, 33/170) than in the rituximab 2 x 0.5g group (10.2%, 17/167). However, fewer overall AEs were recorded in both rituximab treatment groups following the second infusions (19-25% versus 10-11% for rituxumab 2 x 0.5 and 2 x 1g, first course and second course of treatment, respectively). The pattern of AEs observed was similar to that seen for the first infusion with no increased incidence of a specific AE between the two courses of therapy. In the placebo + MTX group, the incidence of IRRs with the first infusion course of placebo (14.0%, 24/172)

was identical to that associated with the first infusion course of rituximab 2 x 0.5g (14.0%, 24/172).

Table 16. SERENE Study

Summary of Infusion Related Reactions and Symptoms Occurring ≥ 2 Patients at Each Infusion (Safety Population)

IRR/Symptom	Placebo + MTX (N=172) No. (%)	Rituximab 2x0.5g + MTX (N=167) No. (%)	Rituximab 2x1.0g + MTX (N=170) No. (%)
First Course Day 1			
Total pts with at least one IRR	**24 (14.0%)**	**31 (18.6%)**	**42 (24.7%)**
Total number of IRR	**28**	**37**	**48**
SYMPTOM			
HEADACHE	6 (3.5%)	10 (6.0%)	9 (5.3%)
PRURITUS	0 (0.0%)	8 (4.8%)	14 (8.2%)
THROAT IRRITATION	2 (1.2%)	5 (3.0%)	15 (8.8%)
FLUSHING	8 (4.7%)	7 (4.2%)	4 (2.4%)
RASH	0 (0.0%)	5 (3.0%)	12 (7.1%)
NAUSEA	6 (3.5%)	3 (1.8%)	3 (1.8%)
HYPERTENSION	3 (1.7%)	5 (3.0%)	3 (1.8%)
PYREXIA	3 (1.7%)	2 (1.2%)	2 (1.2%)
URTICARIA	0 (0.0%)	1 (0.6%)	4 (2.4%)
DYSPNOEA	0 (0.0%)	2 (1.2%)	2 (1.2%)
INSOMNIA	3 (1.7%)	0 (0.0%)	1 (0.6%)
MYALGIA	0 (0.0%)	4 (2.4%)	0 (0.0%)
PHARYNGOLARYNGEAL PAIN	0 (0.0%)	1 (0.6%)	3 (1.8%)
ARTHRALGIA	1 (0.6%)	2 (1.2%)	0 (0.0%)
COUGH	0 (0.0%)	0 (0.0%)	3 (1.8%)
DIARRHOEA	0 (0.0%)	3 (1.8%)	0 (0.0%)
DIZZINESS	1 (0.6%)	2 (1.2%)	0 (0.0%)
ABDOMINAL PAIN	0 (0.0%)	1 (0.6%)	1 (0.6%)
CHILLS	0 (0.0%)	2 (1.2%)	0 (0.0%)
DYSGEUSIA	0 (0.0%)	1 (0.6%)	1 (0.6%)
HYPOTENSION	1 (0.6%)	1 (0.6%)	0 (0.0%)
PARAESTHESIA	0 (0.0%)	0 (0.0%)	2 (1.2%)
PHARYNGEAL OEDEMA	0 (0.0%)	0 (0.0%)	2 (1.2%)
TACHYCARDIA	0 (0.0%)	1 (0.6%)	1 (0.6%)
First Course Day 15			
Total pts with at least one IRR	**14 (8.1%)**	**12 (7.2%)**	**10 (5.9%)**
Total number of IRR	**15**	**14**	**11**
SYMPTOM			
HEADACHE	2 (1.2%)	4 (2.4%)	2 (1.2%)
PYREXIA	4 (2.3%)	0 (0.0%)	3 (1.8%)
FLUSHING	4 (2.3%)	2 (1.2%)	0 (0.0%)
DIZZINESS	1 (0.6%)	0 (0.0%)	1 (0.6%)
NAUSEA	2 (1.2%)	0 (0.0%)	0 (0.0%)
PRURITUS	0 (0.0%)	1 (0.6%)	1 (0.6%)
THROAT IRRITATION	0 (0.0%)	2 (1.2%)	0 (0.0%)
Second Course	**Rituximab 2 x 0.5 g**	**Rituximab 2 x 0.5 g**	**Rituximab 2 x 1.0 g**
Second Course Day 1			
Total pts with at least one IRR	**24 (14.0%)**	**19 (11.4%)**	**17 (10.0%)**
Total number of IRR	**26**	**22**	**17**
SYMPTOM			
THROAT IRRITATION	7 (4.1%)	5 (3.0%)	5 (2.9%)
HEADACHE	4 (2.3%)	6 (3.6%)	4 (2.4%)
PRURITUS	8 (4.7%)	4 (2.4%)	0 (0.0%)
FLUSHING	5 (2.9%)	2 (1.2%)	1 (0.6%)
RASH	2 (1.2%)	0 (0.0%)	3 (1.8%)
DIZZINESS	1 (0.6%)	2 (1.2%)	1 (0.6%)
NAUSEA	2 (1.2%)	1 (0.6%)	1 (0.6%)
HYPOTENSION	1 (0.6%)	1 (0.6%)	1 (0.6%)
PYREXIA	1 (0.6%)	1 (0.6%)	1 (0.6%)
DYSPNOEA	0 (0.0%)	1 (0.6%)	1 (0.6%)
FATIGUE	1 (0.6%)	1 (0.6%)	0 (0.0%)
MYALGIA	0 (0.0%)	1 (0.6%)	1 (0.6%)
PARAESTHESIA	2 (1.2%)	0 (0.0%)	0 (0.0%)
URTICARIA	2 (1.2%)	0 (0.0%)	0 (0.0%)
Second Course Day 15			
Total pts with at least one IRR	**8 (4.7%)**	**6 (3.6%)**	**8 (4.7%)**
Total number of IRR	**9**	**8**	**8**
SYMPTOM			
HEADACHE	1 (0.6%)	4 (2.4%)	2 (1.2%)
THROAT IRRITATION	1 (0.6%)	2 (1.2%)	2 (1.2%)
FLUSHING	1 (0.6%)	1 (0.6%)	1 (0.6%)
PARAESTHESIA	2 (1.2%)	0 (0.0%)	1 (0.6%)
PRURITUS	2 (1.2%)	0 (0.0%)	1 (0.6%)
PYREXIA	0 (0.0%)	1 (0.6%)	1 (0.6%)
TACHYCARDIA	1 (0.6%)	0 (0.0%)	1 (0.6%)

Multiple occurrences of infusion related reactions (IRR) and symptoms in one individual counted only once. Percentages based on safety population

Serious Adverse Events (SAEs)

During the initial 24 week study period, a total of 41 SAEs occurred in 36 patients across all three treatment arms, with the highest incidences in the placebo + MTX group (8.7%, 15/172) and rituximab 2 x 1g group (8.8%, 15/170) compared with 3.6% (6/167) for rituximab 2 x 0.5g. No particular type of SAE occurred in more than two patients per treatment group. Serious infections were more common in the placebo + MTX group (2.3% [4/172] versus one patient [<1%] in both of the rituximab groups. Gastrointestinal SAEs were more frequent in patients who received high dose rituximab (2.4%, 4/170) compared two and one subjects in the placebo and low dose rituximab groups respectively. Three GI SAEs were noteworthy – a case of intestinal perforation (and pneumonia) in a patient who subsequently died (low dose rituximab group), a patient who experienced pancreatitis and another who developed an ileal ulcer (the latter two patients received high dose rituximab). In addition, one patient who received placebo + MTX developed multifocal cerebral demyelination on Day 16 which persisted throughout the study.

The incidence of SAEs over the 48 week period of observation was similar in both rituximab groups; 7.8% (13/167) for rituximab 2 x 0.5g and 10.0% (17/170) for rituximab 2 x 1g, and no dose related difference in the pattern of SAEs was apparent. In the placebo-switch population, the incidence of SAEs following rituximab 2 x 0.5g was numerically lower than the incidence during the placebo infusion period (3.9% versus 7.8%; 6 versus 12/154 patients respectively). One SAE (pleuropericarditis) that was considered related to rituximab occurred in a switched treatment patient.

Infectious Adverse Events

The overall infection rates during the first 24 weeks of study were similar in subjects treated with rituximab + MTX (41.3% [69/167] for low dose rituximab and 35.9% [61/170] for high dose rituximab) to those who received placebo + MTX (43.0%, 74/172). No differential pattern with respect to type of infection was apparent. The most common type of infections were nasopharyngitis (12%), upper respiratory tract infection (8%), urinary tract infections (5%) and gastroenteritis (3%). Serious infections occurred in 7 patients during the first 24 weeks of trial; 4 subjects (2.3% of 172) in the placebo + MTX group (pneumonia and gastroenteritis), one patient (0.6% of 167) in the rituximab 2 x 0.5g + MTX arm (pneumonia) and two patients (1.8% of 170) in the rituximab 2 x 1g + MTX group (pneumonia). No opportunistic infections were identified. The rate of serious infection at 24 weeks was higher in the placebo + MTX group (8.83 infections per 100 patient-years; 95% CI 4.21, 18.53) than in the rituximab + MTX cohorts (1.26 [95% CI 0.18, 8.92] and 2.46 [95% CI 0.61, 9.83] for low and high dose respectively).

The incidence of infections over 48 weeks was slightly higher in the rituximab 2 x 0.5g + MTX group (57.5%, 96/167) than in the rituximab 2 x 1g + MTX group (50.0%, 85/170). A similar pattern and incidence of infections was identified with upper respiratory tract infection (14%), nasopharyngitis (12%), urinary tract infections (7%), and gastroenteritis (3%) being the most common sites of infection. The incidence of serious infections over 48 weeks was 2% in both rituximab groups (that is, three subjects in each group). All of the serious infections related to the respiratory tract apart from one patient who received rituximab 2 x 0.5g and who subsequently died of abdominal sepsis. None of the patients who experienced serious infections had reduced serum immunoglobulin levels immediately prior to or at the time of onset of the infection. One patient who initially received placebo infusions + MTX and then

switched onto therapy with rituximab 2 x 0.5g + MTX also experienced a serious infection (pleuropericarditis) during Weeks 24 and 48.

Lower Gastrointestinal (GI) Events

The incidence of lower GI events during the 24 week placebo-controlled period was similar in the three treatment groups: rituximab 2 x 1g + MTX group (9.4%, 16/170), rituximab 2 x 0.5g + MTX (9.6%, 16/167) and placebo + MTX (11.6%, 20/172). The most common lower GI events were diarrhoea (4-5%), gastroenteritis (3-6%) and constipation (2%) all of which occurred at a similar or lower frequency in the rituximab dose groups. The estimated rate of any lower GI event was higher in the placebo + MTX group (31.55 [95% CI 21.32, 46.69] events per 100 patient-years) compared with 25.12 [95% CI 16.20, 38.93] and 22.12 (95% CI 13.94, 35.11) in the rituximab 2 x 0.5g and 2 x 1g groups respectively. All but 5 of the lower GI events were CTC grade 1 or 2. Three patients in the placebo + MTX group reported serious lower GI events (2 cases of gastroenteritis and one case of diverticular perforation). One patient in each of the rituximab groups also had serious lower GI events (intestinal perforation in a patient who received rituximab 2 x 0.5g + MTX, and a subject who developed an inguinal hernia in the high dose rituximab group). The estimated rate of serious lower GI events was also lower in the rituximab treatment groups (1.26 [95% CI 0.18, 8.92] and 1.23 [95% CI 0.17, 8.73] events per 100 patient-years in the low and high dose groups respectively) compared with 3.79 [95% CI 1.22, 8.73] in the placebo + MTX arm.

The overall rate of lower GI events at Week 48 was similar in both rituximab groups (12.6% [21/167] for low dose and 14.1% [24/170] for high dose) with the most common events being diarrhoea (6-7%), gastroenteritis (2-3%) and constipation (2%). Correspondingly, the estimated event rate frequency was 22.96 (95% CI 16.20, 38.93) per 100 patient-years in the rituximab 2 x 0.5g + MTX group and 16.95 (95% CI 13.94, 35.11) per 100 patient-years in the rituximab 2 x 1g + MTX group. Two patients, both in the low dose rituximab group, had serious lower GI AEs – abdominal sepsis due to intestinal perforation resulting in death, and another patient who died after serious complications following intestinal perforation and intra-abdominal haematoma.

Cardiovascular (CVS) Events

By Week 24, the incidence of CVS events was slightly higher in the rituximab 2 x 1g group (8.2%, 14/170) and rituximab 2 x 0.5g groups (6.6%, 11/167) compared with the placebo + MTX group (4.7%, 8/172). There was no particular type of AE which delineated this difference. The most common event was hypertension (not including that associated with infusions) but this occurred at a similar frequency between the three treatment groups (2-3%). In total, 5 serious CVS AEs occurred by Week 24 (2 patients in the placebo + MTX group, two subjects in the rituximab 2 x 0.5g group and one patient in the rituximab 2 x 1g group). One patient (treated with rituximab 2 x 0.5g + MTX) experienced myocardial infarction, which led to withdrawal from the study, and subsequently died. Another 4 patients (2 in the placebo group and one in each rituximab dose arm) had symptomatic coronary artery disease.

At the 48 Week comparison, both rituximab dose groups had 8 cardiac AEs recorded (incidence 5%). In addition, another 11 patients (6.6% of 167) in the low dose and 8 subjects (4.7% of 170) in the high dose rituximab had vascular AEs. Hypertension explained the difference in frequency with 10 patients (6.0% of 167) in the low dose rituximab group developed this AE compared to 5 subjects (2.9% of 170) in the high dose rituximab group. One patient who initially received placebo infusions + MTX developed pleuropericarditis after

receiving rituximab 2 x 0.5g during the switch-over treatment period between Weeks 24 and 48.

Malignancy

A total of 4 malignancies developed during the initial 24 week period of the SERENE Study: a case of lung adenocarcinoma in a patient who received placebo + MTX (history of benign lung neoplasm and pulmonary fibrosis); squamous cell carcinoma **(**SCC) of the cervix in a patient in the rituximab 2 x 0.5g group; and one case each of oesophageal and pancreatic adenocarcinoma in two patients who received rituximab 2 x 1g. No additional malignancies were reported in the rituximab treatment groups between Weeks 24 and 48. However, one patient who was initially in the placebo + MTX group and then subsequently received rituximab 2 x 0.5g (Day 171) experienced a malignant melanoma with onset on Day 317.

Deaths

Two patients, both of whom received rituximab 2 x 0.5g + MTX, died during the study. One patient, a 44 year old female, died as a consequence of abdominal sepsis due to intestinal perforation on Day 322 which was 20 weeks after receiving her second course of rituximab 2 x 0.5g. The other patient was a 55 year old male who experienced SAEs of pneumonia (Day 137), intestinal perforation (Day 154) and intra-abdominal haematoma (Day 245) who subsequently died on Day 267 of interstitial lung disease (onset Day 190) which demonstrated both inflammatory and fibrotic components. He received a single course of rituximab 2 x 0.5g at study commencement (Days 1 and 15).

In addition, a further three patients (1 in each group) withdrew due to SAEs prior to Week 24 and then died within 48 weeks of their first infusion of study medication. None of these three events appeared to be related to study medication; two cases of cardiac death due to coronary artery disease and one patient with pancreatic cancer.

Use in Pregnancy

Two patients became pregnant prior to Week 48 in the SERENE Study and a further 5 pregnancies (4 on-going at database lock and one missed abortion) also occurred after the study period. An 18 year old female was identified as pregnant 1.5 months after receiving her second course of rituximab 2 x 1g. She ceased all her medications for RA (MTX, deflazacort and paracetamol) and subsequently delivered a healthy baby at 36 weeks of gestation. The other patient, a 29 year old female, had an estimated date of conception 5 months after receiving a single course of rituximab 2 x 1g. She delivered a healthy baby at 37 weeks of gestation.

Laboratory Parameters

There were no unexpected findings with respect to mean changes in laboratory parameters during the study. The most commonly occurring new grade 3 abnormality was lymphopenia which was more common in the rituximab treatment groups (71.9% [120/167] for low dose and 68.2% [116/170] for high dose) than in those received placebo infusions + MTX (33.1%, 57/172). In the majority of patients, the new significant lymphopenia was a transient abnormality immediately following the infusion of rituximab and corticosteroid treatment. No event of significant lymphopenia was associated with serious or severe infection. Two patients (1 in each of the rituximab treatment groups) developed grade 3-4 neutropenia during the study period but without clinical AEs.

A very low number of patients experienced three-fold or greater elevations in hepatic transaminases (AST and/or ALT) in any treatment group: three patients (1.8% of 170) in the

rituximab 2 x 1g + MTX group and one patient (0.6%) in both the placebo + MTX and low dose rituxumab group.

Vital Signs

No treatment-based trend of change in vital signs was observed apart from transient changes in hyper- or hypotension with infusions in a small overall number of patients (up to 4% of subjects) in each treatment group.

Human Anti-Chimeric Antibodies (HACA)

A total of 38 patients had at least one positive HACA titer during the study: 6 (3.5% of 172) in the placebo + MTX group (and then a further 5 patients [2.9%] following their switch to rituximab 2 x 0.5 g compared with 9.6% (16/167) in the rituximab 2 x 0.5g + MTX group and 6.5% (11/170) in the rituximab 2 x 1g + MTX arm. Twenty-five patients had detectable HACA following their first treatment course (placebo or rituximab) and subsequently received further therapy with rituximab. Within this group, two of 25 patients (8%) reported an IRR with re-exposure, which is an incidence of IRRs consistent with that in the overall safety population during the second treatment course. One of these patients who received rituximab 2 x 1g + MTX experienced a grade 3 IRR characterized by pruritus, rash, throat irritation, and diaphoresis requiring the infusion to be ceased.

Safety conclusions

In the SERENE Study, rituximab was generally well tolerated and demonstrated comparable safety to placebo infusions + MTX up until Week 24. In addition, both doses of rituximab showed a similar safety profile through to Week 48. Consistent with previous experience there is a higher incidence of acute infusion-related reactions with rituximab, particularly occurring on the first infusion. Other common adverse events occurring with active treatment included infections (particularly involving the respiratory and urinary tract), as well as gastrointestinal side-effects (mainly diarrhoea).

MIRROR STUDY

Methods

The analysis of safety was performed on the ITT-M2 population which included all treated patients grouped by the actual treatment they received. The study had a 48 week active treatment period and safety information was recorded on Days 1, 15 and 28, and then every 4 weeks thereafter until week 56 (that is, 4 weeks post-study). Additional visits were required in patients whose peripheral CD19+ B cells remained depleted. The ITT-M2 population had a total of 377 patients allocated to 5 separate groups: n=134 for rituximab 2 x 0.5 g, 2 x 0.5 g; n=119 for rituximab 2 x 0.5 g, 2 x 1 g; n=93 for rituximab 2 x 1 g, 2 x 1 g; n=6 for rituximab 2 x 1 g, placebo + MTX; and n=25 for rituximab 2 x 1 g, 2 x 0.5 g. The last two groups are a subset of the high dose rituximab group that failed to receive the appropriate re-treatment dose of rituximab at Week 24.

Overview of Adverse Events

The overall incidence of AEs in the three main treatment groups over 48 weeks was similar at an incidence of approximately 90% (see Table 17). Most recorded AEs (88.5%) were graded as mild or moderate in severity and required no specific action. Approximately one third of all AEs (excluding IRRs) were considered to be treatment related.

The extent of exposure to study medication and follow-up was similar between the three treatment groups up until Week 48. All but 8 patients (4 in the low dose, two in the dose escalation and two in the high dose rituximab groups) received both infusions in their first

course of treatment. At Week 24, approximately 90% of patients received both infusions of their second course of treatment (121/134 for low dose, 108/119 for dose escalation and 88/93 for high dose rituximab). In total, most patients (~90%) were followed for the planned duration of 48 weeks with the average duration of follow-up being 0.86 years per patient. Hence, the number of years of patient observation was 119.20 for the low dose, 105.76 for the dose escalation and 84.42 for the high dose rituximab group.

Table 17. MIRROR Study

Summary of Safety Profile Over 48 Weeks (Safety population)

		Low dose 2 x 0.5g, 2 x 0.5g +MTX N=134	Dose escalation 2 x 0.5g, 2 x 1g +MTX N=119	High dose 2 x 1g, 2 x 1g +MTX N=93	All patients N=377[a]
Treated first course		134	119	93	377
Treated second course		123	110	88	346
Patient-years of observation		119.20	105.76	84.82	327.44
Average duration of follow-up per patient (years)		0.89	0.89	0.91	0.86
AE incidence – no of patients (%)					
Any AE		121 (90)	106 (89)	85 (91)	342 (91)
Serious AE		15 (11)	21 (18)	16 (17)	56 (15)
AE leading to withdrawal[b]		5 (4)	8 (7)	3 (3)	17 (5)
Death		0	0	0	0
Infusion related reaction					
First course	Any	44 (33)	27 (23)	25 (27)	103 (27)
	Serious	2 (1.5)	0	0	2 (<1)
Second course[d]	Any	22 (18)	16 (15)	17 (19)	60 (17)
	serious	0	0	0	0
Infection	Any	75 (56)	73 (61)	60 (65)	225 (67)
	Serious[c]	4 (3)	4 (3)	2 (2)	11 (3)
Lower GI event	Any	20 (15)	13 (11)	18 (19)	57 (17)
	Serious	0	1(<1)	2 (2)	3 (<1)
Cardiac event	Any	6 (4)	7 (6)	5 (5)	20 (5)
	Serious	1 (<1)	2 (2)	2 (2)	6 (2)
Malignancy	Any	1 (<1)	2 (2)	2 (2)	5 (1)
	Serious	0	1 (<1)	1 (1)	2 (<1)
AE rates per 100 pat-years (95% CI)					
Overall infection rate		121 (103-142)	142 (121-166)	159 (134-188)	141
Serious infection* rate		3.36 (1.26-8.94)	4.73 (1.97-11.36)	2.36 (0.59-9.43)	3.66
Lower GI event rate		21 (14-31)	20 (13-30)	27 (18-41)	21
Serious GI event rate		0	0.95 (0.13-6.71)	2.36 (0.59-9.43)	0.92

a includes the rituximab 2x1g, placebo (n=6) and rituximab 2x1g, 2x0.5g (n=25) groups
b includes 5 patients with events of RA flare (primary reason for w/d=lack of efficacy) and two patients who withdrew for AEs whose day of withdrawal was not available on the database at time of the data cut
c Reported as serious and/or treated with IV antibiotics
d % based on no treated second course

Adverse Events Leading to Withdrawal

Seventeen patients (4.5% of 377; 5 in the low dose, 8 in the dose escalation, three in the high dose rituximab group and one patient treated with 2 x 1 g followed by placebo) withdrew from the study due to AEs, 5 of which were due to an exacerbation of RA (4 from the dose escalation and one from the high dose rituximab group). Of the remaining 12 (3.2% of 377) patients withdrawing because of AEs, two patients withdrew after clinically significant IRRs

to their first infusion (both in the low dose rituximab group) and two patients withdrew due to serious infection (1 subject in the low dose rituximab group experienced sepsis and one patient with bronchopneumonia in the dose escalation rituximab group). The other 8 patients who withdrew did so for a variety of reasons including myocardial ischaemia and Hodgkin's Disease from the high dose rituximab group; subdural haematoma, respiratory hypoxia and pulmonary fibrosis from subjects in the dose escalation rituximab arm; pulmonary hypertension and acute respiratory distress syndrome (ARDS) in patients in the low dose rituximab group; and one patient who developed pruritus and flushing from the 2 x 1 g then placebo group.

Common Adverse Events (>1% incidence)

The three most commonly reported AEs were IRRs (30-39%), exacerbation of RA (15-20%) and upper respiratory tract infections (11-14%; see Table 18 for a summary of common AEs recorded in the MIRROR Study). Other common AEs (that is, occurring at an overall incidence >5%) were bronchitis (8%), diarrhoea (7.5%), urinary tract infection (7%), headache (6%) and cough (6%). More cardiac disorders were considered to be related to the study medication by the investigator in the rituximab groups (7% [9/124] of patients in the 2 x 0.5 g rituximab group and 5% [10/192] of patients in the 2 x 1 g rituximab group versus 1% [2/149] in the placebo group). No discernible pattern of different types of AEs between the three main treatment groups was evident and overall the common AEs described met expectations for rituximab treatment in terms of incidence and type.

Table 18. MIRROR Study

Summary of All Adverse Events with an Incidence Rate of at least 1% (≥ 4 patients overall) over 48 Weeks (Safety Population)

Adverse Event	RIX (2x0.5g,2x0.5g) + MTX N = 134 No. (%)	RIX (2x0.5g,2x1g) + MTX N = 119 No. (%)	RIX (2x1g,2x1g) + MTX N = 93 No. (%)	RIX (2x1g,Placebo) + MTX N = 6 No. (%)	RIX (2x1g,2x0.5g) + MTX N = 25 No. (%)
Pts with at least one AE	121 (90)	106 (89)	85 (91)	6	24 (96)
INFUSION RELATED REACTION	52 (39)	36 (30)	28 (30)	3	8 (32)
RHEUMATOID ARTHRITIS	24 (18)	24 (20)	14 (15)	3	5 (20)
NASOPHARYNGITIS	13 (10)	11 (9)	15 (16)	3	4 (16)
UPPER RESPIRATORY TRACT INFECTION	16 (12)	17 (14)	10 (11)	-	3 (12)
BRONCHITIS	12 (9)	5 (4)	11 (12)	-	2 (8)
DIARRHOEA	13 (10)	5 (4)	7 (8)	1	1 (4)
URINARY TRACT INFECTION	10 (7)	8 (7)	6 (6)	-	-
HEADACHE	11 (8)	5 (4)	5 (5)	-	2 (8)
COUGH	9 (7)	7 (6)	6 (6)	-	-
ARTHRALGIA	6 (4)	9 (8)	2 (2)	1	1 (4)
BACK PAIN	13 (10)	4 (3)	1 (1)	1	-
GASTROENTERITIS	6 (4)	7 (6)	4 (4)	-	1 (4)
HYPERTENSION	6 (4)	5 (4)	6 (6)	-	1 (4)
INFLUENZA	6 (4)	4 (3)	6 (6)	1	-
NAUSEA	6 (4)	2 (2)	7 (8)	-	2 (8)
SINUSITIS	3 (2)	6 (5)	5 (5)	1	-
DEPRESSION	4 (3)	7 (6)	2 (2)	-	-
PHARYNGITIS	2 (1)	2 (2)	3 (3)	1	2 (8)
LOWER RESPIRATORY TRACT INFECTION	2 (1)	4 (3)	1 (1)	1	1 (4)
MUSCLE SPASMS	5 (4)	2 (2)	1 (1)	1	-
PHARYNGOLARYNGEAL PAIN	2 (1)	2 (2)	2 (2)	-	3 (12)
INSOMNIA	5 (4)	1 (<1)	-	1	1 (4)
RASH	1 (<1)	3 (3)	2 (2)	1	1 (4)
HEPATOTOXICITY	-	3 (3)	2 (2)	-	2 (8)
MUSCULOSKELETAL PAIN	2 (1)	1 (<1)	1 (1)	2	-
DERMATITIS	1 (<1)	2 (2)	-	1	-
ECZEMA	-	1 (<1)	1 (1)	-	2 (8)
HYPERCHOLESTEROLAEMIA	1 (<1)	-	2 (2)	1	-
TOOTHACHE	2 (1)	1 (<1)	-	1	-

Infusion-related events

A higher proportion of patients experienced IRRs during their first infusion of the first course (23.7% [60/253] for rituximab 0.5g and 23.4% [29/124] for rituximab 1g) compared to subsequent infusions (10% with second infusion of first course; and 12% and 8% for the first and second infusions of the second course over all doses of rituximab). These observations are consistent with previous experience with rituximab. Overall, approximately 75% of all IRRs had an onset either during the infusion (~50%) or after the infusion but while the patient was still in the clinic (~25%). This pattern of onset was consistent across the rituximab doses and also infusion sequence. The same types of IRRs were recorded for the varying doses of rituximab at a similar incidence. The most common IRRs included flushing (4.2-6.7%), headache (3.2-6.7%), throat irritation (2.5-4.3%), pruritus (3.0-6.5%), and rash (2.2-3.7%).

Five patients had clinically significant IRRs: 4 in the rituximab 2 x 0.5g, 2 x 0.5g group and one patient in the rituximab 2 x 0.5g, 2 x 1g arm. Three of the 5 IRRs occurred during the administration of their first infusion and had features consistent with either anaphylactic reaction or angioedema. Two of the patients subsequently withdrew from the study but one patient had subsequent infusions without complications. Another patient in the low dose rituximab group had recurrent headaches with all 4 infusions during the study which onset either during the infusion or soon after leaving the clinic.

The patient who had a grade 3 IRR in the dose escalation rituximab arm suffered bronchospasm, flushing, pruritus and laryngospasm during the infusion of rituximab 2 x 1 g (treatment Day 15 of course 2). All 5 patients were HACA negative.

In addition to patient withdrawals, a total of 56 patients (14.9% of 377) had their infusions modified or interrupted with no clear difference between treatment regimens (high dose rituximab [18.3%, 17/93), dose escalation rituximab [14.3%, 17/119] and low dose rituximab [13.4%, 18/134]. Most of the dose modifications or interruptions were due to IRRs (41 patients with 41 events, usually of a minor grade) or infections (11 events in 10 subjects). A possible dose related relationship was observed for infusion modifications or interruptions due to IRRs: 2-fold higher incidence in the high dose rituximab group (16.1%, 15/93) compared to low dose rituximab (8.2%, 11/134). The dose escalation rituximab group incidence was 11.7% (14/119). There was no apparent rituximab dose relationship with other AEs (including infections) resulting in dose modification for safety reasons.

Serious Adverse Events (SAEs)

During the 48 week study period, a total of 56 patients (14.9% of 377) experienced SAEs with no clear difference in type of events across the three main treatment groups but at a slightly lower frequency in the low dose rituximab group (11.1%, 15/134) compared with 17.6% (21/119) for dose escalation rituximab and 17.2% (16/93) for high dose rituximab. No particular type of safety-related SAE occurred in more than two patients per treatment group. The rates of serious infection (12 events in 11 patients in total), serious GI events (3 patients/events) and serious cardiac events (6 patients/events) were similar in the three treatment groups.

Infections

The overall incidence and type of infections was similar in patients across the different treatment regimens (55.9% [75/134] in the low dose, 61.3% [73/119] in the dose escalation and 64.5% [60/93] in the high dose rituximab group). The incidence rate (120-159 per 100 patient-years) of all infections is comparable between the three main treatment groups. The majority of infections were minor infections of mild to moderate severity. Upper respiratory tract infections (under various reported terms) were the most commonly reported infections: upper respiratory tract (13%), nasopharyngitis (11%), bronchitis (9%), influenza (4%), sinusitis (3%) and pharyngitis (2%). Other common types of infections were urinary tract infections (10/134 patients [7.4%] in the low dose, 8/119 patients [6.7%] in the dose escalation and 6/93 subjects [6.5%] in the high dose rituximab) and gastroenteritis (6/134 patients [4.5%] in the low dose, 7/119 subjects [5.9%] in the dose escalation and 4/93 patients [4.3%] in the high dose rituximab). Of note, oral herpes infection was experienced by one patient (0.7%) in the low dose group, 4 patients (3.4%) in the dose escalation arm and two patients (2.2%) in the high dose rituximab group. Lower respiratory tract infections are more likely to be of bacterial origin and it is bacterial infections that are of particular concern in B-cell depleted patients. Two patients (1.5% of 134) in the low dose rituximab group, 4 patients (3.4% of 119) in the dose escalation arm and one patient (1.1% of 93) in the high dose rituximab group developed lower respiratory tract infections.

In total, 11 patients (3.0% [4/134] of patients in the low dose rituximab group, 3.4% [4/119] of patients in the dose escalation rituximab arm, and 4.3% [3/93] of patients in the high dose rituximab group) experienced 12 serious infections, none of which were fatal. Serious infections were mainly bacterial in origin and most resolved with antibiotic therapy. Regarding the types of infections, there were 6 cases of respiratory tract infection, two gastrointestinal infections (gastroenteritis and diverticulitis) and three other events

(pyelonephritis, post-operative wound infection and an infected skin ulcer). In addition, there was a case of presumed sepsis caused by apical ostitis after a dental procedure. As expected, rituximab-treated patients were B-cell depleted during the study period and at the time of onset of the infection 8 of 11 patients had normal serum immunoglobulin concentrations. For three patients (three cases of respiratory infection and one patient with gastroenteritis as well), serum IgM concentrations were low at or immediately prior to the serious infectious AE. The overall incidence rate (2.36-4.73 per 100 patient-years) of serious infections within the MIRROR Study is comparable within the three main treatment groups and within expectation for the studied population (see Table 17).

Lower Gastrointestinal (GI) Events

The incidence of any lower GI event was slightly different in the three main treatment groups: - low dose rituximab (14.9%, 20/134), dose escalation rituximab (10.9%, 13/119) and high dose rituximab (19.4%, 18/93). However, the estimated rate of any lower GI event was similar in the three main treatment groups with wide and overlapping 95% confidence intervals: 20.97 (95% CI 14.7, 31.04) events per 100 patient-years for low dose, 19.86 (95% CI 12.95, 30.45) for dose escalation and 27.12 (95% CI 18.02, 40.81) for high dose rituximab (see Table 17). The most common lower GI events were diarrhoea (8-10%), gastroenteritis (4-6%) and constipation (2%) all of which occurred at a similar frequency in the different rituximab dose groups.

Five of the lower GI events were classified as CTC grade 3. Three patients in the high dose rituximab group reported serious lower GI events (1 case each of diarrhoea, inguinal hernia and diverticulitis – the latter two patients requiring surgery). One patient in each of the dose escalation and dose descalation rituximab groups also had gastroenteritis which was classified as serious lower GI events. The estimated rate of serious lower GI events was higher in the high dose rituximab (2.36 events per 100 patient-years [95% CI 0.59, 9.43]) compared with 0.95 [95% CI 0.13, 6.71] events per 100 patient-years in the dose escalation and 0 in the low dose rituximab arms.

Cardiovascular (CVS) Events

By Week 48, the overall incidence of CVS events was similar in the three main treatment groups: 14.9% (20/134) for low dose, 13.5% (16/119) for dose escalation and 16.1% (15/93) for high dose rituximab. The most common event was hypertension (not including that associated with infusions) which occurred at a similar frequency between the three treatment groups (4-6%; 6 patients in the low and high dose groups and 5 in the dose escalation arm). Six serious CVS AEs occurred: three patients with myocardial ischaemia (one in each of the three main treatment groups) and singular cases of pericarditis (high dose rituximab), atrial fibrillation (high and then with low dose rituximab) and cardiac valve disease (patient in the dose escalation rituximab group).

Malignancies

Five patients reported malignancies during the 48 week study. There were three skin cancers: two patients developed basal cell carcinoma (1 subject each from the low dose and dose escalation rituximab groups) and one patient had a squamous cell carcinoma (rituximab 2 x 0.5 g, 2 x 1 g). Two patients in the high dose rituximab group experienced cancers; Hodgkin's disease and a benign thyroid neoplasm.

Deaths

No deaths occurred during the reporting period for this study.

Laboratory Test Value Abnormalities

Identical percentages of patients in the three main rituximab treatment groups had newly occurring CTC grade 3 lymphocyte abnormalities (63%) and CTC grade 4 lymphocyte abnormalities (10%). In the majority of patients (~80%), the new CTC grade 3 or 4 lymphopenia was only recorded immediately after the infusions on Day 1 and 15, and cell numbers subsequently recovered. This may be due in part to the short-term effect of the corticosteroid treatment on T-cell counts. Three patients in each treatment group had grade 3 or 4 abnormalities of serum transaminases.

Human anti-chimeric antibodies

Of the 342 patients with post-baseline samples, 23 (6.7%) were positive for HACA on at least one occasion during the study. At Week 24, a higher proportion of patients who received rituximab 2 x 0.5g were HACA positive (5.1% [6/118] for the low dose and 7.3% [8/109] after the first course of rituximab in the dose escalation group) compared to patients treated with high dose rituximab (2.3% [2/86]). By Week 48, the frequency of positive HACA was generally lower but still slightly higher at 4.3% [5/115] in those who received further doses of 0.5g compared to 1.6% [3/191] for patients who received rituximab 2 x 1g at the week 24 re-treatment. Three of the 16 patients (18.8%) with positive HACA titers at Week 24 experienced IRRs during their second exposure to rituximab which is consistent with the overall incidence of IRR during Course 2 of therapy (~17%). In addition, there was no association between HACA positivity and lack of efficacy response.

Safety conclusions

The MIRROR Study demonstrated that adverse reactions related to rituximab are principally acute infusion reactions (particularly with the first infusion) and, to a lesser extent, an increased risk of infection. The proportion of patients affected by adverse events is similar between the higher dose (2 x 1g) compared to the low dose (2 x 0.5g) of rituximab although there was a trend to a higher event rate in the high dose group for some particular AEs like serious lower GI events. The dose escalation regimen of rituximab did not reveal any new safety signals.

SUNRISE STUDY

Methods

The analysis of safety was performed on two patient populations: the overall study population which included all treated patients who received any amount of study drug (that is, during the open-label or controlled re-treatment periods) and the specific re-treatment population (that is, any subject randomized to and received drug in the re-treatment phase). The study collected safety information over a 48 week period on Days 1, 15 and 28, and then every 8 weeks thereafter. The overall safety population had a total of 559 patients in three groups: n=84 for subjects not randomized to re-treatment; n=155 for placebo re-treatment; and n=320 for rituximab re-treatment. The last two groups (with same patient numbers) also formed the re-treatment safety population.

The extent of exposure to study medication was similar between the two re-treatment groups. All patients in the re-treatment population (both arms) received both infusions in their first course of rituximab and all but 5 patients (6.0% of 84) in the no re-treatment group did so as well. At re-treatment, 96.3% (308/320) of patients in the rituximab re-treatment group and 98.7% (153/155) of subjects in the placebo re-treatment arm received both infusions of their second course of treatment.

Overview of Adverse Events

The overall incidence of AEs in the three groups over 48 weeks of follow-up was similar: 85.7% (72/84) for the non-randomized patients, 91.6% (142/155) for the placebo re-treatment group and 89.1% (285/320) for the rituximab re-treatment subjects. Most recorded AEs (>80% for all three groups) were graded as mild or moderate in severity and required no specific action. Approximately 40% of all AEs (excluding IRRs) were considered by the investigator to be treatment related.

Adverse Events Leading to Withdrawal

The rate of withdrawal from the study was higher in the non-randomized group (17.9%, 15/84) than in either of the re-treatment groups (7.1% [11/155] in the placebo re-treatment arm and 3.1% [10/320] in the rituximab re-treatment group). The most frequently reported event that led to withdrawal was an exacerbation of RA (2 [2.4% of 84] from the non-randomized group, 7 [4.5% of 155] from the placebo re-treatment group and 4 [1.3% of 320] from the rituximab re-treatment group). The remaining patients withdrawing because of safety-related events did so for a variety of reasons including dizziness, asthma, chest discomfort, and hyper- or hypotension. There was no specific pattern of AEs related to specific treatment groups.

Common Adverse Events (>4% incidence)

The three most commonly reported AEs were exacerbation of RA (15.3-28.4%), upper respiratory tract infection (9.5-19.1%) and headache (11.6-15.6%; see Table 19). Common AEs with an event frequency at least 2-fold higher in the rituximab re-treatment group compared to the placebo re-treatment group were fatigue, flushing, dizziness, pyrexia, vomiting, pharyngolaryngeal pain, pneumonia, chest discomfort and hypotension. Some of these AEs were infusion associated.

Table 19. SUNRISE Study

Adverse Events Occurring from Day 1 to Week 48
(Reported in ≥4% of Subjects in Any Group): Safety-Evaluable Population

MedDRA Preferred Term	Subjects Not Randomized to Retreatment (n=84)	Retreatment Safety Population	
		Placebo Retreatment (n=155)	Rituximab Retreatment (n=320)
Total [a]	72 (85.7%)	142 (91.6%)	285 (89.1%)
Rheumatoid arthritis	19 (22.6%)	44 (28.4%)	49 (15.3%)
Upper respiratory tract infection	8 (9.5%)	28 (18.1%)	61 (19.1%)
Headache	13 (15.5%)	18 (11.6%)	50 (15.6%)
Urinary tract infection	5 (6.0%)	16 (10.3%)	39 (12.2%)
Sinusitis	5 (6.0%)	15 (9.7%)	38 (11.9%)
Nausea	5 (6.0%)	14 (9.0%)	32 (10.0%)
Arthralgia	5 (6.0%)	15 (9.7%)	28 (8.8%)
Pruritus	10 (11.9%)	15 (9.7%)	22 (6.9%)
Fatigue	8 (9.5%)	6 (3.9%)	30 (9.4%)
Diarrhea	8 (9.5%)	9 (5.8%)	23 (7.2%)
Cough	3 (3.6%)	14 (9.0%)	20 (6.3%)
Bronchitis	4 (4.8%)	13 (8.4%)	19 (5.9%)
Back pain	5 (6.0%)	9 (5.8%)	21 (6.6%)
Flushing	7 (8.3%)	2 (1.3%)	22 (6.9%)
Nasopharyngitis	4 (4.8%)	9 (5.8%)	18 (5.6%)
Rash	4 (4.8%)	7 (4.5%)	20 (6.3%)
Dizziness	2 (2.4%)	2 (1.3%)	26 (8.1%)
Pyrexia	5 (6.0%)	4 (2.6%)	19 (5.9%)
Vomiting	5 (6.0%)	4 (2.6%)	15 (4.7%)
Throat irritation	1 (1.2%)	5 (3.2%)	16 (5.0%)
Bursitis	1 (1.2%)	4 (2.6%)	16 (5.0%)
Insomnia	2 (2.4%)	5 (3.2%)	14 (4.4%)
Edema, peripheral	2 (2.4%)	5 (3.2%)	13 (4.1%)
Pharyngolaryngeal pain	0	3 (1.9%)	17 (5.3%)
Depression	1 (1.2%)	5 (3.2%)	13 (4.1%)
Pain in extremity	2 (2.4%)	3 (1.9%)	13 (4.1%)
Pneumonia	1 (1.2%)	3 (1.9%)	14 (4.4%)
Erythema	1 (1.2%)	7 (4.5%)	4 (1.3%)
Chest discomfort	4 (4.8%)	0	6 (1.9%)
Hypotension	4 (4.8%)	0	6 (1.9%)

MedDRA=Medical Dictionary for Drug Regulatory Affairs.

Notes: Includes treatment-emergent adverse events that started on or after the first day of open-label treatment up to Week 48 or early termination. Multiple occurrences of a specific adverse event for a subject are counted once in the frequency for the adverse event. Multiple occurrences of adverse events within a specific body system for a subject are counted once in the frequency for the body system. Retreatment is classified according to actual treatment received.

[a] Represents the number of subjects with at least one adverse event.

Infusion-related events

Of the 559 subjects who received the first open-label infusion course, a total of 146 (26.1%) subjects (40.5% [34/84] for non-randomized arm, 19.4% [30/155] for placebo re-treatment group and 25.6% [82320] for rituximab re-treatment) experienced IRRs. The most common type of IRR was pruritus (6.4%, 36/559) followed by headache (5.9%, 33/559) and flushing (3.4%, 19/559). Of the 475 patients who received re-treatment infusions, a total of 66 subjects (13.9%) experienced IRRs with a higher incidence in the rituximab re-treatment group (15.9%, 51/320) compared to the placebo re-treatment arm (9.7%, 15/155). The same types of

IRRs were recorded for the re-treatment infusions but at lower frequency. The most common IRRs during the re-treatment courses (affecting more than two patients in either re-treatment group) with a higher incidence in the rituximab group were throat irritation (2.8% [9/320] for rituximab versus 0 for placebo), headache (2.5% [8/320] for rituximab versus 1.9% [3/155] for placebo), flushing (1.9% [6/320] for rituximab versus 0 for placebo), and nausea (1.3% [4/320] for rituximab versus 0.6% [1/155] for placebo). Surprisingly, pruritus was reported more frequently with placebo infusions (2.6% [4/155] for placebo versus 0.3% [1/320] for rituximab).

No patients experienced serious IRRs during the re-treatment infusions and one patient (subsequently in the non-randomized arm) had hypotension with their infusion which was classified as serious.

Serious Adverse Events (SAEs)

During the 48 week study period, SAEs occurred in 17.4% (27/155) of placebo re-treatment patients, 15.9% (51/320) of rituximab re-treatment subjects and 19.0% (16/84) of patients not randomized to re-treatment. Pneumonia, RA and back pain were the most common SAEs with the only difference in type of events across the three groups being a slightly higher frequency of pneumonia in the rituximab re-treatment group (1.6%, 5/320) compared with 0.6% (1/155) for the placebo re-treatment arm and 1.2% (1/84) for subjects not randomized to any re-treatment. Three of the 5 cases of pneumonia in the rituximab re-treatment group occurred during the initial open-label period of the study (that is, prior to randomization).

Infections

The overall incidence of infections was higher in patients who received re-treatment (61.6% [197/320] for rituximab re-treatment and 56.1% [87/155] in the placebo re-treatment group) compared with 41.7% [35/84] of subjects who were not re-randomized. The most commonly reported infections were upper respiratory tract (18-19%), urinary tract (10-12%), sinusitis (10-12%), bronchitis (6-8%) and nasopharyngitis (5-6%). None of these minor infections occurred at a significantly higher frequency in either of the re-treatment groups apart from gastroenteritis (16 of 320 patients [5.0%] in the rituximab re-treatment group compared with three of 155 patients [1.9%] in the placebo re-treatment group). In addition, three patients (0.9% of 320) in the rituximab re-treatment group experienced Herpes Zoster infection compared to 0 patients in the placebo re-treatment arm.

In total, 10 patients (2.2% [7/320] of patients in the rituximab re-treatment group and 1.9% [3/155] of patients in the placebo re-treatment group) experienced 17 serious infections (14 events in patients of the rituximab re-treatment group and three events in patients of the placebo re-treatment group), none of which were fatal. Pneumonia was the only type of serious infection that affected more than one patient per re-treatment group (2 cases in the rituximab group and one case in placebo group).

Malignancies

Eight patients reported 10 malignancies during the 48 week study. There were three non-melanoma skin cancers (2 patients in the placebo and one patient in the rituximab re-treatment groups) and an additional patient in the placebo re-treatment arm had a melanocytic naevus. One other patient in the rituximab re-treatment group had a thyroid neoplasm and one non-randomized subject developed colon cancer.

Deaths

Three deaths, all of which were considered by the investigator to be unrelated to study medication, occurred during the study. Two deaths occurred in patients in the rituximab re-treatment group and included one sudden death of unknown cause and a subject suffered a cardiorespiratory arrest in the setting of *Clostridium difficile* colitis (Day 364, that is, after Week 48). The patient in the placebo re-treatment group died of Acute Respiratory Distress Syndrome.

Laboratory Test Value Abnormalities

No significant treatment differences in mean or newly occurring serious abnormalities were identified by this study.

Human Anti-Chimeric Antibodies (HACA)

In total, 48 patients with post-baseline samples (8.9% of 541) were positive for HACA on at least one occasion during the study (23 patients in each of the re-treatment groups [15.0% of 153 subjects for placebo re-treatment and 7.5% of 308 subjects for rituximab re-treatment]; and two subjects [2.5% of 80] in the group not randomized to re-treatment). There was no association between HACA positivity and an increased frequency of any type of AE (including IRRs and infections).

Safety conclusions

The SUNRISE Study demonstrated that re-treatment with rituximab was associated with a similar safety profile as placebo infusions (with continued background non-biological DMARD therapy) apart from a slightly higher incidence of IRRs, and possibly serious infection (particularly affecting the lower respiratory tract).

SAFETY FOLLOW-UP REPORTS FOR REFLEX STUDY and DANCER

Both of these Phase III studies, REFLEX and DANCER, were pivotal in rituximab obtaining its original marketing approval in Australia for the indication of patients with severely active RA. Both studies had 24 week controlled periods and then extension periods whereby patients could be followed for up to 104 weeks from study commencement. This submission contained the two year Safety Follow-Up (SFU) reports for these trials.

SFU for REFLEX Study

The data for this trial were presented in two safety populations. Firstly, those subjects who received study medication according to their randomization into one of two treatment groups; placebo infusions + MTX (n=208) and rituximab 2 x 1g + MTX (n=308). Secondly, the safety data for patients originally treated with placebo infusions and then who received rescue therapy with rituximab 2 x 1g between Weeks 16 and 24 of the study was presented (n=92). In addition, the study report presented the data on infections in a subset of patients with long-term (at least 104 weeks) of persistent circulating B-cell depletion (n=20).

(a) Safety ITT Population

This section of the addendum report was difficult to interpret as AEs were presented together over the entire 104 weeks of follow-up (that is, the data from the 24 week double-blind period was generally incorporated into the extension period follow-up data). In addition, the duration of follow-up was significantly greater in the rituximab group (358.02 patient-years) compared with 131.36 patient-years for the placebo infusion + MTX arm. The rate of AEs at 104 weeks was higher in the placebo + MTX group compared with the rituximab group (5.49 AEs per year for placebo + MTX and 3.68 AEs per year for rituximab + MTX). The rate of SAEs was comparable between the two treatment groups at 104 weeks (0.205 SAEs per year placebo +

MTX and 0.165 SAEs per year for rituximab + MTX). Furthermore, the overall rate of infections was comparable between the two treatment groups at 104 weeks (1.2332 infections per year [95% CI 1.0572, 1.4385] for placebo + MTX and 0.905 [95% CI 0.8116, 1.0091] infections per year for rituximab + MTX). However, the rate of serious infections per patient year was numerically higher (but with wide and overlapping 95% CIs) in the rituximab group at 0.0587 (95% CI 0.0383, 0.09) compared with 0.0305 (95% CI 0.0114, 0.0813) for placebo + MTX. No opportunistic infections were observed over the 104 weeks of follow-up. In this study, no new safety signals emerged from the 104 week data to indicate an increased incidence or type of AEs with rituximab.

In total, 4 deaths (1 patient in each treatment group from the controlled period, and two patients who initially received placebo infusions and then had rescue therapy with rituximab) occurred during the 104 week of study follow-up. None of the deaths appeared to be related to study medication. In particular, the patient initially treated with rituximab died of intestinal adenocarcinoma 256 days after her second infusion. For the two patients who received rescue therapy with rituximab, one died of myelodysplastic syndrome 217 days after the second infusion of rituximab and the other patient had a sudden unexplained death (no autopsy performed) 339 days after her last rituximab infusion.

Malignancies were recorded in 7 (3.4% of 208) patients who received placebo infusions + MTX and 8 (2.6% of 308) subjects randomized to rituximab. Skin cancers were the most common type of malignancy affecting two patients in the placebo before 24 weeks (basal cell carcinoma and "skin neoplasm"), one patient in the rituximab group before 24 weeks (malignant melanoma) and 4 patients in the rituximab group in post-controlled Phase (2 basal cell carcinomas and squamous cell carcinomas). The other cancers were single instances of different malignancies: one case each of breast and gastric cancer in subjects from the placebo infusion + MTX group, and one case each of intestinal adenocarcinoma and prostate cancer in subjects enrolled in the rituximab arm. No cases of lymphoma were reported during the 104 weeks of follow-up.

(b) Placebo Switch Patient Population

Although the numbers in each of the follow-up groups were equal (n=92), the duration of follow-up was approximately 3-fold greater in the subjects after receiving rescue therapy with rituximab compared to those that stayed in the placebo infusion alone group (99.05 versus 33.63 patient years, respectively). The only safety related AE with a higher rate of occurrence in the treatment switch population (that is, after the receipt of rescue therapy with rituximab) was serious infections: 0.0606 infections per patient year (95% CI 0.0272, 0.1349) for the placebo to rituximab switch population compared with 0 for the placebo infusion + MTX group. Six serious infections in total affected patients switched to rituximab: three respiratory tract infections and singular cases of gastroenteritis, *Clostridium difficile* colitis and pyelonephritis. Surprisingly, the incidence of acute infusion reactions in patients originally treated with placebo infusions and then switched to open-label rescue with rituximab (2 x 1g) was lower at 20.7% (19/92) than that recorded with their original placebo infusions (26.1%, 24/92), as well as the original blinded rituximab infusion population (28.9%, 89/308).

(c) Long-Term B-cell Depletion Population

Twenty of 43 patients (42 treated with rituximab [36 upfront and 6 as rescue therapy] and one administered placebo infusions only + MTX) with B-cell levels below the lower limit of normal for at least 104 weeks, completed two years of follow-up. Twenty-four of the 36 (67%) original rituximab treated patients and 5 of the 6 (83%) placebo switch patients who received rescue treatment with rituximab experienced at least one infection, and two of the 24 (8.3%) rituximab patients had serious infections as did one of the 6 (16.7%) rescue patients. In comparison, 47.1% (243/516) of patients in the overall safety population (with rescue therapy data excluded) experienced infections and 4.8% (25/516) had serious infections. Hence, although the overall patient numbers are low it appears that patients with prolonged B-cell depletion appear to have a higher incidence of both overall and serious infections. The types of infections did not appear to be different in this sub-population with respiratory and skin/soft tissue infections predominately accounting for the types of infection in this group of subjects.

SFU for DANCER Study

The data for this trial were presented in two safety populations. Firstly, those subjects who received study medication according to their original randomization (that is, three original and distinct treatment groups; placebo infusions + MTX [n=149], rituximab 2 x 0.5g + MTX [n=124] and rituximab 2 x 1g + MTX [n=192]). Secondly, the safety data for the patients who received rescue therapy with rituximab 2 x 1g between Weeks 16 and 24 of the study (n=57): placebo switch patients (n=48) and rituximab 2 x 0.5g switch patients (n=9).

(a) Safety ITT Population

The overall incidence of AEs at 104 weeks was numerically higher in the rituximab treatment groups compared with placebo infusions + MTX (90% [172/192] for high dose rituximab and 85% [105/124] for low dose rituximab versus 78% [116/149] for placebo infusion group). However, the duration of follow-up was greatest in the rituximab 2 x 1g group (244 patient-years for high dose rituximab compared with 131 patient-years for both the low dose rituximab and placebo infusion arms). As such, although there were a higher number of infections in the rituximab treatment groups (48% [92/192] for rituximab 2 x 1g and 45% [56/124] for rituximab 2 x 0.5g compared with 34% [50/149] for placebo infusion) the adjusted rate of infection for patient-years of exposure was similar in the rituximab groups with overlapping 95% CIs. Infections per 100 patient-years were 74.17 (95% CI 64.11, 85.80) for rituximab 2 x 1g versus 84.59 (95% CI 70.23, 101.89) for rituximab 2 x 0.5g and 71.4 (95% CI 58.33, 87.40) for placebo + MTX. Serious infections were infrequent and were recorded for 7 (3.6% of 192) of patients in the rituximab 2 x 1g group, 2 subjects (1.6% of 124) in the rituximab 2 x 0.5 g arm and 5 patients (3.4% of 149) in the placebo + MTX group. There were no cases of de novo or reactivated tuberculosis during the 104 week SFU although two patients with a history of tuberculosis (1 was given ionized prophylaxis with study medication) received rituximab treatment. No other opportunistic infections associated with rituximab therapy were recorded.

The incidences of non-infectious SAEs (particularly, cardiac and gastrointestinal) were very low in the SFU and unrevealing as to any new safety signals with rituximab. In addition, no serious events of malignancy or lymphoma were recorded.

(b) Treatment Switch Patient Population

Prior to receiving rescue therapy, 39/48 (81%) of placebo infusion + MTX patients experienced AEs and after rescue therapy with rituximab 2 x 1g, 44 patients (92%) had AEs. However, the duration of follow-up in these two cohorts was uneven and greater in the subjects after receiving rescue therapy (18.45 vs. 47.84 patient years). With respect to safety

related AEs (that is, other than exacerbation of RA), the incidence of some AEs increased after the receipt of rescue therapy. In particular, infections were more frequent after rescue treatment (31% [15/48] before rescue and 44% [21/48] after rescue) as were nervous system disorders such as headache and dizziness (25% [12/48] before rescue and 35% [17/48] after rescue), skin AEs (15% [7/48] before rescue and 25% [12/48] after rescue) and respiratory disorders such as cough, dyspnoea and throat tightness (13% [6/48] before rescue and 23% [11/48] after rescue). The reason for this difference is mainly explained by the higher incidence of infusion reactions with rituximab compared to placebo infusions, and also by the unequal follow-up periods. Two patients (4% of 48) had SAEs while receiving placebo infusions + MTX (respiratory tract infection and food allergy) and 7 patients (15% of 48) had 9 SAEs after receiving rescue therapy with rituximab. These SAEs included three infections (jaw abscess, cellulitis and wound infection), 4 gynaecological problems (such as menorrhagia), one patient with an intervertebral disc protrusion and one subject experienced a stroke. In addition, one patient died of neutropenic sepsis 409 days after receiving rescue therapy with rituximab 2 x 1g. This 72 year old female patient developed a urinary tract infection after being hospitalized for a fractured femur and abdominal pain. The patient received oral trimethoprim in conjunction with continued MTX, and appears to have developed haematological toxicity from this treatment combination. Blood cultures were positive for both methicillin-resistant *Staphylococcus aureus* and *Klebsiella pneumoniae*.

The total number of patients (9) who received rescue therapy with rituximab 2 x 1g after initial treatment with rituximab 2 x 0.5g was too low to allow meaningful interpretation of the comparative AEs. All 9 patients had AEs before and after the high dose rescue therapy with no particular of AEs to raise new safety concerns.

Conclusions for Extended SFU Populations

The extended duration safety data obtained from REFLEX and DANCER Studies suggest that the incidence and type of adverse events following rituximab therapy is similar between the treatment arms (placebo infusions + MTX and rituximab treatment groups) apart from an increased incidence of serious infections in rituximab treated patients, particularly in those subjects with prolonged depletion of B-cells.

SIERRA STUDY

This study explored the effect of rituximab therapy on the immune response to vaccines in patients with active RA, for which previously there was limited information.

Background

The primary response to vaccination involves antigen being recognized by the immune system and then the production of circulating IgM antibodies after 7-10 days. During a second exposure to the same antigen, heightened humoral or cell-mediated responses occur rapidly, typically within 4-5 days. The second response depends on immunologic memory from the first exposure and is characterized by a marked proliferation of IgG antibody producing B-cells and/or effector T-cells. Based on the action of rituximab upon B-cells, it is possible that antibody production may diminish after the administration of such therapy. Rituximab significantly reduces B-cell numbers in the peripheral blood for at least 6 months after administration and other studies in patients with RA have shown small decreases (2-7%) in immunoglobulin levels (particularly, IgM) over the same time frame. The clinical consequences of these effects are unclear in patients with RA.

Some routinely recommended vaccines include Diptheria-Tetanus, Polio, Pneumococcal, Measles-Mumps-Rubella, Hepatitis B and Influenza virus. Although vaccine induced antibodies may decline over time, re-vaccination or exposure to the organism will often elicit

a rapid protective secondary response consisting of IgG antibodies and/or small amounts of IgM antibodies. The effect of rituximab on immune response to vaccines in patients with RA is unclear.

StudyDesign

SIERRA was a randomized, open-label multicentre study involving patients with active RA. Patients were allocated to one of two treatment groups: rituximab + MTX (n=69) or MTX alone (n=34). The primary study period was 12 weeks for patients in the MTX group, however, 36 weeks of observation was required for patients involved in the rituximab + MTX arm so that the effect of rituximab (approximate duration of effect 24 weeks) could be evaluated. Subjects were stratified by study site and age (18-50 years and 51-65 years). Rituximab was administered intravenously at a dose of 1000mg given on Days 3 and 17 with 100 mg of methylprednisolone given 30 minutes prior to infusion. Usual therapeutic doses of MTX (10-25 mg/week) were given to all patients and any background corticosteroids (< 10 mg/day of prednisolone or equivalent) were continued.

The immunizations that were administered:

- Intradermal injection of *C. albicans* to the volar surface of the forearm. For each subject, DTH response was read at 48-72 hours following each injection by the diameter of induration. For both treatment groups the first skin test was administered on Day 1. The second intradermal test was given after Week 24 for the rituximab group and after Week 12 for the MTX monotherapy arm.
- Intramuscular injection of tetanus toxoid booster vaccine (1 mg [0.5 ml]) into the deltoid muscle. For the rituximab treated patients, serum tetanus toxoid titres were obtained at Day 3, immediately prior to the first administration of study drug, and immediately prior to and 4 weeks after receiving the tetanus toxoid vaccine at Week 24. For the MTX alone subjects, tetanus toxoid was given on Day 1 with serum levels taken immediately prior to, and 4 weeks following the receipt of the vaccine.
- Intramuscular injection of the 23-valent pneumococcal polysaccharide vaccine (0.5 ml) into the deltoid muscle. For the rituximab group, serum levels for antibodies to 12 serotypes were measured at Day 3, prior to the administration of rituximab, and immediately prior to and 4 weeks after vaccine administration at Week 28. For the MTX group, the vaccine was given at Week 4 with serum antibody levels collected for the same 12 serotypes immediately prior to and 4 weeks after vaccination.
- Subcutaneous injection of Keyhole Limpet Haemocyanin (KLH) (1 mg) on two occasions, one week apart. For the patients who received rituximab + MTX the injections were given at Weeks 32 and 33. Serum anti-KLH antibody levels were measured at Day 3, immediately prior to rituximab, and at Weeks 32 (prior to KLH administration) and 36. For the MTX monotherapy patients, KLH was administered at Weeks 8 and 9. Serum anti-KLH levels were taken at Day 1, Week 8 (prior to first dose of KLH) and Week 12.

The rationale for choosing these particular vaccines and antigens is as follows. Tetanus toxoid was given to examine whether rituximab affects antibody production to an antigen that the body has an existing immunity to prior to treatment. The 23-valent pneumococcal vaccine was selected to provide an additional measure for a clinically relevant antigen commonly unknown to the majority of patients. KLH was chosen to test primary humoral response as it is a novel immunogen for most individuals. Responses to intradermal skin testing with *C. albicans* antigens were chosen to measure T-cell memory.

Endpoints

Primary: To compare the percentage of subjects with active RA treated with rituximab + MTX or MTX alone who achieved a humoral immune response to tetanus toxoid adsorbed vaccine. A positive primary response to tetanus toxoid was defined as a 4-fold increase in titre, and a positive secondary response was defined as a 2-fold increase at titre (both measured at 4 weeks post-vaccination).

Secondary endpoints (which were all measured 4 weeks post-vaccination) included:

- Proportion of subjects in each treatment group who developed at least a 2-fold increase from baseline in antibody levels to at least 6 of 12 serotypes in the 23-valent pneumococcal polysaccharide vaccine (another measure of humoral immune response),
- Proportion of subjects in each treatment group with detectable levels of anti-KLH (Keyhole Limpet Haemocyanin) IgG, as wells as the corresponding GMT (geometric mean titre) in each of the treatment groups (measure of humoral immune response),
- Proportion of subjects in each treatment group who maintained a positive response to the *Candida albicans* intradermal test as defined by >5mm of skin induration (measure of Delayed Type Hypersensitivity, DTH, that is, T-cell memory), and
- Additional data on the safety and tolerability of rituximab in patients who receive vaccines.

Results

Of the 69 patients randomized to rituximab + MTX, 62 (90%) completed the 36 week treatment period. For patients allocated to continued MTX monotherapy, 79% (27/34) completed the 12 week primary study period. Most subjects who were given rituximab received the full 1000 mg dose at both infusions. In addition, all patients maintained a stable dose of MTX during the study which was within the protocol defined parameters (10-25 mg/week).

Tetanus Vaccine: Similar proportions of patients in each treatment group obtained the primary immune response (that is, a 4-fold titre increase) to tetanus toxoid: 39.1% (25/64) for rituximab + MTX and 42.3% (11/26) for MTX (difference -3.2%; 95% CI -25.7%, 19.2%). As the 95% CI contained zero, the result was not statistically significant. Results for the secondary immune response (that is, a 2-fold titre increase at 4 weeks post-vaccination) were similarly not statistically significant: 54.7% (35/64) for rituximab + MTX and 61.5% (16/26) for MTX (difference -6.9%; 95% CI -29.2%, 15.5%).

Pneumocoocal Vaccine: Rituximab treated patients had significantly decreased response to the 23-valent pneumococcal vaccine as indicated by a statistically significant difference in the proportion of patients in each treatment group who developed an antibody response 4 weeks post-vaccination to at least 6 of the 12 measured serotypes: 19.0% (12/63) for rituximab + MTX compared with 60.7% (17/28) for MTX (difference -41.7%; 95% CI -62.2%, -21.1%). The same result indicating decreased responses in the rituximab treatment group compared to MTX alone was seen when the analysis was done by the proportion of patients in each group with a response to at least 5 of the 12 serotypes, when 11 of the 12 individual serotypes were directly compared and also when mean post-immunization antibody titres were compared.

KLH Vaccine: Responses to the KLH vaccine were comparatively diminished in the patients who received rituximab. Four weeks after receiving the vaccine, 46.9% (30/64) of rituximab treated patients had a quantifiable anti-KLH titre compared to 92.6% (25/27) of subjects on MTX monotherapy. Likewise, the GMT at 4 weeks post-vaccination for MTX alone subjects was almost 3-fold than for the group who received rituximab in addition to MTX (GMT 539.5 [95% CI 461.54, 630.61] for rituximab + MTX versus GMT 1585.5 [95% CI 1065.15,

2360.7). The lack of overlapping 95% CIs for the GMT between the treatment groups indicates that the result is consistent with a genuine difference in immune response.

Skin Test: The ability to maintain a positive response to the *C. albicans* skin test appeared to be conserved in the rituximab treated patients when compared to the MTX monotherapy subjects. Although the rituximab treatment arm had a lower baseline response rate to the skin test (48.4% [31/64] for rituximab + MTX versus 71.4% [20/28] for MTX alone), the ability to maintain a positive DTH response was similar (77.4% [24/31] for rituximab + MTX versus 70.0% [14/20] for MTX; difference 7.4% [95% CI -17.5%, 32.3%]).

Adverse Events: Treatment with rituximab was generally well tolerated although a numerically higher percentage of patients treated with rituximab + MTX (88.2%, 60/68) experienced AEs during the study (versus 65.6% [21/32] of MTX monotherapy subjects during the primary 12 week study period) and 27 subjects (39.7% of 68) developed infectious AEs (versus 25% [8/32] in the comparator group). Furthermore, three patients (4.4% of 68) who received rituximab + MTX experienced SAEs during the 36 week study period: hip fracture, coronary artery disease and non-specified chest pain. For the comparator group, two patients (6.3% of 32) experienced SAEs over the 12 week study period; exacerbation of RA and ovarian cyst.

Conclusion

In Study U3374g (SIERRA), responses to a protein recall antigen (that is, tetanus toxoid vaccine) were comparable between subjects with RA receiving rituximab + MTX and those receiving MTX alone. However, responses to the clinically relevant pneumococcal polysaccharide vaccine and a novel antigen (KLH) were comparatively decreased. DTH response as a measure of T-cell memory was preserved. The implications of these data are that patients with RA receiving rituximab can receive non-live booster vaccines, but new or polysaccharide containing vaccines should be given prior to initiating rituximab to optimize immune response.

POST-MARKETING EXPERIENCE

A specific post-marketing report for rituximab in RA was not submitted with this application. However, the sponsor is scheduled to submit its next Periodic Safety Update Report (PSUR) for rituximab to the TGA in March 2010.

Nonetheless, the sponsor submitted two bodies of relevant information – an update on the reporting of RA cases developing Progressive Multifocal Leukoencephalopathy (PML) in association with rituximab, and a Risk Management Plan (version 4.0, developed for the EU and dated June 2009).

As of November 2009, a total of 4 cases of PML (including one recently reported case in Australia) have been confirmed in patients receiving rituximab for RA. The global database has a total of more than 80,000 patients receiving rituximab for RA so it would appear that this serious and fatal condition is relatively rare. PML is a progressive demyelinating disease of the central nervous system caused by replicative infection of the JC virus. The condition usually leads to death or severe disability. The mechanism by which rituximab increases the risk of PML remains unclear. PML has also been reported to occur in patients receiving rituximab for lymphoma, but may also be a complication of treatment for cancer or occur in patients receiving other immunosuppressive therapy (notably, natalizumab). The rituximab global database also carries information pertaining to another three fatal cases of PML in association with rituximab therapy for autoimmune disease (2 cases in patients with SLE and one subject with systemic vasculitis). In this submission, two reported cases of PML in RA patients were described. One patient participating in the long term extension phase of

REFLEX developed PML during the follow-up observation period. This patient had clinically responded to rituximab after failing to respond to anti-TNF therapy. Approximately 9 months after receiving her last course of rituximab she was diagnosed with oropharyngeal cancer which was treated with cytotoxic chemotherapy, radiotherapy and an anti-EGFR monoclonal antibody (erbitux). A further 9 months later (that is, 18 months after receiving her last dose of rituximab) she developed PML and died soon thereafter. An other recently reported case (November 2009) of PML occurred in a 62 year old Australian female with RA who received 5 doses of rituximab over 13 months and was diagnosed with PML in September 2009 (confirmed by brain biopsy and supported by neuro-imaging) after the onset of neurological symptoms in May 2009. The patient had received her initial course (2 x 1g) of rituximab in June 2008, a second course (2 x 1g) in December 2008, and then a single 1g dose of rituximab in July 2009. She had received concurrent treatment with oral MTX for the preceding 9 years, and had a history of taking multiple non-biologic DMARDs (including leflunomide and gold) as well as several biologic therapies for RA (etanercept, adalimumab and anakinra).

Clinical Summary and Conclusions

The pharmacology of rituximab in adult patients with RA has been further characterized from the analysis of results involving more than 1400 patients who took part in 4 new Phase III clinical studies included in this submission. The results can be summarized as:-

- Rituximab therapy at either dose (0.5g or 1g) results in an immediate, profound, and sustained depletion of circulating peripheral B-lymphocytes for at least 24 weeks after the administration of a single treatment course,
- The extent and duration of B-cell depletion is similar for each repeat treatment course (up to at least 5 infusion courses),
- Following infusion of rituximab, mean concentrations of immunoglobulins (particularly, IgM) progressively decline from baseline up until 52 weeks of follow-up,
- Rituximab does not appear to have an effect on specific protective antibody responses formed to common bacterial and viral vaccinations before B-cell depletion,
- Rituximab demonstrates positive effects on reducing the levels of biomarkers such as disease associated autoantibodies and serum inflammatory markers like ESR and CRP,
- C_{max} values increased in proportion to the increase in dose suggesting linear pharmacokinetics over the limited dose range of 0.5g to 1g that has been studied in RA,
- C_{max} values and mean elimination half-life (15-22 days) following the first and second infusion of rituximab are comparable over the two treatment courses,
- Common concurrent therapies such as methotrexate and corticosteroids have no clinically significant effect on rituximab pharmacokinetics,
- No clinically significant differences in pharmacokinetics according to age, weight, gender, HACA status or prior anti-TNF therapy have been identified, and
- Population pharmacokinetics demonstrated moderate inter-individual variability.

The clinical efficacy data for the extension of indication in RA is supported by two new pivotal Phase III trials (IMAGE and SERENE) of 24-52 weeks duration which involved a total 1267 patients with severely active RA. Supportive data was also supplied from two new Phase III studies (MIRROR and SUNRISE) and the extension periods of two earlier studies (REFLEX and DANCER) which involved more than 1800 additional patients with severely active RA. There are three aspects to the current submission that will be considered.

Firstly, the sponsor proposes to extend the RA treatment population from "severely active" to "moderate-severe active" RA. The baseline disease characteristics of patients recruited into all of the 4 new Phase III studies had severe (not just moderately) active RA at study entry as evidenced by the median DAS28 scores exceeding 6.5. EULAR criteria defines high disease activity as a DAS28 score >5.1 and moderate disease activity as a DAS28 score of between 3.2 and 5.1. In addition, other markers of RA disease activity at baseline such as the median tender (>25) and swollen joint counts (>15) were consistent with a severely active disease state in all of the Phase III studies.

Secondly, the sponsor is proposing to use rituximab earlier in the disease treatment algorithm for active RA, that is, in patients who are inadequately responding to non-biologic DMARDs rather than the more restrictive current status of commencement in patients who have an inadequate response or intolerance to at least one anti-TNF medication. Both of the pivotal studies in this submission included MTX as background treatment. In SERENE, patients were inadequately responding to MTX therapy at baseline and were continued on MTX throughout the trial with the addition of either placebo or rituximab infusions. For the IMAGE study, patients with recent onset disease started MTX and either placebo or rituximab infusions concurrently at baseline. The other two new Phase III studies (MIRROR and SUNRISE) either recruited patients who were inadequately responding to anti-TNF drugs (SUNRISE) or had a significant sub-population (approximately 25% of subjects) who had failed to respond to biologic DMARDs in addition to MTX. The earlier studies in the dataset (REFLEX and DANCER) recruited patients who had either failed to respond to anti-TNF therapy (REFLEX) or were not responding to at least 1-5 non-biologic DMARDs (DANCER). Hence, the majority of patient exposure in the complete dataset was in patients who were inadequate responders to conventional DMARDs (in particular, MTX was a pre-requisite prior therapy in the vast majority of patients) but significant proportions have also failed biologic DMARDs (mainly anti-TNF medications). It also worth noting that the FDA recently declined the sponsor's application to approve rituximab use in patients with RA who were DMARD-IR (inadequate responders). The main reason for this opinion is that the FDA considers that safety concerns related to the prolonged nature of rituximab-induced B-cell depletion and the risk of PML makes the overall benefit to risk ratio unclear in this less treatment refractory RA population at this point in time. Hence, the FDA has recently maintained the current restriction of rituximab use to the anti-TNF-IR patient group.

The third aspect to this current submission is to extend the treatment indication to include additional disease aspects such as reducing the rate of radiographic progression, improving physical function and induction of major clinical response. The efficacy of rituximab in the controlled studies was assessed by a number of means, which were appropriate, clinically meaningful, and relevant to the sponsor's application. The selected endpoints use well accepted, validated metrics that have served as the basis for previous published studies in RA management, and are consistent with the published guidelines recommended by regulatory authorities. The statistical analysis plans for all of the controlled studies were clearly delineated and appropriate. The degree of statistical significance for the primary endpoints and most of the secondary endpoints provides confidence that the effects seen in the studies are unlikely to be due to random chance. In addition, the result of the sensitivity analyses for the primary endpoints and the secondary analyses of radiographic outcomes, ACR response, EULAR response, functional indices and quality of life measures support the primary endpoints and demonstrate internal consistency for the studies. The study populations were adequately defined to assess efficacy in either severely active early disease (IMAGE) or treatment refractory patients with generally long duration RA (SERENE, MIRROR and SUNRISE). The demographic characteristics of the subjects involved in the controlled studies

were representative of patients who may be encountered in routine Australian clinical practice.

The overall efficacy findings included in this submission demonstrate that:

- Rituximab 2 x 1g + MTX significantly slows the rate of radiographic progression in early (MTX naïve) patients with RA over one year, however, treatment with rituximab 2 x 0.5g + MTX did not achieve this outcome compared to MTX alone (IMAGE),
- Rituximab 2 x 1g + MTX was associated with a sustained reduction in rate of radiographic progression for up to two years in patients who were anti-TNF-IR (REFLEX),
- In both MTX naïve (IMAGE) and MTX-IR (SERENE) patients, treatment with either dose of rituximab (2 x 1g or 2 x 0.5g) + MTX for periods of 24-52 weeks resulted in significantly reduced clinical signs and symptoms, including major clinical response, as well as clinically relevant improvements in physical function (as primarily reflected by improvements in HAQ-DI), and generally significant improvements in other patient reported outcomes (namely, the results for the SF-36 and FACIT-Fatigue scale),
- Treatment with either dose of rituximab (2 x 1g or 2 x 0.5g) + MTX over multiple courses for up to 48 weeks resulted in maintenance of improved clinical and physical function responses (MIRROR and SUNRISE),
- Over the longer-term, treatment to DAS28 remission with rituximab + MTX led to tighter control of disease activity compared with treated on an as required (that is, prn) basis (IMAGE, SERENE and MIRROR).

The safety of rituximab use in RA was assessed by reviewing the data collected from the 3095 patients who received at least part of one infusion of rituximab in the clinical development program. This represents a total dose exposure to rituximab for RA patients that exceeds 7000 patient-years. In general, rituximab was well tolerated in patients concurrently receiving MTX. Individual follow-up time ranges from 16 weeks to more than 5 years with the majority of safety data collected from patients involved in the 5 Phase III controlled studies which were of 24-52 weeks duration. The majority of adverse events were of mild or moderate severity, often self-limiting, and did not necessitate permanent withdrawal from treatment.

The safety analyses from the RA clinical trial program reveal two particular safety risks requiring on-going vigilance: - acute infusion reactions and the risk of infection, particularly with opportunistic organisms. In the placebo-controlled studies, acute infusion reactions (IRRs) during or within 24 hours of the first infusion of rituximab was the primary safety signal. These were experienced by a higher proportion of subjects treated with rituximab (23%, 720/3095) than those who received placebo infusions (~15-17%). The majority of these infusion reactions were of mild to moderate severity and could be managed supportively by decreasing the rate of, or temporarily stopping, the infusion. Dose modifications with rituximab infusions was greatest following the first infusion of the first course (9.3%) and was significantly lower (<5%) with subsequent infusions. Serious IRRs were infrequent (0.5%, 14/3095) and rarely led to withdrawal from the study (1.1%, 34/3095). Using the pooled all exposure population, subsequent treatment courses of rituximab were better tolerated than the first with the incidence of acute infusion reactions declining from 23% during the first course to 3-12% with the first infusion of subsequent treatment courses.

Infectious risk is of particular interest because of the mode of action of rituximab (prolonged B-cell depletion) and patients with advanced RA are at a higher risk of infection than the general population. However, in the all exposure population, the overall rate of serious infection was 4.25 per 100 patient-years (95% CI 3.80, 4.75) which was comparable to that observed in the long-term placebo population of 4.33 per 100 patient-years and consistent with that reported for RA patients receiving anti-TNF medications (5.32 per 100 patient-years) and non-biologic DMARDs (4.11 events per 100 patient-years). The rate and types of serious infection remained stable over time (irrespective of treatment course or rituximab dose). The most common serious infections involved the respiratory tract (approximately 1% of all patients) but other serious infections included cellulitis, urinary tract infection and gastroenteritis. In addition, the rate of serious infection did not increase when rituximab was given following anti-TNF therapies. No clear association between reduced serum immunoglobulin concentrations and infections has been established. Nine patients developed opportunistic infections in the all exposure population database with two of these events being *Pneumocystitis jiroveci* pneumonia. There are also concerns about the risk of developing PML with a total of 4 cases in patients with RA treated with rituximab with one case being in the open-label extension period of REFLEX and one case in the post-marketing setting. In the all exposure population, there are no reports of active tuberculosis, which is a recognized safety concern with TNF inhibitors.

Other than the higher incidence of acute infusion reactions with rituximab therapy, the incidence of overall adverse events, overall serious adverse events, deaths, other adverse events of special interest (namely, cardiovascular and gastrointestinal perforation) and malignancies were comparable across treatment groups and consistent with the expected incidence in RA populations from epidemiological studies. The safety profile of rituximab was consistent across the limited doses and regimens studied, as well as the patient populations and subgroups with the exception of a higher rate of serious adverse events in patients with longer duration, treatment refractory disease compared to early onset RA (MTX naïve) populations and patients whose disease was less well controlled using a "prn treatment" dosing strategy (that is, where patients receive re-treatment with rituximab based on clinical evidence of disease activity [such as increased DAS28 score, or more than 8 tender and swollen joints] at treatment intervals of no less than 16 weeks).

The results of the SIERRA study are also noteworthy in that they demonstrate that rituximab therapy impairs the immune response to developing protective recall responses to new or polysaccharide containing vaccines, thus confirming that immunizations with non-live vaccines should be given prior to rituximab to optimize immune protection. Finally, a total of 12.7% (392/3095) RA patients treated with rituximab have tested positive for Human Anti-Chimeric Antibodies (HACA) during the clinical studies, the majority of whom did so following their course of treatment. The emergence of HACA was not clearly associated with an increased risk of acute infusion reactions (or other adverse events) nor loss of response to subsequent infusions.

Conclusion/Recommendation

In conclusion, the data included with this submission shows a favourable benefit to risk ratio for the use of rituximab in patients with severely active RA of variable disease duration that is refractory to biological DMARD therapy. The three aspects of the sponsor's application for an extended indication in patients with RA are considered below.

1) The clinical evaluator recommended rejection of the sponsor's application to expand the treated disease population to those with moderate-severe active RA and suggested maintaining the current restriction to patients with severely active RA. All of the Phase II-III

clinical studies investigated the effect of rituximab in RA recruited patients with baseline disease characteristics consistent with severely active RA according to EULAR (for example, median DAS28 scores > 6.5) and ACR criteria (for example, median swollen and tender joint counts greater than 15 and 25, respectively).

2) The clinical evaluator recommended rejection of the sponsor's application to upgrade the ranking of rituximab in the treatment algorithm of active RA to second line therapy (that is, in DMARD-IR patients) and suggest maintaining the current restriction to third line therapy (that is, in DMARD and anti-TNF-IR patients) because of an unclear risk: benefit analysis in this less treatment refractory patient population. Although the efficacy outcomes in the pivotal and supporting Phase III studies demonstrate a statistically significant improvement in RA disease activity with the addition of rituximab to continued MTX treatment, the risks associated with prolonged B-cell depletion (in particular, opportunistic infection and the development of PML) make the overall assessment of benefit to risk unclear in the DMARD-IR population, but favourably balanced towards benefit in the anti-TNF-IR patient cohort. For PML in particular, there is no current method to identify which patients are at risk of the condition or successfully treat those who develop the disease, and thus limiting the approved patient population is a practical means of mitigating this risk.

3) The clinical evaluator recommended acceptance of the sponsor's application for the extension of indications in the treatment of RA to the slowing of radiographic progression (that is, the lower level of efficacy claim with respect to structural damage in RA), improving physical function and induction of major clinical response. The submitted dataset shows a consistent effect of rituximab when added to MTX in slowing the rate of radiographic progression in RA as evidenced by lower comparative mean changes in the mTSS and its components over two years of observation, as well as the proportion of patients without radiographic or erosive progression. Improvements in physical function with rituximab has been demonstrated in several of the Phase III studies by statistically significant comparative improvements in HAQ-DI (versus continued MTX monotherapy), and the claim of induction of major clinical response has been justified in the new Phase III studies by comparative treatment improvements in either ACR70 response or the achievement of DAS28 scores < 2.6.

V. Pharmacovigilance Findings

Risk Management Plan

The evaluation of the Risk Management Plan (RMP) submitted by Roche Products Pty Ltd to support an application to extend the indications for use of Rituximab (MabThera) in the treatment of Rheumatoid Arthritis (RA) has been completed. Of note, the RMP incorporated the indications of Non-Hodgkin's Lymphoma (NHL) and Chronic Lymphocytic Leukaemia (CLL) as well as RA.

The Risk Management Plan (RMP) proposed by the sponsor outlines the current and planned safety risk management activities for rituximab in patients with RA and haematological malignancies. The sponsor has identified three important risks (infections, acute infusion reactions and impaired immunization responses) and 8 further potential risks that require on-going surveillance. These important potential risks include the development of PML, reactivation and de novo cases of **hepatitis B** virus (HBV) infection (occasionally resulting in acute fulminant hepatitis), opportunistic infections, malignancy, gastrointestinal perforation, impact on cardiovascular disease, and use in pregnancy and lactation. The pharmacovigilance plan outlines routine expected practices including monthly reviews of spontaneously reported adverse events from various established databases as a means of signal detection, review of all suspected cases of serious adverse events, the provision of Periodic Safety Update Reports to

regulatory authorities and the prompt notification of potential serious and/or unexpected adverse events to healthcare professionals. In addition, the product information and labelling shall refer to all of these safety matters. The RMP also acknowledges and outlines the rationale as to why specific populations were excluded from the clinical trials. In particular, women of childbearing potential were advised to not attempt becoming pregnant for at least 12 months after receiving rituximab because of the long time required for B-cell repletion to occur. Patients with significant cardiac disease were also excluded because of concerns about their ability to tolerate haemodynamic instability which may be associated with acute infusion reactions. Subjects with active HBV infection (defined by the presence of hepatitis B surface antigen (HBsAg) or detectable concentrations of HBV) were excluded from the pivotal clinical trials because rituximab treatment in patients with either RA or haematological malignancy has been associated with reactivations of HBV which sometimes results in a life-threatening acute fulminant hepatitis.

There were a number of recommendations with respect to the PI. Other recommendations which arose from the evaluation of the RMP and commentary on the sponsor's response are presented below.

1. ***The TGA is to be notified when data from the British registry and Swedish epidemiological study will be available and what reports from marketing authorisation holders (MAH) sponsored ongoing and completed clinical studies will be available as final or interim analyses during the calendar year 2010, and how these data will be provided to the TGA.***

The sponsor indicated that an interim analysis of data from the British registry will be available in mid 2011, and from the Swedish registry in late 2010/early 2011.

It is stated that results from the IMAGE, TAME and SUNDIAL studies will be available in 2010.

There is also reference to results from the RABBIT study (no details provided) being available in 2012.

It is noted that these reports will be made available to health authorities. This is considered acceptable.

2. ***The sponsor should prepare a Pharmacovigilance Plan* (*PhVP*) *(and assess the need for additional risk minimisation activities) for specified safety concerns for RA that are addressed for NHL and CLL, but not RA and acute myelogenous leukemia (AML)/*myelodysplastic syndromes (MDS)*: prolonged B-cell depletion, neutropenia and increased risk of grade 3/4 and serious blood & lymphatic AEs in elderly patients, or indicate why a plan is not required at this time and what would trigger the need for it to occur.***

The sponsor does not agree that these are specified safety concerns for RA.

The sponsor indicated that:

- Data from RA clinical trials and post marketing safety databases do not support a need for increased pharmacovigilance around these Adverse Events (AEs) and that they are more frequent in NHL/CLL patients.
- Malignant events are being monitored in the Swedish and British registries, and the study SUNSTONE.
- Information on these is AEs being collected in ongoing long term extension studies in the TNF-IR and DMARD-IR patients, namely, REFLEX extension, SERENE and MIRROR, and,

- Across all MAH sponsored RA studies, patients are followed in extended study follow up until their B cells reach the lower limit of normal or baseline, whichever is lower.

This response does not address the question of why these are listed in the RMP and then not considered (as specifically referenced in the OMSM evaluation report). It is suggested that individual case study reports on these AEs should be presented in the PSURs.

Information on how the Alert Card to warn patients and prescribers of the risk of PML will be implemented and monitored is to be provided.

It is stated that this is an EU-RMP and that it includes commitments not applicable in Australia. This specifically applies to the Alert Card. It is indicated that, as a requirement of the European Medicines Agency (EMA), Alert Cards are standard practice for biologics in the European Union for treatment of RA. This has not been confirmed through a preliminary search of the EMA website.

Notwithstanding this, an alert card for MabThera should be considered for Australia.

3. A boxed warning should be included in the Product Information (PI) to ensure patients and health professionals are clearly informed of the risk of PML with use of rituximab.

The sponsor does not agree to this on the basis that this is a rare event and lack of clarity around a mechanism for this reaction. An incidence of 5/110,000 is cited. Changes to the Australian PI giving more prominence to PML in the Precautions section of this document were suggested as an alternative.

The sponsor notes the presence of a boxed warning on natalizumab. It is considered that a black box warning should be implemented for MabThera for consistency in the PIs.

4. The question of whether use of rituximab in RA patients with severe heart failure (NYHA class IV) or severe, uncontrolled cardiac disease is contraindicated needs to be clarified. If it is not contraindicated, the reason for this is to be provided. If it is contraindicated, this should be included in the PI.

It is indicated that this contraindication was included at the request of the EMA even though it is not identified in the Company Core Data Sheet. It is stated this was not included in the proposed Australian PI as discussed in a previous submission.

The sponsor suggests that the Precautions section of the PI include reference to the lack of safety data in this patient population. This would appear to be a reasonable approach.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Clinical

i) The clinical data relies on 7 studies as follows:

- IMAGE: MTX naïve patients early in the disease course with a primary efficacy objective of radiographic progression at Week 52.
- SERENE: MTX-IR (Inadequate Response) patients with a primary efficacy objective of ACR 20 response rate at Week 24.
- MIRROR: MTX and anti-TNF-IR patients using a dose escalation design for the primary efficacy objective of ACR 20 response rate at Week 48.
- SUNRISE: Anti-TNF-IR patients receiving repeat rituximab treatment for the primary efficacy objective of ACR 20 response rate at Week 48.
- REFLEX: Anti-TNF-IR patients with two years radiographic data.

- DANCER: Dose ranging study that provides two year data.
- SIERRA: Immune response following rituximab.

ii) The clinical evaluator recommended rejection of the extension of indications to DMARD-IR patients, rejection of the expansion of the patient population to include moderate RA patients and approval of the radiographic claim, physical function claim and induction of major clinical response claim in the clinical evaluation report. The issues noted by the evaluator in this submission included:

- Patients in the Phase II-III studies all had severe active RA and not moderate RA.
- Although efficacy was seen in RA patients when rituximab was added to MTX, the risk benefit profile was unfavourable due to prolonged B-cell depletion, opportunistic infection and PML.
- Safety concern of PML in rituximab treated patients given there is no current method to identify those at risk or treat them.

Pharmacology:

iii) New data were provided on the effects on lymphocytes, effects on immunoglobulins and effects on biomarkers. These studies showed a single treatment course immediately and profoundly leads to a sustained depletion in circulating B-cell lymphocytes for at least 24 weeks, immunoglobulins (especially IgM) decline, rituximab does not effect antibody responses formed to common bacterial or viral vaccinations before B-cell depletion, rituximab reduces biomarkers such as ESR and CRP, linear pharmacokinetics, no clinically significant pharmacokinetic interaction with methotrexate or corticosteroids and no clinically significant differences in pharmacokinetics according to age, weight, gender, HACA status or prior TNF inhibitor therapy.

Efficacy:

iv) **IMAGE**: This was a randomised, double blind, placebo controlled, parallel group study of rituximab (RTX; 2x0.5g)+MTX versus RTX (2x1g)+MTX versus placebo+MTX for 52 weeks in 755 MTX naïve patients (30% prior DMARDs) with active, severe, early disease (<6 months). The primary efficacy endpoint of mean change in Total Sharp Score (TSS) at Week 52 was 0.359 for high dose RTX+MTX vs. 1.079 for MTX, $p<0.0004$, which was seen across all subgroups and was driven by a change in the erosion score with no significant change in joint space narrowing. The clinical efficacy endpoint of ACR50 was 64.8% for RTX high dose+MTX versus 41.8% for MTX, $p<0.0001$.The functional endpoint of HAQ-DI was -0.916 for high dose RTX+MTX versus -0.628 for MTX, $p<0.0001$. Major clinical response (ACR70 response maintained for 6 consecutive months) was 21.2% for high dose RTX+MTX versus 8.4% for MTX.

v) **SERENE**: This was a randomised, double blind, active controlled, parallel group study of RTX (2x0.5g) +MTX versus RTX (2x1g)+MTX versus placebo+MTX for 48 weeks in 512 severely active RA patients (mean disease of 7.1 years) with an inadequate response to MTX (majority had taken one other DMARD in the past). The primary efficacy endpoint of ACR20 at Week 24 was 50.6% for RTX high dose+MTX versus 23.3% for MTX, $p<0.0001$ with efficacy maintained to 48 weeks.

vi) **MIRROR**: This was a three year ongoing randomised, double blind, active controlled, parallel group study of different RTX re-treatment options that were 24 weeks apart. Patients had either RTX (2x0.5g for two courses) or RTX (2x0.5g then 2x1g) or RTX (2x1g for two courses) with assessment at 48 weeks for 378 severely active RA patients (median disease of 6.5 years) with an inadequate response to MTX (majority had taken two other DMARDs in the past and 25% had prior biologic DMARDs). Patients stayed on background MTX. The primary efficacy endpoint of

ACR20 at Week 48 was 64.2% for RTX (2x0.5g for two courses) versus 64.6% for RTX (2x0.5g then 2x1g) versus 68.1% for RTX (2x1g for two courses), showing no significant difference between the treatment regimens.

vii) **SUNRISE**: This was a two phase study of an initial RTX treatment (2x1g) during an open label period followed by a randomised, double blind, placebo controlled, parallel group treatment of either RTX (2x1g) or placebo at 6 months later if DAS28-ESR>2.6 at this time. Assessment was at 48 weeks for 561 severely active RA patients (mean disease of 10.6 years) with an inadequate response to TNF inhibitors. Patients stayed on background MTX. The primary efficacy endpoint of ACR20 at Week 48 was 53.5% for RTX re-treatment patients versus 44.6% for placebo re-treatment patients, p=0.0195, indicating some benefit to re-treatment over MTX alone at 48 weeks, but the secondary endpoints mostly showed not significantly better efficacy. HACAs developed at any time in 9.6% of placebo re-treatment patients versus 6.3% in the RTX re-treatment group. Within these small numbers, there did not appear to be a negative correlation with efficacy.

viii) **REFLEX and its extension**: This was an extension of the original REFLEX study submitted to support initial registration and concentrates on radiographic endpoints. This was a randomised, double blind, placebo controlled, parallel group study of RTX (2x0.5g)+MTX versus placebo+MTX for 104 weeks in 520 patients with severe, active disease (mean 12 years) who were inadequate responders to TNF inhibitor therapy. Of the 301 patients originally randomised to the RTX+MTX group, only 197 were available at Week 104 (197 with actual x-ray data and 84 imputed). Of the original 209 patients randomised to placebo+MTX, only 187 were available at Week 104 (135 with actual x-ray data and 52 imputed). Patients also received multiple courses of RTX in both groups (29-30% received two courses, 15-20% had three courses and 10-5% had 4 or more courses). The primary efficacy endpoint of mean change in Total Sharp Score (TSS) at Week 104 showed less progression on RTX with a score of 1.14 for RTX+MTX versus 2.81 for MTX alone, p<0.0001, which was seen across all subgroups and both erosion score (0.72 versus 1.80, p<0.0001) and joint space narrowing (0.42 versus 1.00, p=0.0009). The percentages of patients with no evidence of worsening in TSS were 56.9% RTX+MTX versus 38.5% MTX alone. It should be noted however that in the placebo+MTX group, 88% actually received at least one RTX infusion, which although confounding and could lead to a better than expected result in the placebo+MTX group, was still statistically significant for RTX+MTX.

ix) **DANCER extension**: This was an extension of an original 24 week randomised, double blind, multifactorial study of 9 different treatment regimens or RTX, placebo and corticosteroids on background MTX in severe active RA in patients who had failed 1-5 DMARDs (including TNF inhibitors). Three treatment groups of 465 patients total were formed for the extension study however only 15% of patients were available for the Week 104 analysis. The ACR20 result at Week 104 was 14.8% for RTX (2x1g) versus 7.3% for RTX (2x0.5g) versus 4.1% for placebo+MTX. For major clinical response of ACR70 for 6 months, the result was 6.6% for RTX high dose vs. 5.7% RTX low dose versus 0.8% for placebo. The limited numbers completing make it difficult to interpret the findings but imply a single course of treatment may result in sustained responses in some patients.

Safety:

x) Exposure to RTX was seen in 3095 patients for at least one infusion and 1581 for at least three infusions, with 1669 followed for more than two years, though the majority

were also receiving MTX. The evaluator has provided a comprehensive safety analysis of all studies, with the following particularly noted:

- IMAGE: Adverse events overall and their pattern were similar but lower GI events, adverse cardiovascular events (11.6% versus 8%), infusions reactions, lymphopenia and HACAs (15% versus 4%) were noted, along with a relatively low incidence of serious adverse events.
- SERENE: Adverse events overall and their pattern were similar to MTX and between the two RTX doses with infusion reactions, cardiovascular events, infections, HACAs and lymphopenia noted. Two deaths were noted in RTX patients who had an intestinal perforation amongst other events.
- MIRROR: Infusions reactions and infections were noted, with some events such as GI events and infections being higher on the higher dose of RTX.
- SUNRISE: Re-treatment with RTX showed a similar safety profile to placebo on a background of non-biological DMARDs except for higher incidence of infusion reactions and infections.
- REFLEX: Adverse events and serious adverse events were comparable between groups however serious infections and B-cell depletion were higher on RTX.
- DANCER: Adverse events were slightly higher, including infections on RTX but serious infections were similar between groups. In patients who switched to rescue therapy, some adverse events rates increased, such as infections, nervous system disorders, skin events, respiratory disorders and infusion reactions.

xi) **SIERRA**: This was a randomised, open label study in patients with active RA examining the effects of RTX on immune response to vaccines. RTX+MTX (n=69) versus MTX (n=34) alone were compared for 12 weeks with 36 weeks of observation in the RTX arm. The vaccines administered included *C. albicans*, tetanus toxoid, 23-valent pneumococcal vaccine and keyhole limpet haemocyanin (KLH), a novel immunogen. The primary endpoint of a 4 fold titre increase to tetanus toxoid was 39.1% for RTX+MTX versus 42.3% for MTX alone, a non-significant difference. For pneumococcal vaccine, antibody response was 19% for RTX+MTX versus 60.7% for MTX alone, a significantly decreased response in the RTX group. For KLH vaccine, anti-KLH titre was quantifiable in 46.9% of RTX+MTX versus 92.6% for MTX alone, indicating a diminished response in the RTX group. For *C. albicans* skin testing, the baseline response was less in the RTX+MTX group but the ability to maintain a response was similar to the MTX group.

xii) **PML**: The sponsor included an update on progressive multifocal leukoencephalopathy (PML) in the submission noting at the time there were 4 cases in RA patients receiving RTX out of 80,000 patient exposures, including one case in Australia (see update below and from sponsor and RMP), indicating a rare adverse event. PML has also been reported in lymphoma patients receiving RTX. PML is a serious, often fatal disease with no specific treatment. This submission included a case of fatal PML from the long term extension of the REFLEX trial in a patient with cancer, RA and having chemotherapy and a case from Australia in an RA patient receiving RTX + MTX with a background of DMARDs.

xiii) The Office of Medicines Safety Monitoring (OMSM) has found the RMP submitted by the sponsor in June 2009 (and sponsor's response of 8 February 2010) generally acceptable, but has recommended a number of changes to the PI, CMI and RMP. The RMP is not Australian specific but is based on the European RMP. The following risks were noted for rituximab:

- Identified Risks: Infusion related reactions (IRR), infections (including serious, PML, viral reactivation and opportunistic), impaired immunisation response,

Adverse Events (AEs) in the foetus or neonate after exposure in utero, adverse cardiovascular effects.

- Potential Risks: neutropenia, acute myeloid leukaemia (AML)/myelodysplastic syndrome (MDS), malignant events, impact on, adverse effects on the nursing infant, gastrointestinal perforation, prolonged B-cell depletion, increased risk of grade 3/4 and serious blood and lymphatic AEs in elderly patients.

xiv) The following are noted from OMSM's response to the sponsor's comments on the RMP:

- The sponsor agrees to submit reports from registries and ongoing clinical trials to the TGA when completed.
- The sponsor should monitor in the PSUR the specified safety concerns for RA patients of AML/MDS, neutropenia, prolonged B-cell depletion and increased risk of grade 3/4 and serious blood and lymphatic AEs in elderly patients.
- The sponsor disagrees with an Alert Card for use in Australia, however OMSM recommends that one is considered.
- A boxed warning should be included on PML.

Risk-Benefit Analysis

xv) **Efficacy**: The sponsor has submitted a number of clinical trials demonstrating the efficacy of rituximab in different settings. The trials showed efficacy for RTX+MTX compared to MTX in MTX naïve patients with early severe RA using radiographic (1 year), clinical and functional endpoints. Radiographic evidence for inhibition of structural damage was also seen in a two year study in patients who were inadequate responders to TNF inhibitor therapy when comparing RTX+MTX versus MTX alone, which was also seen in the components and in the percentage without radiographic progression. Clinical efficacy was seen to 48 weeks for RTX+MTX vs. MTX alone and re-treatment studies showed no difference between doses of RTX for up to 48 weeks but some benefit for RTX re-treatment over MTX alone. A 104 week study implied a single course of RTX treatment may result in sustained responses in some patients.

xvi) **Safety and RMP**: The safety of RTX was reviewed across all trials and noted it was well tolerated in general. Follow-up was for up to 5 years for some patients and most adverse events were self limiting, mild to moderate and did not require withdrawal. Acute infusion reactions and infections remain a concern although the long term overall rate of serious infection is comparable to placebo and consistent with other RA treatments. Three cases of pneumocystis jiroveci pneumonia were noted (2 in patients treated with rituximab and one in a patient treated with placebo) but no cases of active tuberculosis. PML remains a significant safety concern as too does the long term B-cell depletion. The vaccine study indicated that RA patients receiving RTX can receive non-live booster vaccines but new or polysaccharide vaccines should be given prior to treatment with RTX. HACAs were reported in RTX patients. The Risk Management Plan (RMP) is generally acceptable, however OMSM recommends an Alert Card and boxed warning on PML, along with other PI amendments.

xvii) **DMARD-IR indication**: The extension of indications to DMARD inadequate responders would allow the earlier use of rituximab in the treatment algorithm for RA patients compared to the current indication of inadequate responders or intolerance to TNF inhibitors. To support this, the SERENE study noted efficacy in the setting of inadequate response to MTX (but not necessarily other DMARDs). The other studies however were in different settings: IMAGE was in MTX naïve patients who started RTX and MTX concurrently, MIRROR was in inadequate responders to MTX (but 25% failed a biologic DMARD which affects the validity of the results), SUNRISE

was in inadequate response to TNF inhibitors, RELFEX was in inadequate responders to TNF inhibitors and DANCER although including patients who failed a DMARD, also included TNF inhibitor failure which could confound the results. Also, no study specifically examined the objective of failure of a non-biologic DMARD other than MTX, although many patients had already tried other DMARDs. The safety concerns of prolonged B-cell depletion and opportunistic infections, particularly PML, could potentially expose further patients to these risks if the indication was extended to this less refractory population. One PML case did occur in a patient who had not been previously exposed to a TNF inhibitor. The limited efficacy to MTX inadequate responders, lack of data in other non-biologic DMARD responders and the safety concerns of prolonged B-cell depletion and opportunistic infections, particularly PML, make the risk / benefit profile less clear in this population. Therefore limiting the use to the current indication of TNF inhibitor inadequate responders is a means to mitigate this risk and the extension of the indications to DMARD inadequate responders is therefore not supported at this time.

xviii) **Moderate RA population**: No data have been submitted that includes a patient population of moderate RA for the indications proposed. Baseline disease characteristics were consistent with severe RA, not moderate, disease with a DAS >6.5 (EULAR criteria has high disease activity with a DAS>5.1 and moderate with a DAS of 3.2 to 5.1) and median tender and swollen joint counts of >25 and >15 respectively indicating severe disease. The safety concern of PML also necessitates a cautious approach and therefore limiting the extent of use of rituximab to only those with severe disease. Therefore the expansion of the patient population to moderate RA patients is not supported.

xix) **Physical function and Clinical Response**: Generally, clinical endpoint claims are more appropriate to the Clinical Trials section of the PI, rather than the Indications section. Although it is noted that some other products do include such claims in the Indications, more recent products have tended to have these statements for RA in the Clinical Trials section. The inclusion of claims such as those referring to physical function and clinical response, although noted in the trials above, are better placed in the Clinical Trials section. Although radiographic claims are also endpoint claims and better suited to the Clinical Trials section too, given that other biological agents for RA include such statements in their indication, then this would be acceptable.

xx) **PML:** The TGA has been corresponding with Roche regarding PML and for updates to be made to the PI. The sponsor has been revising the PI on PML and sending letters to healthcare professionals on the risk of PML in patients taking rituximab. At present, the PI includes as its first precaution, information on PML. The TGA has also requested Roche consider the need for a boxed warning for rituximab on PML, which Roche did not consider appropriate at the time. The OMSM has also reviewed the risk of PML in their RMP. A report prepared for the EMEA is expected in March 2010 on PML and the US PI already includes a boxed warning on PML. Another monoclonal antibody in Australia, natalizumab, includes a boxed warning on PML. The sponsor withdrew the indication for use in MTX naïve patients based on the termination of the IMAGE study following a PML case that was reported in a RA patient who was also MTX naive. The sponsor states that the information suggests a risk of PML in RA patients treated with rituximab, there are no clinical or laboratory markers that would reduce the risk, there is no clear mechanism of how rituximab might increase the risk and there are no clear treatments for PML.

xxi) As of 31 December 2009, there were 133 cases of PML in rituximab exposed patients as shown below by indication. For rheumatoid arthritis, the estimated unique patient

exposure was 109,677 patients for a risk of 1 in 21,935. For other autoimmune conditions (SLE, dermatomyositis, Sjogren's syndrome and cryoglobulinemic vasculitis) the unique patient exposures was 29,584 patients for a risk of 1 in 4931. The sponsor added the comment that the estimated rituximab haematological malignancies exposure to 30 November 2009 is 1880000 patient market exposures. Given the use of rituximab may be associated with an increased risk of PML, the seriousness and fatal nature of PML, the risk for rituximab patients from the table below (Table 20), the lack of clinical or laboratory markers that would reduce the risk, no clear treatments for PML, the use of a boxed warning in the US PI for rituximab, the use of a boxed warning here for another monoclonal antibody in Australia about PML and the recommendation of the OMSM in their RMP for a boxed warning, then the sponsor should update the Australian PI with a boxed warning on PML for rituximab. This will ensure that prescribers and patients are clearly aware of the risk of PML with rituximab when considering the risks and benefits of treatment.

Table 20. PML cases recorded:

Indication	Confirmed cases of PML
Oncology (Non CLL)	90
CLL	28
ITP	1
Unknown indication	3
RA	5
SLE	3
Dermatomyositis	1
Sjögren's syndrome	1
Cryoglobulinemic vasculitis	1

xxii) **Data deficiencies**: No studies have been conducted to directly compare this product with a TNF inhibitor or DMARDS other than methotrexate. Although there were data for patients who had an inadequate response to MTX, there were no specific data on patients with an inadequate response to other DMARDs, although patients in the study tended to have already tried and failed other DMARDs. No studies have been submitted in liver or renal impairment, children or drug interactions.

xxiii) ***Summary***: The efficacy and safety of rituximab have been demonstrated in severe rheumatoid arthritis patients who are intolerant or inadequate responders to TNF inhibitor therapy based on clinical, radiographic and physical function endpoints. Efficacy and safety have not been demonstrated in moderate RA patients. Although there is efficacy in the MTX inadequate responders, there are a lack of efficacy data for other non-biologic DMARD inadequate responders to support the DMARD-IR indication and concerns over safety to justify extending the use of rituximab to this group. PML remains a significant safety concern along with the unclear effects of prolonged B-cell depletion.

xxiv) The Delegate proposed to **reject** this submission by Roche Products Pty Ltd to extend the indications for Mabthera (rituximab), to DMARD-inadequate responder patients and to **reject** the expansion of the patient population to include moderate RA patients but to **approve** the radiographic claim in the indication, based on the safety and efficacy of the product being satisfactorily established for the indication below and for the reasons stated above in the Risk / Benefit Discussion:

> *Mabthera (rituximab) in combination with methotrexate is indicated for the treatment of adult patients with severe, active rheumatoid arthritis who have had an inadequate response or intolerance to at least one tumour necrosis factor (TNF) inhibitor therapy. Mabthera has been shown to reduce the rate of progression of joint damage as measured by x-ray when given in combination with methotrexate.*

xxv) The sponsor should address the following issues in their Pre-ACPM response:
   a) An update on the number of PML cases reported in patients taking rituximab by indication, an estimated unique patient exposure per indication and an approximate rate of occurrence.
   b) The use of an Alert Card in Australia for patients and doctors that discusses PML.

The Delegate requested the ACPM's advice on the following issues:

a) Should rituximab have a boxed warning regarding PML?
b) Are the data acceptable to support use in DMARD inadequate responders?
c) Should endpoint claims of physical function and major clinical response be included in the Clinical Trials section of the PI, rather than the Indications?

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

The ACPM recommended approval of the submission from Roche Products Pty Ltd to extend the indications for Rituximab (MABTHERA) solution for injections 100mg/10 mL and 500mg/ 50mL to include the indication:

> *MABTHERA (rituximab) in combination with methotrexate is indicated for the treatment of adult patients with severe, active rheumatoid arthritis who have had an inadequate response or intolerance to at least one tumour necrosis factor (TNF) inhibitor therapy.*
>
> *Mabthera has been shown to reduce the rate of progression of joint damage as measured by x-ray when given in combination with methotrexate.*

The ACPM could not support the application for the proposed expansion of the indication to include moderate active rheumatoid arthritis patients when the response to methotrexate has been inadequate. Although there was evidence of efficacy, the committee was concerned about the long term safety in this less refractory population given prolonged B-cell depletion and risk of progressive multifocal leukoencephalopathy (PML). However, there was sufficient evidence to support the inclusion in the indication of the statement relating to the reduction of the joint damage as measured by x-ray when given in combination with methotrexate.

The ACPM advised that the risk of PML is sufficient to warrant a boxed warning in the PI and did not consider that the use of a patient alert card was a feasible risk management strategy on the grounds of practicality.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of MabThera, 10 mg of antibody/mL, for the following indication:

> *"Mabthera (rituximab) in combination with methotrexate is indicated for the treatment of adult patients with severe, active rheumatoid arthritis who have had an inadequate response or intolerance to at least one tumour necrosis factor (TNF) inhibitor therapy.*

Mabthera has been shown to reduce the rate of progression of joint damage as measured by x-ray when given in combination with methotrexate."

The Delegate proposed to reject the extension of indications to include methotrexate inadequate responder patients and to approve the radiographic claim in the indication but place the physical function claim in the Clinical Trials section of the PI. The proposed actions are providing the issues raised by ACPM and those by the Delegate below are satisfactorily addressed.

Conditions of Registration

The implementation in Australia of the Mabthera Risk Management Plan (RMP), version 4.0, June 2009, included with the sponsors submission for the rheumatoid arthritis indication only as submitted to the Office of Medicines Safety Monitoring, TGA, except for the following amendments:

•The Periodic Safety Update Reports must include reporting on the specified safety concern for RA patients of neutropenia.
•A report must be submitted to the Office of Medicines Safety Monitoring on AML/MDS and increased risk of grade 3/4 and serious blood and lymphatic AEs in elderly patients by September 2010. This report should also address the discrepancy between Table 69 and Table 26 of the RMP.
•A boxed warning for rituximab is to be included in the Australia Product Information document regarding progressive multifocal leukoencephalopathy (PML).
•No Alert Card is required in Australia.
•The RMP must include the submission of reports from the ARTIS, BSRBR and RABBIT registries and clinical study reports from the IMAGE (2 year), TAME and SUNDIAL clinical trials to the TGA when completed.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

MABTHERA®

Rituximab, recombinant for intravenous infusion (CAS registry number: 174722-31-7).

***WARNING**

Use of MABTHERA may be associated with an increased risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability. Patients must be monitored for any new or worsening neurological symptoms or signs suggestive of PML. If such symptoms occur, further administration of MABTHERA should be immediately suspended until a diagnosis of PML has been excluded. To establish or exclude a diagnosis of PML evaluation including MRI scan, CSF testing for JC viral DNA and repeat neurological assessments, should be considered. If a diagnosis of PML is confirmed MABTHERA must be permanently discontinued (see PRECAUTIONS).

DESCRIPTION

MABTHERA (rituximab) is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. The antibody is a glycosylated IgG_1 kappa immunoglobulin containing murine light- and heavy-chain variable region sequences (Fab domain) and human constant region sequences (Fc domain). Rituximab is composed of 1,328 amino acids and has an approximate molecular weight of 144 kD. Rituximab has a high binding affinity for the CD20 antigen of 5.2 to 11.0 nM.

The chimeric anti-CD20 antibody is produced by mammalian (Chinese hamster ovary) cell suspension culture in a nutrient medium containing 100 mg/mL of the antibiotic gentamicin. The antibiotic is not detectable in the final product. The anti-CD20 antibody is purified by affinity chromatography and ion exchange, including specific viral inactivation and removal procedures.

MABTHERA is a sterile, clear, colourless, preservative-free, concentrated solution for intravenous infusion. MABTHERA is supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials. The product is formulated in 7.35 mg/mL sodium citrate buffer containing 0.7 mg/mL polysorbate 80, 9.0 mg/mL sodium chloride and sterile water for injection. The pH is adjusted to 6.5 with sodium hydroxide or hydrochloric acid.

PHARMACOLOGY

Pharmacodynamics

General: Rituximab binds specifically to the antigen CD20, a transmembrane molecule located on pre-B and mature B lymphocytes. The antigen is expressed on > 95% of all B-cell non-Hodgkin's lymphomas (NHL). CD20 (human B lymphocyte-restricted differentiation antigen, Bp35) is a hydrophobic transmembrane protein with a molecular weight of approximately 35 kD. This non-glycosylated phosphoprotein is found on both normal and malignant B cells, but not on haematopoietic stem cells, pro-B cells, normal plasma cells or

other normal tissues. CD20 regulates (an) early step(s) in the activation process for cell cycle initiation and differentiation, and possibly functions as a calcium ion channel. CD20 does not internalise upon antibody binding and is not shed from the cell surface. This antigen does not circulate in the plasma. Thus, free antigen does not compete for rituximab binding.

In rheumatoid arthritis (RA) the putative mechanism of action of rituximab involves the depletion of surface antigen-positive B lymphocytes from synovial tissue, with downstream effects potentially including reduced activation of T-cells and the associated release of pro-inflammatory cytokines.

In Vitro Mechanisms of Action: The Fab domain of rituximab binds to the CD20 antigen on B-lymphocytes and the Fc domain recruits immune effector functions to mediate B-cell lysis. Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC). The antibody also induces apoptosis in the DHL-4 human B-cell lymphoma line. Finally, *in vitro* studies have demonstrated that rituximab sensitises drug-resistant human B-cell lymphoma lines to the cytotoxic effects of some chemotherapeutic agents.

Binding specificity: In human tissue, the expression of the CD20 antigen is highly restricted; rituximab binding to CD20 was found only on lymphoid cells in the thymus, the white pulp of the spleen and a majority of B lymphocytes in peripheral blood and lymph nodes. Little or no non-specific binding was observed.

In Vivo: In cynomolgus monkeys, four or eight weekly doses of 269 mg/m^2 of rituximab resulted in plasma concentrations of 161 to 386 μg/mL, approximately 24 hours after the first dose. Two weeks after the last dose, rituximab was still detected in the plasma of 3/6 monkeys treated for four weeks and in 4/6 monkeys treated for eight weeks.

B lymphocyte numbers were reduced by 99% or more in comparison with pre-test values in the peripheral blood of all monkeys, approximately 24 hours after the first dose. Two weeks after the last dose, B lymphocyte numbers were still reduced by more than 99% in 3/6 monkeys dosed for four weeks and in 4/6 monkeys dosed for eight weeks, and B lymphocyte numbers were also depleted in the mandibular lymph nodes and femoral bone marrow. A partial recovery of B lymphocyte numbers in the peripheral blood of some monkeys in both dose groups was correlated with the development of antibodies against rituximab.

Human Pharmacodynamics: A marked decline in median peripheral blood B-cell counts was seen beginning after the first dose of MABTHERA.

In patients treated for haematological malignancies, B-cell recovery began at approximately six months following the completion of treatment. B-cell levels returned to normal between nine and twelve months following completion of treatment.

In patients with RA, the duration of peripheral B cell depletion was variable. The majority of patients who received further treatment did so prior to full B cell recovery.

Pharmacokinetics

Non-Hodgkin's Lymphoma

Pharmacokinetic studies performed in a Phase I study in which patients (N=15) with relapsed B-cell lymphoma were given single doses of rituximab at 10, 50, 100 or 500 mg/m² indicated that serum levels and half-life of rituximab were proportional to dose.

In a cohort of 14 patients among the 166 patients with relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma enrolled in the Phase III pivotal trial and given rituximab 375mg/m² as an IV infusion for 4 weekly doses, the mean serum half-life was 76.3 hours (range 31.5 to 152.6 hours) after the first infusion and 205.8 hours (range 83.9 to 407.0 hours) after the fourth infusion. The mean C_{max} after the first and fourth infusion were 205.6 ±59.9 µg/mL and 464.7 ±119.0 µg/mL, respectively. The mean plasma clearance after the first and fourth infusion was 0.0382 ±0.0182 L/h and 0.0092 ±0.0033 L/h, respectively. However variability in serum levels was large. Rituximab serum concentrations were statistically significantly higher in responding patients than in non-responding patients just prior to and after the fourth infusion and post-treatment. Serum concentrations were negatively correlated with tumour burden and the number of circulating B-cells at baseline. Typically, rituximab was detectable for three to six months following completion of treatment.

Elimination and distribution have not been extensively studied in patients with diffuse large B-cell non-Hodgkin's lymphoma, but available data indicate that serum levels of rituximab in these patients are comparable to those in patients with follicular non-Hodgkin's lymphoma following treatment with similar doses.

Chronic Lymphocytic Leukaemia (CLL)

Rituximab was administered as an IV infusion at a first-cycle dose of 375 mg/m^2 increased to 500 mg/m^2 each cycle for a further 5 doses in combination with fludarabine and cyclophosphamide (FC) in CLL patients. The mean C_{max} (N=15) was 408 µg/mL (range, 97 – 764 µg/mL) after the fifth 500 mg/m^2 infusion.

Rheumatoid Arthritis

Following two intravenous infusions of rituximab at a dose of 1000 mg, two weeks apart, the mean terminal half-life was 20.8 days (range 8.58 to 35.9 days), mean systemic clearance was 0.23 L/day (range 0.091 to 0.67 L/day), and mean steady-state distribution volume was 4.6 L (range 1.7 to 7.51 L). Population pharmacokinetic analysis of the same data gave similar mean values for systemic clearance and half-life, 0.26 L/day and 20.4 days, respectively. Population pharmacokinetic analysis revealed that BSA and gender were the most significant covariates to explain inter-individual variability in pharmacokinetic parameters. After adjusting for BSA, male subjects had a larger volume of distribution and a faster clearance than female subjects. The gender- related pharmacokinetic differences are not considered to be clinically relevant and dose adjustment is not required.

The pharmacokinetics of rituximab were assessed following two IV doses of 500 mg and 1000 mg on days 1 and 15 in four studies. In all these studies, rituximab pharmacokinetics were dose proportional over the limited dose range studied. Mean C_{max} for serum rituximab following first infusion ranged from 157 to 171 µg/mL for 2 x 500 mg dose and ranged from 298 to 341 µg/mL for 2 x 1000 mg dose. Following second infusion, mean C_{max} ranged from 183 to 198 µg/mL for the 2 x 500 mg dose and ranged from 355 to 404 µg/mL for the 2 x 1000 mg dose. Mean terminal elimination half-life ranged from 15 to 16.5 days for the 2 x 500

mg dose group and 17 to 21 days for the 2 x 1000 mg dose group. Mean C_{max} was 16 to 19% higher following second infusion compared to the first infusion for both doses.

Upon re-treatment with a second course the pharmacokinetics of rituximab were again assessed following two IV doses of 500 mg and 1000 mg. Mean C_{max} for serum rituximab following first infusion was 170 to 175 µg/mL for 2 x 500 mg dose and 317 to 370 µg/mL for 2 x 1000 mg dose. C^{max} following second infusion, was 207 µg/mL for the 2 x 500 mg dose and ranged from 377 to 386 µg/mL for the 2 x 1000 mg dose. Mean terminal elimination half-life after the second infusion, following the second course, was 19 days for 2 x 500 mg dose and ranged from 21 to 22 days for the 2 x 1000 mg dose. PK parameters for rituximab were comparable over the two treatment courses.

CLINICAL TRIALS

Non-Hodgkin's Lymphoma

Relapsed/Refractory Low Grade or Follicular non-Hodgkin's Lymphoma

Monotherapy

In the pivotal study, an open label, single arm trial of 166 patients with relapsed or refractory low-grade or follicular B-cell NHL, subjects received 375 mg/m^2 of MABTHERA as an IV infusion once a week for four weeks (4 doses). The overall response rate (ORR) in the intent-to-treat (ITT) population was 48% ($CI_{95\%}$ 41% – 56%), comprising a 6% complete response (CR) and 42% partial response (PR). The projected median time to progression (TTP) for responding patients was 13.0 months.

In a subgroup analysis, the ORR was significantly higher in patients with IWF B, C, and D histological subtypes as compared to IWF A subtype (58% vs 12%) and in patients with prior autologous bone marrow transplantation (ABMT) compared to those with no prior ABMT (78% vs 43%). Age, sex, lymphoma grade, years since initial diagnosis, presence or absence of bulky disease, normal or high LDH, or presence of extranodal disease did not have a significant effect (Fisher's exact test) on response to MABTHERA.

ORR was also significantly higher in patients with no bone marrow involvement compared to those with bone marrow involvement (59% vs 40%). This finding was not supported by a stepwise logistic regression analysis in which the following factors were identified as prognostic factors: histologic type, bcl-2 positivity at baseline, resistance to last chemotherapy and bulky disease.

Re-treatment

In a multicentre, single-arm study, 58 patients with relapsed or refractory low grade or follicular B-cell NHL, who had achieved an objective clinical response to a prior course of MABTHERA, were re-treated with 375 mg/m^2 of MABTHERA as IV infusion weekly for four doses. Three of the patients had received two courses of MABTHERA before enrolment and thus were given a third course in the study. Two patients were re-treated twice in the study. For the 60 re-treatments on study, the ORR was 38% (CR 10% and PR 28%) with a projected median TTP for responding patients of 17.8 months (range 5.4 – 26.6). This compares favourably with the TTP achieved after the prior course of MABTHERA 12.4 months.

Bulky Disease

In pooled data from three studies, 39 patients with relapsed or refractory, bulky disease (single lesion ≥ 10cm in diameter), low-grade or follicular B-cell NHL received 375 mg/m^2 of MABTHERA given as an IV infusion once weekly for four doses). The overall response rate (ORR) was 36% (CR 3%, PR 33%) with a median TTP for responding patients of 9.6 months (range 4.5 to 26.8 months).

Clinical Laboratory Findings

Molecular Genetic Markers: Results from the exploratory analysis of the bcl-2 gene rearrangement showed that samples of peripheral blood obtained at baseline were positive for the bcl-2 rearrangement (bcl-2 positive) by nested Polymerase Chain Reaction (PCR) in 70 (42%) of the 166 enrolled patients. Of these 70 patients, 55 patients had a follow-up blood sample at 3 months and more than 60% showed a conversion to negative bcl-2 gene rearrangement.

With regard to bone marrow assessment, of 71 (45%) of the 166 enrolled patients who were bcl-2 positive in marrow at baseline, 22 were assessed for bcl-2 rearrangement at 3 months. Of these, 12 (55%) were bcl-2 negative at three months.

Of 67 patients evaluated for human anti-mouse antibody (HAMA), none were positive. Of 356 patients evaluated for HACA, 1.1% (4 patients) were positive.

Previously Untreated Follicular non-Hodgkin's Lymphoma

Combination with chemotherapy

In an open-label randomised study (M39021), a total of 322 previously untreated Stage III or IV follicular B cell NHL patients were randomised to receive either CVP chemotherapy (cyclophosphamide 750 mg/m^2, vincristine 1.4 mg/m^2 up to a maximum of 2 mg on day 1, and prednisolone 40 mg/m^2/day on days 1 –5) every 3 weeks for 8 cycles or MABTHERA 375 mg/m^2 in combination with CVP (R-CVP). MABTHERA was administered on the first day of each treatment cycle. A total of 321 patients (162 R-CVP, 159 CVP) received therapy and were analysed for efficacy.

The median follow-up of patients was 53 months. Addition of MABTHERA to CVP significantly increased time to treatment failure (the primary endpoint), tumour response, progression-free survival (PFS) and overall survival (OS) (Table 1).

Table 1 Summary of key results from study M39021

	CVP (N=159)	**R-CVP (N=162)**	**Hazard Ratio [95% CI] log-rank p**
Median Time to Treatment Failure (months)	6.6	27.0	0.34 [0.26, 0.44] p<0.0001
Median Progression-free Survival (months)	14.7	33.6	0.44 [0.33, 0.57] p<0.001
Overall Tumour Response[1] (%)	57	81	-
Overall Survival (%)	71	81	0.60 [0.38, 0.95] p=0.029[2]

[1] Tumour response = CR (complete response), CRu (complete response unconfirmed) and PR (partial response)
[2] Stratified by centre

Results from three other randomised studies using MABTHERA in combination with chemotherapy regimens other than CVP (CHOP, MCP, CHVP/interferon-alfa 2a) have also demonstrated significant improvements in response rates, time dependent parameters as well as in overall survival (Table 2).

Table 2 Summary of key results from three phase III randomised studies evaluating the benefit of MabThera with different chemotherapy regimens in follicular lymphoma

Study	Treatment, n	Median follow up, months	ORR, %	CR, %	Outcome[1] (months)	OS rates, %
GLSG'00	CHOP, 205 R-CHOP, 223	18	90 96	17 20	Median TTF: 31.2 Not reached p<0.001	90 95 p=0.016
OSHO-39	MCP, 96 R-MCP, 105	47	75 92	25 50	Median PFS: 28.8 Not reached p<0.0001	74 87 p=0.0096
FL2000	CHVP-IFN, 183 R-CHVP-IFN, 175	42	85 94	49 76	Median EFS: 36 Not reached p<0.0001	84 91 p=0.029

Abbreviations: ORR – overall response rate; CR – complete response; OS rates – overall survival rates at the time of the analyses; R – MABTHERA; CHOP - cyclophosphamide, doxorubicin, vincristine, prednisone; MCP – mitoxantrone, chlorambucil, prednisolone; CHVP - cyclophosphamide, doxorubicin, etoposide, prednisolone ; IFN – interferon-alfa 2a.
[1]GLSG'00 outcome: TTF (time to treatment failure); OSHO-39: PFS (progression free survival); FL2000 outcome: EFS (event free survival)

Maintenance Therapy

In a prospective, open label, international, multicentre, Phase III trial, 465 patients with relapsed/refractory follicular NHL were randomised in a first step to induction therapy with either CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone; n=231) or MABTHERA plus CHOP (R-CHOP, n=234), one dose of rituximab combined with each cycle of chemotherapy. The two treatment groups were well balanced with regard to baseline characteristics and disease status. A total of 334 patients achieving a complete or partial remission following induction therapy were randomised in a second step to MABTHERA maintenance therapy (n=167) or observation (n=167). MABTHERA maintenance treatment consisted of a single infusion of MABTHERA at 375 mg/m^2 body surface area given every 3 months until disease progression or for a maximum period of two years. Patients with hypogammaglobulinaemia (IgG <3g/L) or known HIV infection were excluded from the trial.

The final efficacy analysis included all patients randomised to both parts of the study. After a median observation time of 31 months for patients randomised to the induction phase, R-CHOP significantly improved the outcome of patients with relapsed/refractory follicular NHL when compared to CHOP (see Table 3).

Table 3 Induction phase: overview of efficacy results for CHOP vs R-CHOP (31 months median observation time)

	CHOP	R-CHOP	p-value	Risk Reduction[1)]
Primary Efficacy				
ORR[2)]	74%	87%	0.0003	NA
CR[2)]	16%	29%	0.0005	NA
PR[2)]	58%	58%	0.9449	NA
Secondary Efficacy				
OS (median)	NR	NR	0.0508	32%
PFS(median)	19.4 mo.	33.2 mo.	0.0001	38%

[1)] Estimates were calculated by hazard ratios

[2)] Last tumour response as assessed by the investigator. The "primary" statistical test for "response" was the trend test of CR versus PR versus non-response ($p < 0.0001$)

Abbreviations: NA, not available; NR, not reached; mo, months; ORR: overall response rate; CR: complete response; PR: partial response; OS : overall survival ; PFS : progression free survival

For patients randomised to the maintenance phase of the trial, the median observation time was 28 months from maintenance randomisation. Maintenance treatment with MABTHERA led to a clinically relevant and statistically significant improvement in the primary endpoint, PFS, (time from maintenance randomisation to relapse, disease progression or death) when compared to observation alone ($p< 0.0001$ log-rank test). The median PFS was 42.2 months in the MABTHERA maintenance arm compared to 14.3 months in the observation arm. Using a cox regression analysis, the risk of experiencing progressive disease or death was reduced by 61% with MABTHERA maintenance treatment when compared to observation (95% CI; 45%-72%). Kaplan-Meier estimated progression-free rates at 12 months were 78% in the MABTHERA maintenance group vs 57% in the observation group. An analysis of overall survival confirmed the significant benefit of MABTHERA maintenance over observation ($p=0.0039$ log-rank test). MABTHERA maintenance treatment reduced the risk of death by 56% (95% CI; 22%-75%).

The median time to new anti-lymphoma treatment was significantly longer with MABTHERA maintenance treatment than with observation (38.8 months vs. 20.1 months, $p< 0.0001$ log-rank test). The risk of starting a new treatment was reduced by 50% (95% CI; 30%-64%). In patients achieving a CR/CRu (complete response unconfirmed) as best response during induction treatment, MABTHERA maintenance treatment significantly prolonged the median disease free survival (DFS) compared to the observation group (53.7 vs 16.5 months, $p=0.0003$) log-rank test (Table 4). The risk of relapse in complete responders was reduced by 67% (95% CI; 39%-82%).

Table 4 Maintenance phase: overview of efficacy results MABTHERA vs. observation (28 months median observation time)

Efficacy Parameter	Kaplan-Meier Estimate of Median Time to Event (Months)			Risk Reduction
	Observation (N=167)	MabThera (N=167)	Log-Rank p value	(95% CI)
Progression-free survival (PFS)	14.3	42.2	<0.0001	61% (45-72%)
Overall Survival	NR	NR	0.0039	56% (22-75%)
Time to new lymphoma treatment	20.1	38.8	<0.0001	50% (30-64%)
Disease-free survival[a]	16.5	53.7	0.0003	67% (39-82%)
Subgroup Analysis				
PFS				
CHOP	11.6	37.5	<0.0001	71% (54-82%)
R-CHOP	22.1	51.9	0.0071	46% (15-65%)
CR	14.3	52.8	0.0008	64% (33-81%)
PR	14.3	37.8	<0.0001	54% (33-69%)
OS				
CHOP	NR	NR	0.0348	55% (4-79%)
R-CHOP	NR	NR	0.0482	56% (-2-81%)

NR: not reached; [a]: only applicable to patients achieving a CR

The benefit of MABTHERA maintenance treatment was confirmed in all subgroups analysed, regardless of induction regimen (CHOP or R-CHOP) or quality of response to induction treatment (CR or PR) (Table 4). MABTHERA maintenance treatment significantly prolonged median PFS in patients responding to CHOP induction therapy (median PFS 37.5 months vs 11.6 months, p< 0.0001) as well as in those responding to R-CHOP induction (median PFS 51.9 months vs 22.1 months, p=0.0071). Although analysed subgroups were small, and the median survival had not been reached after an overall median observation period of 47.2 months, a clinically meaningful benefit in terms of overall survival was observed for patients receiving MABTHERA maintenance treatment when compared to observation, in the overall population.

MABTHERA maintenance treatment provided consistent benefit in all subgroups tested [gender (male, female), age (≤ 60 years, > 60 years), stage (III, IV), WHO performance status (0 versus > 0), B symptoms (absent, present), bone marrow involvement (no versus yes), IPI (0-2 versus 3-5), FLIPI score (0-1, versus 2 versus 3-5), number of extra-nodal sites (0-1 versus > 1), number of nodal sites (< 5 versus ≥ 5), number of previous regimens (1 versus 2), best response to prior therapy (CR/PR versus NC/PD), haemoglobin (< 12 g/dL versus ≥ 12 g/dL), β_2-microglobulin (< 3mg/L versus ≥ 3 mg/L), LDH (elevated, not elevated) except for the small subgroup of patients with bulky disease.

Diffuse Large B-cell non-Hodgkin's Lymphoma

In a randomised, Phase III, open-label trial, a total of 399 previously untreated elderly ambulatory patients (age 60 to 80 years, ECOG performance status 0-2) with moderate to advanced (Ann Arbor stage II-IV) diffuse large B-cell lymphoma received standard CHOP

chemotherapy (cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 up to a maximum of 2 mg on day 1, and prednisone 40 mg/m^2/day on days 1-5) every 3 weeks for eight cycles, or MABTHERA 375 mg/m^2 administered as an intravenous infusion plus CHOP (R-CHOP). MABTHERA was administered on the first day of the treatment cycle.

The final efficacy analysis included all randomised patients (197 CHOP, 202 R-CHOP), and had a median follow-up duration of approximately 31 months. The two treatment groups were well balanced in baseline characteristics and disease status. The final analysis confirmed that R-CHOP significantly increased the duration of event-free survival (the primary efficacy parameter, where events were death, relapse or progression of lymphoma, or institution of a new anti-lymphoma treatment) (p=0.0001). Kaplan Meier estimates of the median duration of event-free survival were 35 months in the R-CHOP arm compared to 13 months in the CHOP arm, representing a risk reduction of 41%. At 24 months, estimates for overall survival were 68.2% in the R-CHOP arm compared to 57.4% in the CHOP arm. A subsequent analysis of the duration of overall survival, carried out with a median follow-up duration of 38 months, confirmed the benefit of R-CHOP over CHOP treatment (p=0.0094), representing a risk reduction of 33%.

The analysis of all secondary parameters (response rates, progression-free survival, disease-free survival, duration of response) verified the treatment effect of R-CHOP compared to CHOP. The complete response rate after cycle 8 was 76.2% in the R-CHOP group and 62.4% in the CHOP group (p=0.0028). The risk of disease progression was reduced by 46% and the risk of relapse by 51%.

In all patient subgroups (gender, age, age-adjusted IPI, Ann Arbor stage, ECOG, Beta 2 Microglobulin, LDH, Albumin, B-symptoms, Bulky disease, extranodal sites, bone marrow involvement), the risk ratios for event-free survival and overall survival (R-CHOP compared with CHOP) were less than 0.83 and 0.95 respectively, although the benefit with R-CHOP was not always statistically significant.

A subsequent analysis of the duration of overall survival, carried out with a median follow-up duration of 60 months, confirmed the benefit of R-CHOP over CHOP treatment (p=0.0071), representing a risk reduction of 32%.

Chronic Lymphocytic Leukaemia (CLL)

In two open-label randomised studies, a total of 817 previously untreated patients and 552 patients with relapsed/refractory CLL were randomised to receive either fludarabine and cyclophosphamide (FC) chemotherapy (fludarabine 25 mg/m^2, cyclophosphamide 250 mg/m^2, days 1-3) every 4 weeks for 6 cycles or MABTHERA in combination with FC (R-FC). MABTHERA was administered at a dosage of 375 mg/m^2 during the first cycle one day prior to chemotherapy and at a dosage of 500 mg/m^2 on day 1 of cycles 2-6. A total of 810 patients (403 R-FC, 407 FC) from the first-line study (Table 5) and 552 patients (276 R-FC, 276 FC) for the relapsed/refractory study (Table 6) were analysed for efficacy.

In the first-line study, the primary endpoint of progression-free survival (PFS) was a median of 40 months in the R-FC group and a median of 32 months in the FC group (p<0.0001, log-rank test). The analysis of overall survival demonstrated improved survival in favour of the R-FC arm (p=0.0427), however longer follow-up is needed to confirm this observation. The

benefit in terms of PFS was consistently observed in most patient subgroups analysed according to disease risk at baseline.

Table 5 First-line treatment of Chronic Lymphocytic Leukaemia - overview of efficacy results for MABTHERA plus FC vs. FC alone (20.7 months median observation time)

Efficacy Parameter	Kaplan-Meier Estimate of Median Time to Event (Months)			Hazard Ratio R-FC vs FC [95% CI]
	FC (N=407)	R-FC (N=403)	Log-Rank p value	
Progression-free survival	32.2	39.8	<0.0001	0.56 [0.43, 0.72]
Overall Survival	NR	NR	0.0427	0.64 [0.41, 1.00]
Response rate (CR, nPR, or PR)	72.7%	86.1%	<0.0001	NA
CR rates	17.2%	36.0%	<0.0001	NA

Response rate and CR rates analysed using Chi-squared Test.
Abbreviations: CR: complete response; nPR: nodular partial response; PR: partial response; NA: not available; NR: not reached
Standard definitions and assessments for response were used in accordance with the National Cancer Institute-sponsored Working Group guidelines for CLL.

In a case series of 30 previously untreated patents with CLL, an overall response rate of 97% was achieved with MABTHERA in combination with fludarabine, cyclophosphamide and mitoxantrone (FCM). Survival was not reported. In another case series of 64 previously untreated patients with CLL, an overall response rate of 91% and a median progression-free survival of 32.6 months were achieved with MABTHERA in combination with pentostatin and cyclophosphamide (PC).

In the relapsed/refractory study, the median PFS (primary endpoint) was 30.6 months in the R-FC group and 20.6 months in the FC group (p=0.0002, log-rank test). The benefit in terms of PFS was observed in almost all patient subgroups analysed according to disease risk at baseline. A non-significant trend towards improvement in overall survival was reported in the R-FC arm compared to the FC arm.

Table 6 Treatment of relapsed/refractory Chronic Lymphocytic Leukaemia – overview of efficacy results for MABTHERA plus FC vs. FC alone (25.3 months median observation time)

Efficacy Parameter	Kaplan-Meier Estimate of Median Time to Event (Months)			Hazard Ratio R-FC vs FC [95% CI]
	FC (N=276)	R-FC (N=276)	Log-Rank p value	
Progression-free survival	20.6	30.6	0.0002	0.65 [0.51, 0.82]
Overall Survival	51.9	NR	0.2874	0.83 [0.59, 1.17]
Response rate (CR, nPR, or PR)	58.0%	69.9%	0.0034	NA
CR rates	13.0%	24.3%	0.0007	NA

Response rate and CR rates analysed using Chi-squared Test.

Abbreviations: CR: complete response; nPR: nodular partial response; PR: partial response; NA: not available; NR: not reached
Standard definitions and assessments for response were used in accordance with the National Cancer Institute-sponsored Working Group guidelines for CLL.

In relapsed/refractory CLL patients, response rates of 70% or greater have been reported in small studies of the following chemotherapy regimens with MABTHERA: FCM (fludarabine, cyclophosphamide, mitoxantrone), PC (pentostatin, cyclophosphamide), PCM (pentostatin, cyclophosphamide, mitoxantrone), CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), bendamustine and cladribine.

Rheumatoid Arthritis

The efficacy and safety of MABTHERA in alleviating the symptoms and signs of RA was demonstrated in three randomised, controlled, double-blind, multicentre studies.

Study 1, WA17042 (REFLEX), was a double blind comparative study which included 517 patients that had experienced an inadequate response or intolerance to one or more TNF inhibitor therapies. Eligible patients had severe active RA, diagnosed according to the criteria of the American College of Rheumatology (ACR). The study population was comprised of adult patients aged ≥ 18 years with RA for at least 6 months who had experienced an inadequate response to previous treatment with an anti-TNF therapy. The primary endpoint was the percent of patients who achieved an ACR20 response at week 24. Patients received 2 x 1000 mg IV infusions of MABTHERA, each following an IV infusion of 100 mg methylprednisone and separated by an interval of 15 days. All patients received concomitant oral methotrexate (MTX) (10-25 mg/week) and 60 mg oral prednisone on days 2-7 and 30 mg on days 8-14 following the first infusion. Patients were followed beyond week 24 for long term endpoints, including radiographic assessment at 56 weeks. During this time patients could receive further courses of MABTHERA under an open label extension study protocol (see Radiographic Response).

Study 2, WA17043 (DANCER), was a randomised, double-blind, double-dummy, controlled, 3 x 3 multifactorial study which compared two different dose levels of MABTHERA (2 x 1000 mg or 2 x 500 mg) given with or without one of two corticosteroid infusion regimens in combination with weekly MTX. All patients received concomitant oral methotrexate. The primary endpoint was the proportion of RF (Rheumatoid Factor) positive patients with an ACR20 response at week 24. The study population was comprised of adult patients aged ≥ 18 years with RA who had previously failed 1-5 DMARDs and who currently had an inadequate response to MTX.

Study 3 was a double-blind, double-dummy, controlled study evaluating MABTHERA monotherapy, and MABTHERA in combination with either cyclophosphamide or MTX in patients with active RA who had not responded to one or more prior DMARDs. The primary endpoint was the proportion of patients with an ACR50 response at week 24. The study population was comprised of adult patients aged ≥ 21 years with RA who had failed 1-5 DMARDs, were RF seropositive at screening, and who currently had a partial clinical response to MTX monotherapy.

An ACR20 response was defined as at least a 20% improvement, compared to baseline, in both swollen and tender joint counts (SJC and TJC), as well as in 3 out of 5 additional parameters: physician's global assessment of disease activity, patient's global assessment of

disease activity, patient's assessment of pain, Health Assessment Questionnaire Disability Index (HAQ-DI) and C-reactive protein (CRP).

The comparator drug in all three studies was weekly MTX (10-25 mg weekly).

Disease Activity Outcomes

In all three studies, MABTHERA 2 x 1000 mg + MTX significantly increased the proportion of patients achieving at least a 20% improvement in ACR score compared with patients treated with MTX alone (Table 7). The treatment effect was similar in patients independent of age, gender, body surface area, race, number of prior treatments or disease status.

Clinically and statistically significant improvement was also noted on all individual components of the ACR response (tender and swollen joint counts, patient and physician global assessment, disability index scores (HAQ), pain assessment and CRP (mg/dL).

Table 7 Cross-study comparison of ACR responses at Week 24 (ITT Population)

	ACR Response	**Placebo+MTX**	**MABTHERA +MTX**
Study 1 REFLEX		(N=201)	(N=298)
	ACR20 ACR50 ACR70	36 (18%) 11 (5%) 3 (1%)	153 (51%)[1] 80 (27%)[1] 37 (12%)[1]
Study 2 DANCER		(N=143)	(N=185)
	ACR20 ACR50 ACR70	45 (31%) 19 (13%) 6 (4%)	96 (52%)[2] 61 (33%)[2] 28 (15%)[2]
Study 3		(N= 40)	(N= 40)
	ACR20 ACR50 ACR70	15 (38%) 5 (13%) 2 (5%)	28 (70%)[3] 17 (43%)[3] 9 (23%)[3]

[1] $p \leq 0.0001$; [2] $p \leq 0.001$; [3] $p < 0.05$

MABTHERA + MTX treated patients had a significantly greater reduction in disease activity score (DAS28) than patients treated with MTX alone. A good to moderate EULAR response was achieved by significantly more MABTHERA + MTX treated patients compared to patients treated with MTX alone (Table 8).

Table 8 Cross-Study Comparison of DAS and EULAR Responses at Week 24 (ITT Population)

	Placebo+MTX	**MABTHERA +MTX 2 × 1g**
Study 1	(N=201)	(N=298)
Change in DAS28 [Mean (SD)]	-0.4 (1.2)	-1.9 (1.6)*
EULAR Response (%)		
None	78%	35%
Moderate	20%	50%*
Good	2%	15%
Study 2	(N= 143)	(N=185)
Mean change in DAS28 (SD)	–0.8 (1.4)	–2.0 (1.6)

	Placebo+MTX	**MABTHERA +MTX 2 × 1g**
EULAR response None Moderate Good	 61% 35% 4%	 37% 40% 23%
Study 3	(N=40)	(N=40)
Change in DAS [Mean (SD)]	-1.3 (1.2)	-2.6 (1.3)
EULAR response None Moderate Good	 50% 45% 5%	 18% 63% 20%

*****p value <0.0001. p values not calculated for studies 2 and 3.

Radiographic Response

In Study WA17042 (REFLEX), structural joint damage was assessed radiographically and expressed as changes in Genant-modified Total Sharp Score (TSS) and its components, the erosion score (ES) and the joint space narrowing (JSN) score. MABTHERA + MTX slowed the progression of structural damage compared to placebo + MTX after 1 year (Table 8). 70% of patients initially randomised to MABTHERA + MTX and 72% of patients initially randomised to placebo + MTX were evaluated radiographically at year 2. Progression of structural damage in MABTHERA + MTX patients was further reduced in the second year of treatment (Table 8).

Table 8 Mean radiographic change from baseline to 104 weeks

Inadequate Response to TNF Antagonists				
Parameter	**MABTHERA + MTX[b]** (2 x 1000 mg)	**Placebo + MTX[c]**	**Treatment Difference (Placebo – MABTHERA)**	**95% CI**
Change during first year				
TSS	0.66	1.78	1.12	(0.48, 1.76)
ES	0.44	1.19	0.75	(0.32, 1.18)
JSN score	0.22	0.59	0.37	(0.11, 0.63)
Change during second year[a]				
TSS	0.48	1.04	-	-
ES	0.28	0.62	-	-
JSN score	0.20	0.42	-	-

[a] Based on radiographic scoring following 104 weeks of observation

[b] Patients received up to 2 years of treatment with MABTHERA + MTX

[c] Patients receiving placebo + MTX could receive retreatment with MABTHERA + MTX from week 16 onwards

Following 2 years of treatment with MABTHERA + MTX, 57% of patients had no progression of structural damage. During the first year, 60% of MABTHERA + MTX treated patients had no progression, defined as a change in TSS of zero or less compared to baseline, compared to 46% of placebo +_MTX treated patients. In their second year of treatment with MABTHERA + MTX, more patients had no progression than in the first year (68% vs. 60%), and 87% of the MABTHERA + MTX treated patients who had no progression in the first year also had no progression in the second year.

Quality of life outcomes
MABTHERA + MTX treated patients reported an improvement in all patient-reported outcomes such as Health Assessment Questionnaire Disability Index (HAQ-DI), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) and Short Form-36 (SF-36) questionnaires. Significant reductions in disability index (HAQ-DI), fatigue (FACIT-F) (Table 9), and improvement in both the physical health score (PHS) and mental health score (MHS) of the SF-36 were observed in patients treated with MABTHERA + MTX compared to patients treated with MTX alone.

Table 9 Physical Function and Quality of Life Outcomes at Week 24 in Study 1

	Outcome	Placebo + MTX	MABTHERA + MTX (2 x 1000 mg)
WA17042 (REFLEX; TNF-IR)			
		n=201	n=298
	Mean change in HAQ-DI	-0.1	-0.4***
	% HAQ-DI MCID	20%	51%
	Mean change in FACIT-F	-0.5	-9.1***
		n=197	n=294
	Mean Change in SF-36 PHS	0.9	5.8***
	% SF-36 PHS MCID	13%	48%***
	Mean Change in SF-36 MHS	1.3	4.7**
	% SF-36 MHS MCID	20%	38%**

Significant difference from placebo at the primary time point: **p ≤ 0.001 ***p ≤ 0.0001
MCID (minimum clinically important difference): HAQ-DI ≥0.22, SF-36 PHS >5.42, SF-36 MHS >6.33

At week 24, in all three studies, the proportion of MABTHERA + MTX treated patients showing a clinically relevant improvement in HAQ-DI (defined as an individual total score decrease of > 0.25) was higher than among patients receiving MTX alone.

Laboratory evaluations
Approximately 10% of patients with RA tested positive for HACA (Human Anti-Chimeric Antibody) in clinical studies. The emergence of HACA was not associated with clinical deterioration or with an increased risk of reactions to subsequent infusions in the majority of patients. The presence of HACA may be associated with worsening of infusion or allergic reactions after the second infusion of subsequent courses, and failure to deplete B cells after receipt of further treatment courses has been observed rarely.

In Study 1 WA17042 (REFLEX), 15/308 (4.8%) MABTHERA + MTX treated patients and 8/209 (3.8%) patients treated with MTX alone were anti-nuclear antibody (ANA) negative at day 1 and became ANA positive at week 16 and/or week 24. The adverse event profile in these patients did not provide any evidence of new onset autoimmune disease.

In RF positive patients, marked decreases were observed in RF concentrations following treatment with MABTHERA in all three studies (range 45-64%).

Hyperuricaemia (Grade 3/4) occurred in 143/950 (15%) patients, with the majority post-infusion on days 1 and/or 15. It was not associated with any clinical symptoms, and none of

these patients developed evidence of renal disease. Increases in serum uric acid are often associated with the catabolism of DNA. This finding is consistent with the destruction of B cells resulting from MABTHERA therapy.

Hypophosphataemia (Grade 3) occurred in 193/950 (21%) patients. There was also one case of Grade 4 hypophosphataemia. Most cases occurred post-infusion, where patients received oral and/or IV corticosteroids. Low phosphate levels are associated with corticosteroid treatment and osteoporosis.

Plasma total immunoglobulin concentrations, total lymphocytes counts, and white cells generally remained within normal limits following MABTHERA treatment, with the exception of a transient drop in white cell counts over the first four weeks following therapy. Lymphopenia (Grade 3/4) was experienced by 679/1003 (68%) of patients compared to 52%-54% of patients who experienced Grade 3 lymphopenia and 1%-3% of patients who experienced Grade 4 lymphopenia in the 24-week double-blind populations. Most cases occurred immediately after the first infusion, consistent with peripheral B-cell depletion, and lymphocyte numbers recovered thereafter. The majority of the Grade 4 cases were transient though 6 patients had more persistent Grade 4 lymphopenia, one of whom had a serious infection (2 occurrences of pneumonia in a diabetic patient; both cases resolved). All 6 patients had low lymphocyte counts before exposure to MABTHERA, including 2 patients who experienced up to Grade 4 lymphopenia whilst on placebo. A total of 17 non serious infections were reported all of which resolved without sequelae.

Titres of IgG antigen specific antibody to mumps, rubella, varicella, tetanus toxoid, influenza and streptococcus pneumococci remained stable over 24 weeks following exposure to MABTHERA in RA patients.

The effect of MABTHERA on a variety of biomarkers was evaluated in patients enrolled into Study 3. This substudy evaluated the impact of a single treatment course of MABTHERA on levels of biochemical markers, including markers of inflammation [Interleukin 6, C Reactive protein, Serum amyloid type A protein, Protein S100 isotypes A8 and A9], autoantibody (RF and anti-CCP immunoglobulin) production and bone turnover [osteocalcin and procollagen 1 N terminal peptide (P1NP). MABTHERA treatment, whether as monotherapy or in combination with MTX or cyclophosphamide reduced the levels of inflammatory markers significantly, relative to MTX alone, over the first 24 weeks of follow-up. Levels of markers of bone turnover, osteocalcin and P1NP, increased significantly in the MABTHERA + MTX groups compared to MTX alone.

Multiple Course Therapy

Following completion of the 24-week double blind comparative study period, patients were permitted to enrol into an open-label long term follow up study. Patients received subsequent courses of MABTHERA as needed according to the treating clinician's assessment of disease activity and irrespective of the peripheral B lymphocyte count.

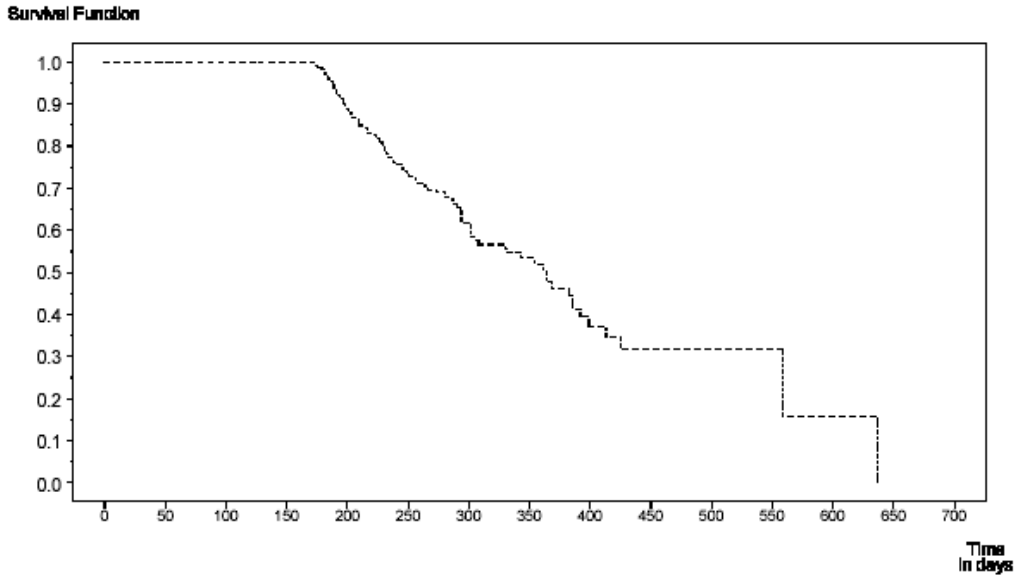
The all exposure population in the three double blind controlled trials (one Phase III and two Phase II trials) was 990 patients. Of these, 301 patients received a second course of MABTHERA 2 x 1000 mg + MTX, and 46 patients received a third course of MABTHERA 2 x 1000 mg + MTX.

At the point of data cut-off, 24.7% (193/781) of patients who had enrolled in the MABTHERA 2 x 1000 mg + MTX arms of the Phase II and Phase III studies had been retreated (point of data cut-off was defined as the time when all patients had been followed up for at least 24 weeks). Also at the data cut-off point, the majority of patients from the double blind comparative study period had received one course of treatment in the year. Kaplan-Meier analysis of time to second treatment course (censoring patients who did not receive a second treatment course or who withdrew from the study) shows an estimated median time for retreatment in the prior anti-TNF population of 364 days (interquartile range: 245-559 days), Figure 1, and 547 days (interquartile range: 302-889 days) in the no prior anti-TNF population, Figure 2.

The time interval between courses was variable. The majority of patients, who had two treatment courses at the time of cut-off, received their second course of treatment 6 to 12 months after the first treatment course. Some patients required even less frequent retreatment. The response to further therapy was at least the same magnitude as that following the initial treatment course, as evidenced by the change from baseline DAS28 (Figure 3).

Since many patients in the prior anti-TNF population remain in the studies after a single course of treatment with MABTHERA + MTX, these results are subject to change as the observation period increases.

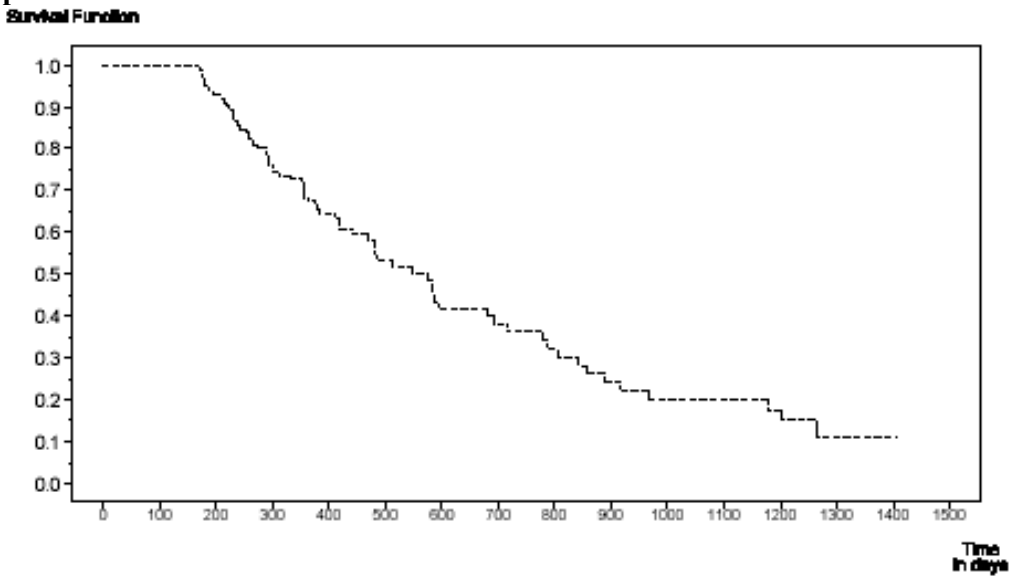
Figure 1 Kaplan-Meier Analysis of Time to Second Treatment Course, Prior Anti-TNF Population



Survival function = Probability of not switching to re-treatment
n = 525

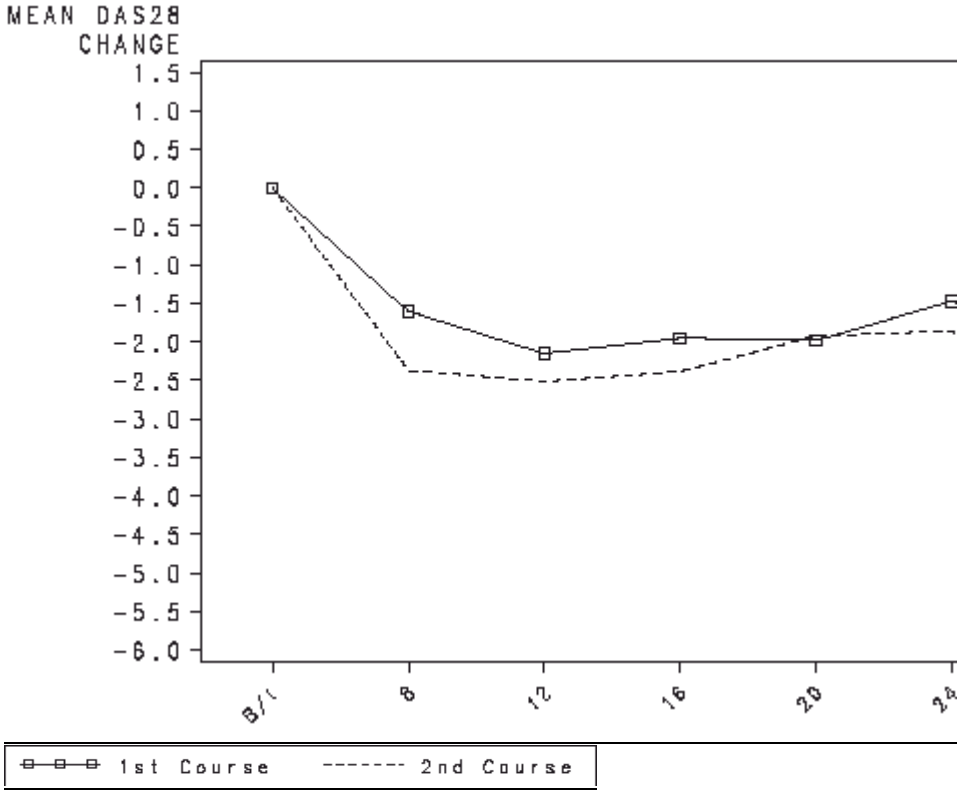
ρ

Figure 2 Kaplan-Meier Analysis of Time to Second Treatment Course, No Prior Anti-TNF Population



Survival function = Probability of not switching to re-treatment
n = 256

Figure 3 Mean Change in DAS28 Over Time Following First and Second Course Therapy (Prior anti-TNF population)



INDICATIONS

Non-Hodgkin's Lymphoma

MABTHERA is indicated for treatment of patients with:

- CD20 positive, previously untreated, Stage III/IV follicular, B-cell non-Hodgkin's lymphoma,
- CD20 positive, relapsed or refractory low grade or follicular, B-cell non-Hodgkin's lymphoma,
- CD20 positive, diffuse large B-cell non-Hodgkin's lymphoma, in combination with chemotherapy.

Chronic Lymphocytic Leukaemia

MABTHERA is indicated for the treatment of patients with CD20 positive chronic lymphocytic leukaemia (CLL) in combination with chemotherapy.

Rheumatoid Arthritis

MABTHERA (rituximab) in combination with methotrexate is indicated for the treatment of adult patients with severe, active rheumatoid arthritis who have had an inadequate response or intolerance to at least one tumour necrosis factor (TNF) inhibitor therapy.

*MABTHERA has been shown to reduce the rate of progression of joint damage as measured by x-ray when given in combination with methotrexate.

CONTRAINDICATIONS

MABTHERA is contraindicated in patients with known hypersensitivity to murine proteins or to any component of the product.

PRECAUTIONS

Progressive multifocal leukoencephalopathy (PML)

Use of MABTHERA may be associated with an increased risk of progressive multifocal leukoencephalopathy (PML). Patients must be monitored for any new or worsening neurological symptoms or signs suggestive of PML. Physicians treating patients should consider PML in the differential diagnosis of patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated.

Physicians should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g. cognitive, neurological or psychiatric symptoms). If such symptoms occur, further administration of MABTHERA should be immediately suspended until a diagnosis of PML has been excluded. To establish or exclude a diagnosis of PML evaluation including MRI scan, CSF testing for JC viral DNA and repeat neurological assessments, should be considered. Once PML has been excluded, the administration of MABTHERA may resume.

If a diagnosis of PML is confirmed MABTHERA must be permanently discontinued.Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.

Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukaemia

Infusion-related reactions

MABTHERA is associated with infusion-related reactions, which may be related to release of cytokines and/or other chemical mediators. Severe infusion-related reactions might be clinically indistinguishable from hypersensitivity reactions or cytokine release syndrome. Severe infusion-related reactions with fatal outcome have been reported during post-marketing use. Severe reactions usually manifested within 30 minutes to 2 hours after starting the first MABTHERA infusion, were characterised by *pulmonary events* and included, in some cases, *rapid tumour lysis* and *features of tumour lysis syndrome* in addition to fever, chills, rigors, hypotension, urticaria, angio-oedema and other symptoms. Patients with a high tumour burden or with a high number (>25 x 10^9/L) of circulating malignant cells such as patients with chronic lymphocytic leukaemia (CLL) and mantle cell lymphoma may be at higher risk of developing severe infusion-related reactions. Infusion reaction symptoms are usually reversible with interruption of the infusion. Treatment of infusion-related symptoms with diphenhydramine and paracetamol (acetaminophen) is recommended. Additional treatment with bronchodilators or IV saline may be indicated. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g. from 100 mg/h to 50 mg/h) when symptoms have completely resolved. Most patients who have experienced non-life threatening infusion-related reactions have been able to complete the full course of MABTHERA therapy. Further treatment of patients after complete resolution of signs and symptoms has rarely resulted in repeated severe infusion-related reactions. Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration of proteins to patients. Adrenaline, antihistamines and corticosteroids should be available for immediate use in the event of a hypersensitivity reaction to MABTHERA.

Patients with a high number (>25 x 10^9/L) of circulating malignant cells or high tumour burden such as patients with CLL and mantle cell lymphoma, who may be at higher risk of especially severe infusion-related reactions, should only be treated with extreme caution and when other therapeutic alternatives have been exhausted. These patients should be very closely monitored throughout the first infusion. Consideration should be given to the use of a reduced infusion rate for the first infusion in these patients, or a split dosing over two days during the first cycle and any subsequent cycles if the lymphocyte count is still >25 x 10^9/L.

Pulmonary events

Pulmonary events have included hypoxia, pulmonary infiltrates, and acute respiratory failure. Some of these events have been preceded by severe bronchospasm and dyspnoea. In some cases, symptoms worsened over time, while in others initial improvement was followed by clinical deterioration. Therefore, patients experiencing pulmonary events or other severe infusion-related symptoms should be closely monitored until complete resolution of their symptoms occurs. Patients with a history of pulmonary insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome and should be treated with increased caution. Acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest x-ray. The syndrome usually manifests itself within one or two hours of initiating the first infusion. Patients who experience severe pulmonary events should have their infusion interrupted immediately and should receive aggressive symptomatic treatment. Since initial improvement of clinical

symptoms may be followed by deterioration, these patients should be closely monitored until the pulmonary event has resolved.

Rapid tumour lysis
MABTHERA mediates the rapid lysis of benign and malignant CD20-positive cells. Signs and symptoms (e.g. hyperuricaemia, hyperkalaemia, hypocalcaemia, acute renal failure, elevated LDH) consistent with tumour lysis syndrome (TLS) have been reported to occur after the first MABTHERA infusion in patients with high numbers of circulating malignant lymphocytes. Prophylaxis for TLS should be considered for patients at risk of developing rapid tumour lysis (e.g. patients with a high tumour burden or with a high number (>25 x 10^9/L) of circulating malignant cells such as patients with CLL and mantle cell lymphoma). These patients should be followed closely and appropriate laboratory monitoring performed. Appropriate medical therapy should be provided for patients who develop signs and symptoms consistent with rapid tumour lysis. Following treatment for and complete resolution of signs and symptoms, subsequent MABTHERA therapy has been administered in conjunction with prophylactic therapy for TLS in a limited number of cases.

Cardiovascular
Since hypotension may occur during MABTHERA infusion, consideration should be given to withholding antihypertensive medications 12 hours prior to and throughout MABTHERA infusion. Angina pectoris or cardiac arrhythmia, such as atrial flutter and fibrillation have occurred in patients treated with MABTHERA. Therefore patients with a history of cardiac disease should be monitored closely. Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias.

Monitoring of Blood Counts
Although MABTHERA is not myelosuppressive in monotherapy, caution should be exercised when considering treatment of patients with neutrophil counts of <1.5 x 10^9/L and/or platelet counts of <75 x 10^9/L, as clinical experience with such patients is limited. MABTHERA has been used in patients who underwent autologous bone marrow transplantation and in other risk groups with a presumable reduced bone marrow function without inducing myelotoxicity.

Consideration should be given to the need for regular full blood counts, including platelet counts, during monotherapy with MABTHERA. When MABTHERA is given in combination with CHOP or CVP chemotherapy, regular full blood counts should be performed according to usual medical practice.

Infections
MABTHERA treatment should not be initiated in patients with severe active infections.

Cases of Hepatitis B virus (HBV) reactivation, occasionally with fulminant hepatitis, hepatic failure, and death have been reported in some patients with haematologic malignancies treated with MABTHERA. The majority of patients received MABTHERA in combination with chemotherapy. Isolated cases have been reported in patients who either had evidence of antibodies against Hepatitis B surface antigen before treatment or did not have any such antibodies. The median time to diagnosis of hepatitis was approximately 4 months after the initiation of MABTHERA and approximately one month after the last dose.

Persons at high risk of HBV infection should be screened before initiation of MABTHERA. Reactivation of HBV infection is a well-known complication in patients with chronic hepatitis

B, especially in those receiving cytotoxic or immunosuppressive therapy. In addition, non-Hodgkin's lymphoma of itself may be an independent risk factor for HBV reactivation. Carriers of hepatitis B, and patients with evidence of having recovered from hepatitis B, should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis during and up to one year following therapy with MABTHERA.

In patients who develop reactivation of viral hepatitis B, MABTHERA and any concomitant chemotherapy should be discontinued and appropriate treatment including antiviral therapy initiated. There are insufficient data regarding the safety of resuming therapy with MABTHERA in patients who develop hepatitis subsequent to HBV reactivation.

The following additional serious viral infections, either new, reactivated or exacerbated, have been identified in clinical studies or post-marketing reports. The majority of patients were profoundly immune-suppressed. These viral infections included JC virus [progressive multifocal leukoencephalopathy (PML)], cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus and hepatitis C. In some cases, the viral infections occurred up to one year following discontinuation of MABTHERA and have resulted in death.

Immunisation
The safety of immunisation with live viral vaccines, following MABTHERA therapy has not been studied and vaccination with live virus vaccines is not recommended.

*Patients treated with MABTHERA may receive non-live vaccinations. However, with non-live vaccines response rates may be reduced. In a non-randomised study, patients with relapsed low-grade NHL who received MABTHERA monotherapy when compared to healthy untreated controls had a lower rate of response to vaccination with tetanus recall antigen (16% vs 81%) and Keyhole Limpet Haemocyanin (KLH) neoantigen (4% vs 69% when assessed for > 2-fold increase in antibody titer).

Mean pre-therapeutic antibody titers against a panel of antigens (Streptococcus pneumoniae, influenza A, mumps, rubella, varicella) were maintained for at least 6 months after treatment with MABTHERA.

Progressive multifocal leukoencephalopathy (PML)
*Cases of progressive multifocal leukoencephalopathy (PML) have been reported during use of MABTHERA in NHL and CLL. The majority of patients had received MABTHERA in combination with chemotherapy or as part of a haematopoietic stem cell transplant. (See BOXED WARNING, ADVERSE EFFECTS and *Post-Marketing Experience*.)

Rheumatoid Arthritis

Methotrexate (MTX) naïve populations
The use of MABTHERA is not recommended in MTX-naïve patients since a favourable benefit-risk relationship has not been established.

Infusion-related Reactions
MABTHERA is associated with infusion-related reactions (IRRs), which may be related to release of cytokines and/or other chemical mediators. Premedication with IV glucocorticoid significantly reduced the incidence and severity of these events.

*Most infusion events reported were mild to moderate in severity. The most common symptoms were headache, pruritus, throat irritation, flushing, rash, urticaria, hypertension, and pyrexia. In general, the proportion of patients experiencing any infusion reaction was higher following the first infusion of any treatment course than following the second infusion. Subsequent MABTHERA infusions were better tolerated by patients than the initial infusion. Fewer than 1% of patients experienced serious IRRs, with most of these reported during the first infusion of the first course (see Adverse Effects - *Experience from Rheumatoid Arthritis Clinical Trials*).The reactions reported were usually reversible with a reduction in rate, or interruption, of MABTHERA infusion and administration of an anti-pyretic, an antihistamine, and, occasionally, oxygen, IV saline or bronchodilators, and glucocorticoids if required. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g. from 100 mg/h to 50 mg/h) when symptoms have completely resolved.

Anaphylactic and other hypersensitivity reactions have been reported following the IV administration of proteins to patients. Medicinal products for the treatment of hypersensitivity reactions, e.g., adrenaline, antihistamines and glucocorticoids, should be available for immediate use in the event of an allergic reaction during administration of MABTHERA. The presence of HACA may be associated with worsening infusion or allergic reactions after the second infusion of subsequent courses.

Infections

*Serious infections, including fatalities, can occur during therapy with MABTHERA. Based on the mechanism of action of MABTHERA and the knowledge that B cells play an important role in maintaining normal immune response, patients may have an increased risk of infection following MABTHERA therapy. MABTHERA should not be administered to patients with an active infection or severely immunocompromised patients (e.g. where levels of CD4 or CD8 are very low). Physicians should exercise caution when considering the use of MABTHERA in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection. Patients who develop infection following MABTHERA therapy should be promptly evaluated and treated appropriately.

*Cases of hepatitis B reactivation have been reported in patients with non-Hodgkin's lymphoma receiving MABTHERA in combination with cytotoxic chemotherapy (see Precautions for Infections under *Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukaemia*). Reactivation of hepatitis B infection has also been very rarely reported in RA patients receiving MABTHERA.

Progressive multifocal leukoencephalopathy (PML)

Cases of progressive multifocal leukoencephalopathy (PML) have been reported following use of MABTHERA for the treatment of autoimmune diseases including RA. Several but not all of the reported cases involved patients with recognised risk factors for PML, including the underlying disease and long term immunosuppressive therapy or chemotherapy. (See BOXED WARNING and PRECAUTIONS.) The efficacy and safety of MABTHERA for the treatment of autoimmune diseases other than
RA has not been established.

Immunisation

*Physicians should review the patient's vaccination status and follow current immunisation guidelines prior to treatment with MABTHERA. Vaccination should be completed at least 4 weeks prior to first administration of MABTHERA.

The safety of immunisation with live viral vaccines following MABTHERA therapy has not been studied. Therefore vaccination with live virus vaccines is not recommended whilst on MABTHERA or whilst peripherally B cell depleted.

Patients treated with MABTHERA may receive non-live vaccinations. However, response rates to non-live vaccines may be reduced. In a randomised study, patients with RA treated with MABTHERA and MTX had comparable response rates to tetanus recall antigen (39% vs 42%), reduced rates to pneumococcal polysaccharide vaccine (43% vs 82% to at least 2 pneumococcal antibody serotypes), and KLH neoantigen (47% vs 93%), when given at least 6 months after MABTHERA as compared to patients only receiving MTX. Should non-live vaccinations be required whilst receiving MABTHERA therapy, these should be completed at least 4 weeks prior to commencing the next course of MABTHERA.

In the overall experience of MABTHERA repeat treatment over one year, the proportions of patients with positive antibody titers against S. pneumoniae, influenza, mumps, rubella, varicella and tetanus toxoid were generally similar to the proportions at baseline.

Cardiovascular Events

*Patients with a history of cardiac disease should be monitored closely during infusions. Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias (see Precautions for Cardiovascular Events under *Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukaemia* section). There are no data on the safety of MABTHERA in patients with moderate or severe heart failure (NYHA class III or IV) or severe, uncontrolled cardiovascular disease. In patients treated with MABTHERA, the occurrence of pre-existing ischaemic 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, consideration should be given to withholding anti-hypertensive medications 12 hours prior to the MABTHERA infusion.

Concomitant/Sequential Use of Other DMARDs

The concomitant use of MABTHERA and antirheumatic therapies other than those specified under the RA indication and dosing is not recommended.

Limited data are available on the safety of the use of biologic agents or DMARDs other than MTX in patients exhibiting peripheral B cell depletion following treatment with MABTHERA. If biologic agents and/or DMARDs are used following MABTHERA therapy, patients should be observed for signs of infection.

Malignancy

Immunomodulatory drugs may increase the risk of malignancy. On the basis of limited experience with MABTHERA in RA patients (see 'ADVERSE EFFECTS - *Experience from Rheumatoid Arthritis Clinical Trials*') a possible risk for the development of solid tumours

cannot be excluded at this time, although present data do not seem to suggest any increased risk.

Patients with Renal or Hepatic Impairment
*The safety and effectiveness of MABTHERA in patients with renal or hepatic impairment has not been established. MTX is contraindicated in such patients and since MABTHERA is given in combination with MTX these patients were not included in the clinical studies for RA.

General Precautions

Carcinogenicity, Mutagenicity and Impairment of Fertility
No animal studies have been performed to establish the carcinogenic or mutagenic potential of MABTHERA, or to determine its effects on fertility in males or females.

Use in Pregnancy (Category C)
It is not known whether MABTHERA can cause foetal harm when administered to a pregnant woman. There are no adequate and well-controlled data from studies in pregnant women, however transient B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to rituximab. In clinical studies in patients with RA, three pregnancies occurred following exposure to MABTHERA + MTX with two resulting in spontaneous abortions and the third ongoing at the time. Rituximab has been shown to cause B-cell depletion in the monkey foetus. MABTHERA should not be given to a pregnant woman, unless the potential benefit outweighs the potential risk.

Individuals of child-bearing potential should use effective contraceptive methods during treatment and for up to 12 months following MABTHERA therapy.

Developmental toxicity studies performed in cynomolgus monkeys revealed no evidence of embryotoxicity in utero at relative exposure levels (AUC) similar to that anticipated clinically. New born offspring of maternal animals exposed to MABTHERA during lactation and/or gestation showed no untoward toxicity except for depleted B cell populations during the post-natal phase at the same relative exposure. B cell levels in human neonates following maternal exposure to MABTHERA have not been studied.

Use in Lactation
It is not known whether MABTHERA is excreted in human milk. In monkey studies, rituximab was excreted in the milk and was detected in the serum of breast-fed infants. Reversible B-cell depletion was observed in all monkey infants exposed to rituximab via maternal transfer during lactation and/or gestation. It is recommended that a nursing woman discontinue breast-feeding whilst undergoing treatment with MABTHERA.

Use in Children
The safety and effectiveness of MABTHERA in children have not been established.

Driving and Operating Machinery

It is not known whether MABTHERA has an effect on the ability to drive and operate machines, though the pharmacologic activity and adverse events reported to date do not indicate that such an effect is to be expected.

Drug /Laboratory Interactions
Currently, there are limited data on possible drug interactions with MABTHERA.

In CLL patients, co-administration with MABTHERA did not appear to have an effect on the pharmacokinetics of fludarabine or cyclophosphamide. In addition, there was no apparent effect of fludarabine and cyclophosphamide on the pharmacokinetics of MABTHERA.

Co-administration with MTX had no effect on the pharmacokinetics of MABTHERA in RA patients.

Patients with human anti-mouse antibody or human anti-chimeric antibody (HAMA/HACA) titres may have allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic monoclonal antibodies.

The tolerability of simultaneously or sequential combination of MABTHERA with chemotherapy other than CHOP or CVP, or agents which are liable to cause depletion of normal B cells is not well defined.

In a small cohort of patients with RA, 110 patients received subsequent therapy with other DMARDs (including biologicals). Patients received subsequent DMARDs 4-6 months following therapy with MABTHERA and generally while peripherally B cell depleted. The rate of clinically relevant infections was 7.8 per 100 patient years.

ADVERSE EFFECTS

Experience from Clinical Trials in Haemato-Oncology

The most common adverse reactions of MABTHERA (incidence ≥ 25%) observed in patients with NHL are infusion reactions, fever, chills, infection, asthenia and lymphopenia. The most important serious adverse reactions of MABTHERA are infusion reactions, tumour lysis syndrome, mucocutaneous toxicities, hepatitis B reactivation with fulminant hepatitis, PML, other viral infections, cardiac arrhythmias, renal toxicity, and bowel obstruction and perforation.

The frequencies of adverse drug reactions (ADRs) reported with MABTHERA alone or in combination with chemotherapy are summarised in the tables below and are based on data from clinical trials. These ADRs had either occurred in single arm studies or had occurred with at least a 2% difference compared to the control arm in at least one of the major randomised clinical trials. ADRs are added to the appropriate category in the tables below according to the highest incidence seen in any of the major clinical trials. Within each frequency grouping ADRs are listed in descending order of severity. Frequencies are defined as very common ≥ 1/10 (≥ 10%), common ≥ 1/100 to < 1/10 (≥ 1% to < 10%) and uncommon ≥ 1/1,000 to < 1/100 (≥ 0.1% to < 1%).

MABTHERA monotherapy/maintenance therapy

The ADRs in the table below are based on data from single-arm studies including 356 patients with low-grade or follicular lymphoma, treated with MABTHERA weekly as a single agent for the treatment or re-treatment of non-Hodgkin's lymphoma up to 4 weeks in most patients and from 25 patients who received doses other than 375 mg/m^2 for four doses and up to 500 mg/m^2 single dose in the Phase I setting (see CLINICAL TRIALS). The table also contains ADRs based on data from 166 patients with follicular lymphoma who received MABTHERA as maintenance therapy for up to 2 years following response to initial induction with CHOP or R-CHOP (see CLINICAL TRIALS). The ADRs were reported up to 12 months after treatment with monotherapy and up to 1 month after treatment with MABTHERA maintenance.

Table 9 Summary of ADRs reported in patients with low-grade or follicular lymphoma receiving MABTHERA monotherapy (N = 356) or MABTHERA maintenance treatment (N = 166) in clinical trials

System Organ Class	Very Common (≥ 10%)	Common (≥1% - < 10%)	Uncommon (≥0.1% - < 1%)
Infections and infestations	bacterial infections, viral infections	sepsis, +pneumonia, +febrile infection, +herpes zoster, +respiratory tract infection, fungal infections, infections of unknown aetiology	
Blood and the lymphatic system disorders	neutropenia , leucopenia	anaemia, thrombocytopenia	coagulation disorders, transient aplastic anaemia, haemolytic anaemia, lymphadenopathy
Immune system disorders	angioedema	hypersensitivity	
Metabolism and nutrition disorders		hyperglycaemia, weight decrease, peripheral oedema, face oedema, increased LDH, hypocalcaemia	
Psychiatric disorders			depression, nervousness
Nervous system disorders		paresthesia, hypoesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety	dysgeusia
Eye disorders		lacrimation disorder, conjunctivitis	
Ear and labyrinth disorders		tinnitus, ear pain	
Cardiac disorders		+myocardial infarction, arrhythmia, +atrial fibrillation, tachycardia, +cardiac disorder	+left ventricular failure, +supraventricular tachycardia, +ventricular tachycardia, +angina, +myocardial ischaemia, bradycardia
Vascular disorders		hypertension, orthostatic hypotension, hypotension	
Respiratory, thoracic and mediastinal disorders		bronchospasm , respiratory disease, chest pain, dyspnoea , cough , rhinitis	asthma , bronchiolitis obliterans, lung disorder, hypoxia
Gastrointestinal disorders	nausea	vomiting , diarrhoea, abdominal pain , dysphagia, stomatitis, constipation	abdominal enlargement

		dyspepsia, anorexia, throat irritation	
Skin and subcutaneous tissue disorders	pruritis , rash	urticaria , +alopecia, sweating, night sweats	
Musculoskeletal, connective tissue and bone disorders		hypertonia, myalgia , arthralgia, back pain , neck pain, pain	
General disorders and administration site conditions	fever , chills , asthenia , headache	tumour pain, flushing, malaise, cold syndrome	pain at the infusion site
Investigations	decreased IgG levels		

For each term, the frequency count was based on reactions of all grades (from mild to severe), except for terms marked with "+" where the frequency count was based only on severe (≥ Grade 3 NCI common toxicity criteria) reactions. Only the highest frequency observed in either trial is reported.

MABTHERA in combination with chemotherapy in NHL and CLL

The ADRs listed in the table below are based on rituximab-arm data from controlled clinical trials that occurred in addition to those seen with monotherapy/maintenance therapy and/or at a higher frequency grouping: 202 patients with diffuse large B-cell lymphoma (DLBCL) treated with R-CHOP, from 234 and 162 patients with follicular lymphoma treated with R-CHOP or R-CVP, respectively, and from 397 previously untreated CLL patients and 274 relapsed/refractory CLL patients treated with rituximab in combination with fludarabine and cyclophosphamide (R-FC) (see CLINICAL TRIALS).

The safety information of MABTHERA in combination with certain chemotherapy regimens is limited. When MABTHERA is used with other chemotherapy medicines, prescribers are advised to consider the adverse reaction profile of the component medicine(s).

Table 10 Summary of severe ADRs reported in patients receiving R-CHOP in DLBCL (N=202), R-CHOP in follicular lymphoma (N=234), R-CVP in follicular lymphoma (N=162) and R-FC in previously untreated (N=397) or relapsed/refractory (N=274) CLL

System Organ Class	Very Common (≥ 10%)	Common (≥ 1% - < 10%)
Infections and infestations	bronchitis	acute bronchitis, sinusitis, hepatitis B*
Blood and the lymphatic system disorders	febrile neutropenia, thrombocytopenia	pancytopenia, granulocytopenia
Skin and subcutaneous tissue disorders	alopecia	skin disorder
General disorders and administration site conditions	-	fatigue, shivering

*includes reactivation and primary infections; frequency based on R-FC regimen in relapsed/refractory CLL
Frequency count was based on only severe reactions defined in clinical trials as ≥ Grade 3 NCI common toxicity criteria. Only the highest frequency observed in any trial is reported.

The following terms have been reported as adverse events, however, were reported at a similar (<2% difference between the groups) or lower incidence in the MABTHERA-arms compared to control arms: haematotoxicity, neutropenic infection, urinary tract infection, septic shock, superinfection lung, implant infection, septicaemia staphylococcal, lung infection, rhinorrhoea, pulmonary oedema, cardiac failure, sensory disturbance, venous thrombosis, mucosal inflammation nos, influenza-like illness, oedema lower limb, abnormal ejection fraction, pyrexia, general physical health deterioration, fall, multi-organ failure, venous thrombosis deep limb, positive blood culture, diabetes mellitus inadequate control.

Further information on selected, serious adverse drug reactions

Infusion-related reactions

Monotherapy – 4 weeks treatment

Hypotension, fever, chills, rigors, urticaria, bronchospasm, sensation of tongue or throat swelling (angioedema), nausea, fatigue, headache, pruritus, dyspnoea, rhinitis, vomiting, flushing, and pain at disease sites have occurred in association with MABTHERA infusion as part of an infusion-related symptom complex. Such infusion-related symptoms occurred in the majority of patients during the first MABTHERA infusion (see PRECAUTIONS). The incidence of infusion-related symptoms decreased from 77% (7% Grade 3/4) with the first infusion to approximately 30% (2% Grade 3/4) with the fourth infusion and to 14% (no Grade 3/4 events) with the eighth infusion.

Maintenance Treatment (NHL) up to 2 years

Non-serious signs and symptoms suggestive of an infusion-related reaction were reported in 41% of patients for general disorders (mainly asthenia, pyrexia, influenza like illness, pain) and in 7% of patients for immune system disorders (hypersensitivity). Serious infusion-related reactions (defined as serious adverse events starting during or within one day of a rituximab infusion) occurred in < 1% of patients treated with MABTHERA maintenance.

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL; R-FC in CLL)

Severe infusion-related reactions occurred in up to 12% of all patients at the time of the first treatment cycle with rituximab in combination with chemotherapy. The incidence of Grade 3 or 4 infusion-related reactions decreased to less than 1% by the eighth cycle of therapy. The signs and symptoms were consistent with those observed during monotherapy (see PRECAUTIONS), but also included dyspepsia, rash, hypertension, tachycardia, features of tumour lysis syndrome. Additional reactions reported in isolated cases at the time of R-chemotherapy were myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia.

Infections

Monotherapy – 4 weeks treatment

MABTHERA induced B-cell depletion in 70% to 80% of patients and was associated with decreased serum immunoglobulins in only a minority of patients. Infectious events, irrespective of causal assessment, occurred in 30.3% of 356 patients: 18.8% of patients had bacterial infections, 10.4% had viral infections, 1.4% had fungal infections, and 5.9% had infections of unknown aetiology. Severe infectious events (Grade 3 or 4), including sepsis occurred in 3.9% of patients; in 1.4% during the treatment period and in 2.5% during the follow-up period.

Maintenance Treatment (NHL) up to 2 years

The proportion of patients with Grade 1 to 4 infections was 25% in the observation group and 45% in the MABTHERA group with Grade 3 or 4 infections in 3% of patients on observation and 11% receiving MABTHERA maintenance treatment. Grade 3 to 4 infections reported in ≥ 1% of patients in the MABTHERA arm were pneumonia (2%), respiratory tract infection (2%), febrile infection (1%) and herpes zoster (1%). In a large proportion of infections (all grades), the infectious agent was not specified or isolated, however, where an infectious agent was specified, the most frequently reported underlying agents were bacterial (observation 2%, MABTHERA 10%), viruses (observation 7%, MABTHERA 11 %) and fungi (observation

2%, MABTHERA 4%). There was no cumulative toxicity in terms of infections reported over the 2-year maintenance period.

Data from a phase III clinical trial included 2 cases of fatal PML in NHL patients that occurred after disease progression and retreatment (see BOXED WARNING and PRECAUTIONS).

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL; R-FC in CLL)
In the R-CVP study the overall proportion of patients with infections or infestations during treatment and for 28 days after trial treatment end was comparable between the treatment groups (33% R-CVP, 32% CVP). The most common infections were upper respiratory tract infections which were reported for 12.3% patients on R-CVP and 16.4% patients receiving CVP; most of these infections were nasopharyngitis. Serious infections were reported in 4.3% of the patients receiving R-CVP and 4.4% of the patients receiving CVP. No life threatening infections were reported during this study.

In the R-CHOP study the overall incidence of Grade 2 to 4 infections was 45.5% in the R-CHOP group and 42.3% in the CHOP group. Grade 2 to 4 fungal infections were more frequent in the R-CHOP group (4.5% vs 2.6% in the CHOP group); this difference was due to a higher incidence of localised Candida infections during the treatment period. The incidence of Grade 2 to 4 herpes zoster, including ophthalmic herpes zoster, was higher in the R-CHOP group (4.5%) than in the CHOP group (1.5%), with 7 of a total of 9 cases in the R-CHOP group occurring during the treatment phase. The proportion of patients with Grade 2 to 4 infections and/or febrile neutropenia was 55.4% in the R-CHOP group and 51.5% in the CHOP group. Febrile neutropenia (i.e. no report of concomitant documented infection) was reported only during the treatment period, in 20.8% in the R-CHOP group and 15.3% in the CHOP group.

In patients with CLL, the overall incidence of Grade 3 or 4 infections during treatment and for 28 days after the end of trial treatment was comparable between the treatment groups both in the first-line (18% R-FC vs 17% FC) and in the relapsed/refractory setting (19% R-FC vs 18% FC). The incidence of Grade 3 or 4 hepatitis B infection (reactivation and primary infection) was 2% R-FC vs 0% FC.

Haematologic Events
Monotherapy – 4 weeks treatment
Severe (Grade 3 and 4) neutropenia was reported in 4.2% of patients, severe anaemia was reported in 1.1% of patients and severe thrombocytopenia was reported in 1.7% of patients. A single occurrence of transient aplastic anaemia (pure red cell aplasia) and two occurrences of haemolytic anaemia following MABTHERA therapy were reported.

Maintenance Treatment (NHL) up to 2 years
Leucopenia (all grades) occurred in 26% of patients on observation vs 31% of patients in the MABTHERA arm, and neutropenia was reported in 13% of patients on observation and in 25% of patients on MABTHERA. There was a higher incidence of Grade 3-4 neutropenia (observation 5%, MABTHERA 11%) and leucopenia (observation 2%, MABTHERA 5%) in the MABTHERA arm compared to the observation arm. The incidence of Grade 3 to 4 thrombocytopenia (observation 1%, MABTHERA < 1%) was low.

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL; R-FC in CLL)

Severe (Grade 3 or 4) Neutropenia: There was a higher incidence of Grade 3 or 4 neutropenia in the MABTHERA containing study arms compared to the chemotherapy arms. In the R-CVP study, the incidence of neutropenia was 24% in the R-CVP arm versus 14% of patients in the CVP arm. These laboratory findings were reported as adverse events and resulted in medical intervention in 3.1% of patients on R-CVP and 0.6% of patients on CVP. The higher incidence of neutropenia in the R-CVP group was not associated with a higher incidence of infections and infestations. In patients with previously untreated CLL, Grade 3 or 4 neutropenia was reported as an adverse event in 30% of patients in the R-FC arm and in 19% of patients in the FC arm. In patients with relapsed/refractory CLL, the incidence of Grade 3 or 4 neutropenia adverse events was slightly higher in the R-FC arm (42% R-FC) compared to FC arm (40%).

Severe (Grade 3 or 4) Leucopenia: In the R-CHOP study, the incidence of severe leucopenia was 88% in the R-CHOP arm versus 79% in the CHOP arm. In CLL first-line, more patients receiving R-FC experienced Grade 3 or 4 leucopenia (23%) compared with patients receiving FC (12%). In patients with relapsed/refractory CLL, the overall incidence of Grade 3 or 4 leucopenia adverse events was comparable between the treatment arms (4% R-FC vs 3% FC).

Severe (Grade 3 or 4) Anaemia and Thrombocytopenia: No relevant difference between the treatment arms was observed with respect to Grade 3 and 4 anaemia or thrombocytopenia for the R-CHOP and R-CVP studies. In the R-CVP study, the incidence of anaemia was 0.6% in the R-CVP arm versus 1.9% in the CVP arm. The incidence of thrombocytopenia was 1.2% in the R-CVP arm versus 0% in the CVP arm. In the R-CHOP study, the incidence of anaemia was 14% in the R-CHOP arm versus 19% in the CHOP arm. The incidence of thrombocytopenia was 15% in the R-CHOP arm versus 16% in the CHOP arm. The time to recovery from all haematological abnormalities was comparable in the two treatment groups. In the CLL first-line study, Grade 3 or 4 anaemia was reported by 4% of patients treated with R-FC compared to 7% of patients receiving FC, and Grade 3 or 4 thrombocytopenia was reported by 7% of patients in the R-FC group compared to 10% of patients in the FC group. In the relapsed/refractory CLL study, adverse events of Grade 3 or 4 anaemia were reported in 12% of patients treated with R-FC compared to 13% of patients receiving FC and Grade 3 or 4 thrombocytopenia was reported by 11% of patients in the R-FC group compared to 9% of patients in the FC group.

Cardiovascular Events

Monotherapy – 4 weeks treatment

Cardiovascular events were reported in 18.8% of patients during the treatment period. The most frequently reported events were hypotension and hypertension. Two patients (0.6%) experienced Grade 3 or 4 arrhythmia (including ventricular and supraventricular tachycardia) during a MABTHERA infusion and one patient with a history of myocardial infarction experienced angina pectoris, evolving into myocardial infarction 4 days later.

Maintenance Treatment (NHL) up to 2 years

The incidence of Grade 3 to 4 cardiac disorders was comparable between the two treatment groups (4% in observation, 5% in MABTHERA). Cardiac events were reported as serious adverse event in < 1 % of patients on observation and in 3% of patients on MABTHERA: atrial fibrillation (1%), myocardial infarction (1%), left ventricular failure (< 1%), myocardial ischaemia (< 1%).

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL; R-FC in CLL)

In the R-CVP study the overall incidence of cardiac disorders in the safety population was low (4% R-CVP, 5% CVP), with no relevant differences between the treatment groups.

In the R-CHOP study the incidence of Grade 3 and 4 cardiac arrhythmias, predominantly supraventricular arrhythmias such as tachycardia and atrial flutter/fibrillation, was higher in the R-CHOP group (14 patients, 6.9%) as compared to the CHOP group (3 patients, 1.5%). All of these arrhythmias either occurred in the context of a MABTHERA infusion or were associated with predisposing conditions such as fever, infection, acute myocardial infarction or pre-existing respiratory and cardiovascular disease. No difference between the R-CHOP and CHOP group was observed in the incidence of other Grade 3 and 4 cardiac events including heart failure, myocardial disease and manifestations of coronary artery disease.

In CLL, the overall incidence of Grade 3 or 4 cardiac disorders was low both in the first-line study (4% R-FC vs 3% FC) and in the relapsed/refractory study (4% R-FC vs 4% FC).

IgG Levels

Maintenance Treatment (NHL) up to 2 years

After induction treatment, median IgG levels were below the lower limit of normal (LLN) (< 7 g/L) in both the observation and the MABTHERA groups. In the observation group, the median IgG level subsequently increased to above the LLN, but remained constant during MABTHERA treatment. The proportion of patients with IgG levels below the LLN was about 60% in the MABTHERA group throughout the 2 year treatment period, while it decreased in the observation group (36% after 2 years). Monitoring of IgG levels should be considered for patients treated with MABTHERA. IV Ig substitution may be indicated for patients with decreased IgG levels.

Neurologic Events

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL; R-FC in CLL)

During the treatment period, four patients (2%) in the R-CHOP group, all with cardiovascular risk factors, experienced thromboembolic cerebrovascular accidents during the first treatment cycle. There was no difference between the treatment groups in the incidence of other thromboembolic events. In contrast, three patients (1.5%) had cerebrovascular events in the CHOP group, all of which occurred during the follow-up period.

In CLL, the overall incidence of Grade 3 or 4 nervous system disorders was low both in the first-line study (4% R-FC vs 4% FC) and in the relapsed/refractory study (3% R-FC vs 3% FC).

Subpopulations

The adverse events described below are only those considered by the investigator to be related to treatment with MABTHERA.

Elderly patients (≥ 65 years)

Monotherapy – 4 weeks treatment: The incidence of any ADR and of Grade 3 and 4 ADRs was similar in elderly (N=94) and younger (N=237) patients (88.3% versus 92.0% for any ADR and 16.0% versus 18.1% for Grade 3 and 4 ADR).

Combination Therapy: The incidence of Grade 3 or 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.

Bulky disease: Patients with bulky disease (N=39) had a higher incidence of Grade 3 and 4 ADRs than patients without bulky disease (N=195; 25.6% versus 15.4%). The incidence of any ADR was similar in these two groups (92.3% in bulky disease versus 89.2% in non-bulky disease).

Re-treatment: The percentage of patients reporting any adverse event and Grade 3 and 4 ADRs upon re-treatment (N=60) with further courses of MABTHERA was similar to the percentage of patients reporting any ADR and Grade 3 and 4 ADRs upon initial exposure (N=203; 95.0% versus 89.7% for any ADR and 13.3% versus 14.8% for Grade 3 and 4 ADRs).

Experience from Clinical Trials in Rheumatoid Arthritis

The clinical efficacy of MABTHERA, given together with methotrexate, was studied in three double blind controlled clinical trials (one Phase III and two Phase II trials) in patients with rheumatoid arthritis. 1039 patients received at least one treatment course, 570 patients received two or more courses of treatment during the follow up period, 191 patients three or more courses, 40 patients four or more courses and 3 patients received 5 or more courses during the follow up period. So far 839 patients have been followed for more than a year, 139 for more than 2 years and 89 for more than 3 years post MABTHERA treatment.

In clinical trials patients received 2 x 1000 mg of MABTHERA separated by an interval of two weeks; in addition to MTX (10-25 mg/week) (see DOSAGE AND ADMINISTRATION – *Rheumatoid Arthritis*). MABTHERA infusions were administered after an IV infusion of 100 mg methylprednisolone; the majority of patients also received treatment with oral prednisone for 15 days. ADRs, which occurred with at least a 2% difference compared to the control arm and more frequently by patients who had received at least one infusion of MABTHERA than among patients that had received placebo in the Phase III trial and the combined population included in Phase II studies, are listed in the table below. Frequencies are defined as very common (≥ 10%) and common (≥ 1% to < 10%).

The most frequent ADRs considered due to receipt of 2 x 1000 mg MABTHERA in Phase II and III studies were acute infusion reactions. Infusion reactions occurred in 15% patients following the first infusion of MABTHERA and 5% in placebo patients. Infusion reactions decreased to 2% following the second infusion in both MABTHERA and placebo groups.

Table 11 Summary of Adverse Reactions Occurring in Patients with Rheumatoid Arthritis receiving MABTHERA during Phase II and III Clinical Studies †

	Phase II Study Population		**Phase III Study Population**	
	Very Common (≥ 10%)	**Common** (≥ 1 % - < 10%)	**Very Common** (≥ 10%)	**Common** (≥ 1% - < 10%)
Acute Infusion reactions*		hypertension, rash, pruritus, chills, pyrexia, rhinitis, throat irritation		hypertension, nausea, rash, pyrexia, pruritus, urticaria, throat irritation, hot flush, hypotension
Gastrointestinal disorders		dyspepsia		dyspepsia
Infections and Infestations	any infection	urinary tract infections	any infection, upper respiratory tract infection	

	Phase II Study Population		Phase III Study Population	
Metabolism and Nutritional disorders				hypercholesterolemia
Musculo skeletal disorders		arthralgia/ musculoskeletal pain		arthralgia/ musculoskeletal pain, osteoarthritis
Nervous System disorders		migraine		paraesthesia

† This table include all events with an incidence difference of ≥ 2 % for rituximab compared to placebo
* Reactions occurring during or within 24 hours of infusion

The following adverse events were reported at a frequency between 1% and 2% greater in the MABTHERA-arms compared to control arms: lower respiratory tract infections/pneumonia, abdominal pain upper, muscle spasms, asthenia.

In addition to the events tabulated above, medically significant events reported rarely in the MABTHERA treated population and considered potential reactions to treatment include the following:

General Disorders:	Generalised oedema
Respiratory Disorders:	Bronchospasm, wheezing, laryngeal oedema
Skin and Subcutaneous Disorders:	Angioneurotic oedema, generalised pruritis
Immune system Disorders:	Anaphylaxis, anaphylactoid reaction.

Multiple Courses
Multiple courses of treatment are associated with a similar ADR profile to that observed following first exposure. However, worsening of infusion or allergic reactions and failure to B cell deplete following rituximab cannot be excluded in HACA positive patients after repeated exposure to rituximab on the basis of the available data. The incidence of acute infusion reactions following subsequent treatment courses was generally lower than the incidence following the first infusion of MABTHERA.

Further information on selected, serious adverse drug reactions

Infusion-related Reactions (IRRs)
Symptoms suggesting an acute infusion reaction (pruritis, fever, urticaria/rash, chills, pyrexia, rigors, sneezing, angioneurotic oedema, throat irritation, cough and bronchospasm, with or without associated hypotension or hypertension) were observed in 79/540 (15%) patients following their first exposure to MABTHERA. In a study comparing the effect of glucocorticoid regimen, these events were observed in 5/149 (3%) of patients following their first placebo infusion and 42/192 (22%) of patients receiving their first infusion of 1000 mg MABTHERA. Premedication with IV glucocorticoid significantly reduced the incidence and severity of these events (see PRECAUTIONS – *Rheumatoid Arthritis*). Of the patients who received 1000 mg MABTHERA without premedication with glucocorticoids, 18/65 (28%) experienced an acute infusion reaction, compared with 24/127 (19%) in patients given IV glucocorticoid premedication, respectively.

In Study 1 (REFLEX) 5/308 (1.6%) patients from the MABTHERA + MTX group and no patients from the placebo + MTX group withdrew from the study due to acute infusion reactions. A reduced number of acute infusion reactions occurred during the second infusion, and none resulted in withdrawal of a patient.

In Study 2 (DANCER) 5/192 (3%) patients in the 2 x 1000 mg MABTHERA + MTX group were withdrawn due to acute infusion reactions. No patients in the placebo or 2 x 500 mg MABTHERA groups withdrew from treatment.

In Study 3 one patient in the 2 x 1000 mg MABTHERA group withdrew due to an acute infusion reaction.

Infections
The rate of infection was approximately 0.9 per patient year in MABTHERA treated patients. The infections consisted mostly of upper respiratory tract infections and urinary tract infections. Clinically significant infections (defined as those which were reported as serious and/or were treated with IV antibiotics) were observed in 68/1039 (7%) of patients treated with MABTHERA compared to 3/107 (3%) of patients treated with only placebo. The rate of clinically significant infection was 0.05 per patient year in MABTHERA treated patients. Clinically significant infections predominantly included those of the lower respiratory, urinary and gastrointestinal tracts. Three clinically significant infections resulted in fatal outcomes, one was considered related to MABTHERA (septic shock) and two unrelated (neutropenic sepsis and bronchopneumonia).

Malignancies
The observed incidence of malignancies following exposure to rituximab (1.6 per 100 person years) lies within the range expected for a population with similar age and gender profile. A total of 26 malignancies have been reported in 22/1039 (2%) patients treated with MABTHERA. The most common types were skin cancer (basal cell carcinoma squamous cell cancer, or melanoma) and breast cancer. Four malignancies (thyroid gland cancer, oligodendroglioma, basal cell carcinoma and malignant melanoma) were assessed by the investigator as being related to trial treatment.

Latency of onset was variable, ranging from 35 to 1324 days. There was no evidence that the incidence of malignancies altered over time, with fourteen malignancies occurring following the first course of MABTHERA, ten following the second course, and two following the third course. Malignancies were reported mainly in patients aged ≥60 years (mean 60 years; range 37-80 years).

Post-Marketing Experience

Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukaemia

The reporting frequencies in this section (rare, very rare) are based on estimated marketed exposures and largely data derived from spontaneous reports.

Additional cases of severe infusion-related reactions have been reported during post-marketing use of MABTHERA.

As part of the continuing post-marketing surveillance of MABTHERA safety, the following serious adverse reactions have been observed:

– *Cardiovascular system*: Severe including fatal cardiac events, such as heart failure and myocardial infarction have been observed, mainly in patients with prior cardiac condition

and/or cardiotoxic chemotherapy and mostly associated with infusion-related reactions. Vasculitis, predominantly cutaneous, such as leucocytoclastic vasculitis, has been reported very rarely.

- *Blood and lymphatic system*: Rarely the onset of neutropenia has occurred more than four weeks after the last infusion of MABTHERA. Cases of infusion-related acute reversible thrombocytopenia have been reported.

- *In post-marketing*: Studies of rituximab in patients with Waldenstrom's macroglobulinaemia, transient increases in serum IgM levels have been observed following treatment initiation, which may be associated with hyperviscosity and related symptoms. The transient IgM increase usually returned to at least baseline level within 4 months.

- *Respiratory system*: Fatal bronchiolitis obliterans and pneumonitis (including interstitial pneumonitis) have been reported. Respiratory failure/insufficiency and pulmonary infiltrates in the context of infusion-related reactions. In addition to pulmonary events associated with infusions, interstitial lung disease, some with fatal outcome, has been reported.

- *Skin and appendages*: Severe bullous skin reactions including fatal cases of toxic epidermal necrolysis have been reported rarely.

- *Nervous system*: Cases of posterior reversible encephalopathy syndrome (PRES) / reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Signs and symptoms include visual disturbance, headache, seizures and altered mental status, with or without associated hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The reported cases had recognised risk factors for PRES/RPLS, including the patients underlying disease, hypertension, immunosuppressive therapy and/or chemotherapy. Cases of cranial neuropathy with or without peripheral neuropathy have been reported rarely. Signs and symptoms of cranial neuropathy, such as severe vision loss, hearing loss, loss of other senses and facial nerve palsy, occurred at various times up to several months after completion of MABTHERA therapy.

- *Body as a whole*: Serum sickness-like reactions have been reported rarely.

- *Infections and infestations:* Cases of hepatitis B reactivation have been reported in subjects receiving MABTHERA in combination with cytotoxic chemotherapy (see PRECAUTIONS). Other serious viral infections, either new, reactivation or exacerbation, some of which were fatal, have been reported with rituximab treatment. The majority of patients had received rituximab in combination with chemotherapy or as part of a haematopoietic stem cell transplant. Examples of these serious viral infections are infections caused by the herpes viruses (cytomegalovirus (CMV), Varicella zoster virus and Herpes simplex virus), JC virus (progressive multifocal leukoencephalopathy (PML) seeBOXED WARNING) and Hepatitis C virus. Progression of Kaposi's sarcoma has been observed in rituximab-exposed patients with pre-existing Kaposi's sarcoma. These cases occurred in non-approved indications and the majority of patients were HIV (Human Immunodeficiency Virus)-positive.

- *Gastro-intestinal system:* Gastro-intestinal perforation, in some cases leading to death, has been observed in patients receiving rituximab in combination with chemotherapy for non-Hodgkin's lymphoma.

– *Renal and urinary system:* Renal failure has been reported.

Rheumatoid Arthritis

In addition to ADRs seen in RA clinical trials for MABTHERA (see ADVERSE EFFECTS - *Experience from Clinical Trials in Rheumatoid Arthritis*), progressive multifocal leukoencephalopathy (PML) and serum sickness-like reaction have been reported during post-marketing experience.

DOSAGE AND ADMINISTRATION

*MABTHERA may be administered in an outpatient setting. MABTHERA should be administered in an environment where full resuscitation facilities are immediately available, and under the close supervision of an experienced healthcare professional.

Dosage

Non-Hodgkin's Lymphoma

Relapsed or refractory Low Grade or Follicular non-Hodgkin's lymphoma

The recommended dosage of MABTHERA when used in monotherapy is 375 mg/m^2 administered as an intravenous infusion once weekly for four weeks.

The recommended dosage of MABTHERA when used in combination with CHOP chemotherapy is 375 mg/m^2 administered on day 1 of each chemotherapy cycle (6 cycles).

Previously untreated stage III/IV Follicular non-Hodgkin's lymphoma

The recommended dosage of MABTHERA in combination with chemotherapy is 375 mg/m^2 administered on day 1 of each chemotherapy cycle for up to 8 cycles as induction therapy.

MABTHERA should be administered prior to the administration of chemotherapy. Any infusion related reactions should have settled before chemotherapy is instituted.

Maintenance treatment

Patients who have responded to induction treatment may receive maintenance therapy with MABTHERA given at 375 mg/m^2 body surface area once every 3 months until disease progression or for a maximum period of two years.

Diffuse large B-cell non-Hodgkin's lymphoma

The recommended dosage for MABTHERA in combination with CHOP chemotherapy is 375 mg/m^2, administered as an intravenous infusion on day 1 of each chemotherapy cycle, for up to 8 cycles.

Chronic Lymphocytic Leukaemia

The recommended dosage of MABTHERA in combination with chemotherapy is 375 mg/m^2 administered on day 1 of the first treatment cycle followed by 500 mg/m^2 administered on day 1 of each subsequent cycle, for a total of 6 cycles (see CLINICAL TRIALS). The chemotherapy should be given after the infusion of MABTHERA.

Prophylaxis with adequate hydration and administration of uricostatics starting 48 hours prior to the start of therapy is recommended for CLL patients to reduce the risk of tumour lysis syndrome. For CLL patients whose lymphocyte counts are >25 $x10^9$/L it is recommended to administer prednisone/prednisolone 100 mg IV shortly before infusion with MABTHERA to decrease the rate and severity of acute infusion reactions and/or cytokine release syndrome.

Dosage adjustments during treatment
No dose reductions of MABTHERA are recommended. When MABTHERA is given in combination with chemotherapy, standard dose reductions for the chemotherapeutic drugs should be applied.

First Infusion: The recommended initial rate of infusion is 50 mg/h. If hypersensitivity or infusion-related events do not occur, escalate the infusion rate in 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h. If hypersensitivity or an infusion-related event develops, the infusion should be temporarily slowed or interrupted (see PRECAUTIONS). The infusion can continue at one-half the previous rate upon improvement of patient symptoms.

Subsequent Infusions: Subsequent MABTHERA infusions can be administered at an initial rate of 100 mg/h and increased by 100 mg/h increments at 30-minute intervals, to a maximum of 400 mg/h.

Rheumatoid Arthritis
A course of MABTHERA consists of two 1000 mg IV infusions. The recommended dosage of MABTHERA is 1000 mg by intravenous infusion followed by a second 1000 mg intravenous infusion two weeks later. The course of MABTHERA is given concomitantly with the dose of MTX tolerated by the patient. The minimal effective dose is not yet known.

*Patients should receive 100 mg IV methylprednisolone to be completed 30 minutes prior to both MABTHERA infusions to decrease the incidence and severity of IRRs (see PRECAUTIONS – *Rheumatoid Arthritis*).

Background therapy with glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs, or analgesics can be continued during treatment with MABTHERA.

Disease activity should be regularly monitored. Patients may receive further courses of treatment, based on signs and symptoms of disease. In clinical studies, no patient received a second course of MABTHERA treatment within 16 weeks of the first infusion of the first course. The time interval between courses was variable, with the majority of patients who received additional courses doing so 6 -12 months after the previous course. Some patients required even less frequent retreatment. The efficacy and safety of further courses is comparable to the first course.

Human anti chimeric antibodies (HACA) develop in some patients after the first course of MABTHERA. The presence of HACA may be associated with the worsening of infusion or allergic reactions after the second infusion of subsequent course. Furthermore, in one case with HACA, failure to deplete B-cells after receipt of further treatment courses has been observed. Thus, the benefit/risk balance of therapy with MABTHERA should be carefully considered before administering subsequent courses of MABTHERA. If a repeat course of treatment is considered it should not be given at an interval less than 16 weeks.

First infusion of each course: The recommended initial rate for infusion is 50 mg/h; after the first 30 minutes, it can be escalated in 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h.

***Second infusion of each course*:** Subsequent doses of MABTHERA can be infused at an initial rate of 100 mg/h, and increased by 100 mg/h increments at 30 minutes intervals, to a maximum of 400 mg/h.

Special Populations

Elderly: No dose adjustment is required in elderly patients (aged > 65 years).

Preparation
MABTHERA vials do not contain an antimicrobial agent or preservative; therefore, care must be taken to ensure the sterility of the vials and prepared solution. Each vial should be used once only and any residue discarded.

Aseptically withdraw the necessary amount of MABTHERA and dilute to a calculated concentration between 1 mg/mL to 4 mg/mL of rituximab into an infusion bag containing either 0.9% sodium chloride or 5% dextrose in water. To mix the solution, gently invert the bag to avoid foaming. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration.

To reduce microbiological hazard, prepared infusion solutions of MABTHERA should be used as soon as practicable after dilution. If necessary, the prepared solutions may be stored in the refrigerator (2^{O}C to 8^{O}C) for up to 24 hours. This timeframe allows for the temporary interruption of the infusion and subsequent recommencement if the patient has an infusion reaction (see *Administration* below).

No incompatibilities between MABTHERA and polyvinyl chloride or polyethylene bags have been observed.

Administration
The MABTHERA solution for infusion should be administered intravenously through a dedicated line.

As with all parenteral products, appropriate aseptic technique should be used during the administration of MABTHERA. Do not administer as an intravenous push or bolus. Hypersensitivity reactions may occur whenever protein solutions such as MABTHERA are administered (see PRECAUTIONS). Premedication, consisting of an analgesic/antipyretic such as paracetamol and an antihistamine such as diphenhydramine should always be administered 30 to 60 minutes before each infusion of MABTHERA. Premedication with glucocorticoids should also be considered, particularly if MABTHERA is not given in combination with steroid-containing chemotherapy.

OVERDOSAGE

There has been no experience of overdosage in human clinical trials. Single doses higher than

1000 mg have not been tested in controlled clinical trials. The highest dose tested to date is 5 g in patients with CLL. No additional safety signals were identified. Patients who experience overdose should have immediate interruption or reduction of their infusion and be closely supervised. Consideration should be given to the need for regular monitoring of blood cell count and for increased risk of infections while patients are B cell-depleted.
Treatment of overdose should also consist of general supportive measures.

Contact the Poisons Information Centre for advice on management of overdosage.

PRESENTATION AND STORAGE

Packs of 2:

- Single-use vials containing concentrated solution for dilution and intravenous infusion 100 mg/10 mL

Pack of 1:

- Single-use vial containing concentrated solution for dilution and intravenous infusion 500 mg/50 mL

Rituximab 100 mg (10 mL) or 500 mg (50 mL) is formulated in a 7.35 mg/mL sodium citrate buffer containing 0.7 mg/mL polysorbate 80, 9.0 mg/mL sodium chloride and sterile water for injection. The pH is adjusted to 6.5 with sodium hydroxide and/or hydrochloric acid.

Storage
MABTHERA vials must be refrigerated between 2°C to 8°C. Do not freeze MABTHERA vials. MABTHERA vials must be protected from direct sunlight. Do not use beyond the expiry date stamped on the carton/vial. MABTHERA vials should be used once only and any unused portion left in the vials should be discarded.

Disposal of Medicines
The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

POISON SCHEDULE

Prescription only medicine- Schedule 4

SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
4-10 Inman Road
Dee Why NSW 2099
AUSTRALIA

Customer Enquires: 1800 233 950

Date of TGA approval: 28 May 2010

ρ

* Please note changes in Product Information

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au