1. Introduction

Mabthera (rituximab) is a chimeric anti-CD20 antibody with high affinity for the CD20 surface antigen that is expressed selectively on B lymphocytes. It is currently approved in EU for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy, for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with CVP chemotherapy and for treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP chemotherapy. The first approval for the treatment of non-Hodgkin's lymphoma (NHL) was obtained in 1998. It is estimated that over 700,000 patients with haematological malignancies have been treated with rituximab worldwide.

The applicant has submitted a type II variation in order to extend the approved malignancy indication to include rituximab for the treatment of signs and symptoms of RA in patients who have not responded adequately to treatment with anti-tumour necrosis factor inhibitors (anti-TNFs).

The recommended dosage of MabThera is 1000 mg by i.v. infusion followed by a second 1000 mg IV infusion two weeks later. Patients may receive further courses of treatment, based on signs and symptoms of disease. In clinical studies, no patient received a second course of rituximab treatment within 16 weeks of the first infusion of the first course. The time interval between courses was variable, with the majority of patients receiving further therapy 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.
Rheumatoid arthritis patients should receive treatment with 100 mg IV methylprednisolone 30 minutes prior to MabThera to decrease the rate and severity of acute infusion reactions.

2. Clinical aspects

B lymphocytes (B cells) are thought to play a central role in the pathogenesis of Rheumatoid Arthritis. B cells are the primary source of rheumatoid factors and anti-citrullinated protein antibodies, which contribute to immune complex formation and complement activation in affected joints. B cells are highly efficient antigen-presenting cells and contribute to T-cell activation through expression of co-stimulatory molecules. B cells both responds to, and produce, chemokines and cytokines that promote leukocyte infiltration into the joints, formation of ectopic lymphoid structures, angiogenesis, and synovial hyperplasia that characterize the pathophysiological changes observed in the rheumatoid joint.

In some patients, rheumatoid synovitis is associated with the formation of complex lymphoid microstructures, to the extent that the rheumatoid process induces the formation of T cell-B cell follicles with germinal center reactions in the synovium of affected joints. Thus, B-cell targeted therapy could play a variety of roles in RA through reduction in B-cell effector cells, as well as downstream effects on other cells that participate in the inflammatory response.

Rituximab is a chimeric anti-CD20 antibody with high affinity for the CD20 surface antigen, which is expressed selectively on B lymphocytes. CD20 is found on pre-B lymphocytes and mature B lymphocytes, but not on haematopoietic stem cells, pro-lymphocytes or plasma cells. The binding of rituximab to CD20 interferes with the activation and differentiation of B cells. In vitro, rituximab has been shown to induce apoptosis, complement-mediated lysis, and antibody-dependent cellular cytotoxicity. Rituximab causes rapid peripheral B-cell depletion in vivo. Several pilot studies in patients with autoimmune conditions including idiopathic thrombocytopenia purpura, autoimmune haemolytic anemia, myasthenia gravis and polyneuropathy, suggest that rituximab induced peripheral B-cell depletion may also be efficacious in these conditions.

The clinical efficacy data for rituximab (2 x 1 g infusions) in combination with methotrexate (MTX) and an infusional and oral corticosteroid regimen in rheumatoid arthritis (RA) derives from one pivotal, double-blind, randomized, phase III, global study **(WA17042)** in RA patients who have had an

inadequate response to 1) at least one anti-tumor necrosis factor (anti-TNF) therapy and 2) no more than five disease modifying anti-rheumatic drugs (DMARDs).
Supportive data come from two double-blind, randomized, phase II studies (**WA16291** and **WA17043**) in patients who have previously failed one to five DMARDs, which may include anti-TNF medications.
The duration of each of these studies was 104 weeks, with a primary endpoint at 24 weeks, after a single course of therapy (two rituximab infusions 15 days apart). Additional information, including efficacy of repeated treatment with rituximab, is provided from the interim analyses of data from the following sources:

- patients remaining in the original studies beyond week 24
- open-label rescue treatment of placebo and lower-dose (2 x 0.5 g) rituximab-treated patients from phase IIb (WA17043) and phase III (WA17042) studies.
- open-label treatment under the extension protocols **WA16855** and **WA17531** providing the opportunity to administer further courses of rituximab treatment (2 x 1 g).

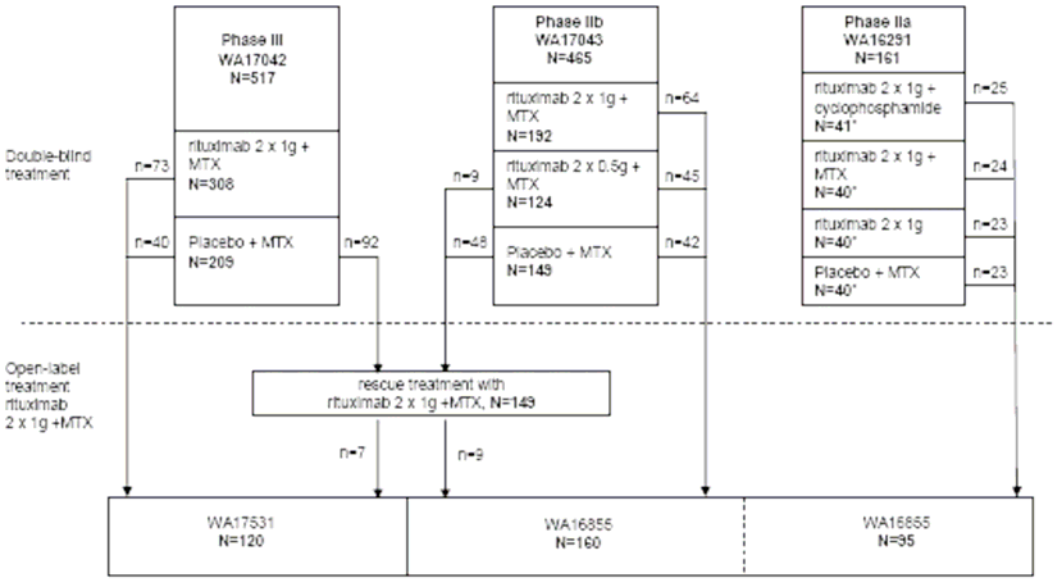
The clinical cut off date for the inclusion of data in this application was 13 January 2005, the date of the last week-24 visit for the last patient enrolled into WA17042. The design of the pivotal study, WA17042, included in the application was discussed with regulatory authorities (Denmark, Spain, Holland, USA) prior to study start. The application consists of the following studies:

- Phase IIa study WA16291 – a randomised double dummy controlled parallel group study with four treatment arms (~ 40 patients per arm): methotrexate (MTX) alone, rituximab alone, rituximab + cyclophosphamide or rituximab + MTX. 1000 mg was given by i.v. infusion on day 1 and 15.

- Phase IIb Study WA17043 - a randomised, double-blind, double-dummy, controlled, international, multi-factorial study of nine different treatment regimens in a 3 x 3 configuration. The study design was comprised of three different dose levels of rituximab (including placebo) and three different corticosteroid regimens (including placebo), along with a weekly regimen of MTX and folate. Approximately 40 RF-positive patients were to be enrolled into each of the nine possible combinations. In addition, 20 RF-negative patients were to be studied in four different treatment regimens: Placebo and high-dose rituximab with differing corticosteroid regimens. Rituximab 500 or 1000 mg was given by i.v. infusion on day 1 and 15.

- Phase III Study WA17042 - a randomised, placebo-controlled, double-blind, international study of two treatment regimens, including one dose level of rituximab and corticosteroids (including placebo) along with a weekly regimen of MTX and folate in patients who had an inadequate response to anti-TNF therapies. A total of 520 patients were enrolled in this study (311 active and 209 placebo patients). 1000 mg was given by i.v. infusion on day 1 and 15.

In addition, the extension of study 16291 included an extended observation period out to two years post-treatment. In this study patients were eligible to receive re-treatment initially with their original regimen (based on presence of RA symptoms and in accordance with predefined criteria for re-treatment) and once the optimal regimen had been identified from the 24-week analysis, re-treatment with that regimen was permitted under a new protocol (WA16855).



Pharmacology

The Pharmacology dossier includes data from the three efficacy studies where pharmacological parameters have been collected:

- Phase IIa study WA16291: Blood samples were obtained in all patients for PK, PD and HACA assessments.

- Phase III Study WA17042: Blood samples were obtained in all patients for PK, PD and HACA assessments. As blood sampling was limited, only the maximum concentration achieved and $t_{1/2}$ calculated.

- Phase IIb Study WA17043: Blood samples were obtained in all patients for PK (C_{max}, T_{max} and $t_{1/2}$), PD and HACA assessments.

Pharmacokinetics

The pharmacokinetics of rituximab following two IV doses at 500 mg and 1000 mg on days 1 and 15 is similar to other IgG antibodies. The mean Cmax values for serum rituximab were 453 µg/mL for the 2 x 1000 mg dose. Mean volume of distribution at steady state was 4.6 L, which is approximately equivalent to total blood volume. Mean systemic serum clearance was 0.0096 L/h, and mean terminal half-life after the second infusion ranged from 18 to 21 days. Rituximab is to be infused 1000 mg twice 15 days apart. The infusions may be repeated after return of symptoms. Liniar pharmacokinetics is observed within the chosen dose range. C_{max} was compared for doses of 500 mg, 1000 mg and 2000 mg and proportionality was confirmed.

There are no data on kinetics in patients with renal disease, hepatic disease or hypo-proteinemia. However, taking into consideration that rituximab has been used in NHL patients without specific dose recommendations for these populations it is considered as acceptable.

No specific drug interaction studies have been performed. But based pharmacokinetic data from phase II and III studies rituximab is not influenced of cyclophosphamides or MTX. However, the C_{max} may be increased by high doses of cortisteroids. In addition, there are no data on effect on pharmacokinetics of NSAIDS or other drugs frequently used in the RA population.

Human anti-chimeric antibody (HACA). The overall incidence of immunodepletable HACA was around 5.5-5.6% for all rituximab treated patients in RA studies. Re-treatment of rituximab did not increase the HACA incidence or titre.

Pharmacodynamics

A pattern of peripheral B cell depletion over the first 24 weeks after the first treatment course was seen in all rituximab 2 x 1000 mg + MTX treated patients who were previously exposed to anti-TNF therapy (primarily patients from the pivotal WA17042 study plus a smaller number of patients from the phase II studies) and patients who did not receive prior anti- TNF therapy (the majority of patients from the supportive phase II studies).The lower dose (2 x 500 mg) of rituximab was associated with a higher proportion (approx. 34%) of patients who showed signs of B cell return by week 24 when compared to the higher dose.
The extent and duration of B cell depletion was similar for each treatment course with repeat treatments given at ≥ 16 week intervals, by protocol. Re-treatment was based on clinical symptoms and not on the patients' B cell counts which may or may not have returned to LLN/baseline prior to re-treatment.

Patients with long term responses maintain B-cell depletion. There was no correlation between the extent of B-cell depletion and the decrease in disease activity measurements; however, recrudescence of disease after initial improvement was usually associated with evidence of increasing numbers of B cells in the peripheral blood. After a course of rituximab treatment, three patients had B cell counts that never decreased below 40 cells/µL, i.e., 50% of LLN, or levels of B cells that returned to above 50% of LLN by Week 8. Of these 3 patients, two achieved an ACR20 response or better, and the other was a non-responder at week 24. Thus, partial depletion did not preclude a good clinical response.

Patients with prolonged B-cell depletion. Ten out 121 patients who have been followed for at least two years or until B cell return after the first course of treatment with rituximab have shown prolonged depletion (i.e., B cell counts <20% LLN at week 104). Three of these patients received rituximab 2 x 1000 mg alone, and seven received rituximab 2 x 1000 mg + MTX as their first course of treatment in the phase IIa study. Three of these patients have received a second course of treatment, one of whom was still significantly B cell depleted (i.e. <20% LLN) at the time of re-treatment. Five of the ten patients were still B-cell depleted at their last evaluation, and each patient had consistently low counts for a period of three to three and half years. The mean pharmacokinetic parameters of rituximab for the patients with prolonged B cell depletion were comparable to the combined data for all subjects in study WA16291. Rituximab treatment resulted in significant decreases in concentrations of certain biomarkers for inflammation and disease e.g., C-reactive protein (CRP) concentrations, erythrocyte sedimentation rates (ESR), and concentrations of RF (in RF-positive patients).
There was no clinically relevant difference between treatment groups in mean changes from baseline in total T-cell (CD3+) counts, helper T-cell (CD4+), and cytotoxic T-cell (CD8+) counts.
The observed transient decrease in mean counts after each infusion (recovered again to baseline levels by Week 4) is likely to be associated with the use of corticosteroids during the initial phase of the study. The latter seemed to be confirmed by the impact of the corticosteroid regimen on T cell counts observed in the phase IIb study.

In the phase III study, mean concentrations of total immunoglobulin and each isotype were slightly reduced at week 24 compared with baseline in the placebo+MTX group but larger decreases were observed in the rituximab+MTX group. The greatest reduction was seen in IgM immunoglobulin, which declined from a mean concentration of 1.62 mg/mL at baseline to 1.14 mg/mL at week 24 (mean change from baseline of -0.48 in rituximab patients compared with -0.08 in placebo patients). These findings are consistent with the reduction in RF immunoglobulin, which are predominantly of the IgM isotype. Immunoglobulin concentrations generally remained within normal.

Treatment with rituximab was not seen to have any effect on serum complement (C3 and C4) and ANA titre. However, in the phase III study, 15/308 (4.8%) patients in the rituximab + MTX group and 8/209 (3.8%) patients in the placebo + MTX group became ANA positive at week 16 and/or week 24.

Acute infusion reaction. Following administration of rituximab, B cell lysis results in the acute release of cytokines. This cytokine release is characterised by a cluster of signs and symptoms (e.g., pruritis, fever, urticaria/rash, chills, pyrexia, rigors, sneezing, angioneurotic oedema, throat irritation, cough

and bronchospasm, with or without associated hypotension or hypertension) and is considered to be an acute infusion reaction. After infusion of the first course of rituximab, 11% of patients in the Phase III trial experienced such a reaction compared to 7% on placebo. As expected, given the lower numbers of circulating B cells, the second infusion resulted in infusion reactions in only 2% of patients on rituximab compared to 3% on placebo.

Clinical efficacy
In the provided 3 studies patients had longstanding, severe active RA at study entry and ≥ 79% of the patients were RF positive at baseline. Patient ages at entry of the studies ranged from 18 to 81 years, with a median of approximately 53 years. The majority of patients (~80%) were female and Caucasian.

In total, 540 RA patients were randomized to receive rituximab 2 x 1000 mg in combination with MTX (weekly dose 10-25 mg), 40 patients received rituximab 2 x 1000 mg monotherapy, 41 patients received rituximab 2 x 1000 mg in combination with IV cyclophosphamide 2 x 750 mg and 124 patients received rituximab 2 x 500 mg in combination with MTX (weekly dose 10-25 mg).

Patients randomized to rituximab + MTX or placebo + MTX who had achieved a clinical response (≥ 20% improvement from baseline in both SJC and TJC) after week 16 following receipt of rituximab + MTX/placebo + MTX, and who relapsed or had remaining evidence of disease activity (at least 8 swollen and tender joints), were eligible to receive further courses of 2 x 1000 mg of rituximab. Patients were to have completed the week-24 visit prior to re-treatment following the first course of therapy. With the exception of this initial stipulation, and allowing a minimum interval between treatment courses of 16 weeks, the timing of re-treatment was at the discretion of the treating investigator.

Several steroid regimens were tested i.v. vs. oral or the combination of the two. The patient population consisted primarily of RF positive RA and to a minor extent of RF negative patients. The study was conducted at multiple centres in the US and non-US countries.

The traditional and validated RA response criteria have been used which include the ACR and EULAR (DAS28) scores together with a number of secondary efficacy parameters. Radiographs of hand and feet have been included, but so far only data from 24 weeks treatment are presented. The design and conductance of these randomised controlled trials including handling of missing data seem to be in accordance with internationally accepted standards. The statistical evaluation of data is acceptable.

Pivotal Phase III Study WA 17042
In this phase III study the Applicant has focused on the group or RA patients with previous failure on anti-TNF therapy. Based on the experience with the phase II studies protocol 17042 was designed to compare the RTM 1000 mg x 2 dose to placebo. All patients were on weekly MTX (p.o. or i.m.).

The primary endpoint was the ACR20 at week 24 – the secondary endpoints were the same as for the phase II studies. Five hundred twenty patients were enrolled (311 were randomized to receive RTM+MTX and 209 to receive placebo+MTX). Eighty-two percent of the patients in the RTM group completed the 24 weeks of the study compared with 54% in the placebo group. A total of 96 patients in the placebo + MTX group who received study medication withdrew prematurely, with 80 patients going on to receive RTM rescue therapy and 1 patients entering the Safety follow-up. Fifty-three patients in the RTM + MTX group who received study medication withdrew into the Safety follow-up prior to week 2 (RTM rescue therapy was not available to these patients).

There is a surprisingly large differential drop-out due to lack of efficacy. This may be viewed is a strong argument for dealing with an effective treatment (without too many side effects), but it should be emphasized that such differences in favour of the treatment arm is trials is rather rare. Importantly, however, the estimates of the magnitude of the effect may be exaggerated by considering all dropouts an as non-responder and by the LOCF procedure given this differential drop-out. Especially comparing the effect size at 16 weeks (no differential dropout up to then) versus 24 weeks but also

comparing the effect size / scores of the ITT versus the PP population may indicate how large this exaggeration is.

Both RF positive and negative patients were included and subjects were recruited from US and non-US countries. Baseline demographic parameters were comparable between groups.
The primary efficacy endpoint was reached by 51% in the RTM arm vs. 18% in the placebo group ($p<0.0001$). RTM was also superior to placebo in the secondary efficacy parameters (ACR50 27% RTM vs. 5% placebo, and ACR70 12% RTM vs. 1% placebo). In general the ACR response was reached around week 4 and stayed relative constant throughout the 24 week period. The mean DAS28 score changed from mean 6.9 to 5.0 in the RTM arm vs. 6.9 to 6.4 in the placebo arm which was statistically significant.
Low disease activity and remission as defined by DAS scores below 3.2 and 2.6 respectively was obtained by 15% RTM and 2% placebo patients (low activity) and 9% vs. 0% (remission).
The clinical significance of these figures is less impressing. The mean DAS of 5.0 is just below the limit of high disease activity (5.1) and only small number in the active group actually achieved good response or remission.

The results from the fatigue, physical and mental health scores are in accordance with the results from the clinical efficacy variables. Radiographic evaluation was performed at week 24, but due to the short observation period only joint space narrowing showed statistical significance in favour of the RTM group. Further, it should be remarked that the used radiographic evaluation method according to Sharp as modified by Genant is rarely used as method to evaluate structural damage. This method is less validated as the modified Sharp-v/d Heijde score.

Fewer US-patients achieved the ACR response criteria compared to non-US patients. This difference was most obvious in the groups with only one previous anti-TNF therapy regimen. When the DAS score (which is not a relative efficacy measurement such as the ACR score) was applied this difference minimised.

The RF-positive patients performed better compared to the RF-negative patients. In RF-negative patients, significance was achieved at the ACR20 level, but not at ACR50, and only borderline efficacy was observed at ACR70. This seems to indicate that RTM has lesser effect in the RF-negative population as also shown in the phase II study.

No correlations between RTM concentrations and changes from baseline in CD19+ B-cell counts, total RF, ACRn and DAS28 at week 24 were observed.

Supportive Phase IIa Study WA 16291.
In this 4-arm study MTX alone was compared to RTM monotherapy (1 g x 2), RTM + cyclophosphamide 750 mg x 2, or RTM + MTX. The primary endpoint was ACR50 at week 24. The aim of the extension phase was to collect safety data and to explore further efficacy outcome measures such as duration of clinical efficacy over a 2-year period.
The ITT population consisted of 161 patients in 4 treatment arms. Subjects are well balanced with respect to demographic parameters, but the RTM-mono arm has a statistically significant lower disease activity as measured by mean CRP concentration. This may have affected the outcome because the RTM-mono arm was the only group among the 3 active treatment arms that did not reach level of significance compared to placebo at the ACR50 response criteria. Both the RTM+cyclo and the RTM+MTX were statistically superior to placebo.
Statistical significance was also achieved for the secondary efficacy parameter, ACR20 in all groups but for the ACR70 level only in the RTM+MTX group. According to the EULAR score all active RTM arms performed equally with 61%-65% obtaining moderate response and 20%-24% obtaining good response. Mean disease activity over time (DAS) was indistinguishable between the 3 active RTM arms. Also the pharmacokinetic profiles including CD19 positive cell counts were almost identical in the 3 arms.

One hundred forty-two patients entered the extension phase of study 16291 and 81 were re-treated. However, only 11 subjects received blinded re-treatment with their original randomised regimen. The remaining 70 individuals entered the open label protocol WA 16855 (RTM 1 g x 2 + MTX).
At week 48 there was significantly more ACR20, ACR50, and ACR70 responders in the RTM+MTX arm compared to MTX alone. At week 104 no statistically significant differences were found between groups. Although the mean duration of ACR70 response was longer in the RTM+MTX arm it did not reach statistical significance compared to MTX-mono. No significance was found for DAS and HAQ scores between the same groups.
It cannot be excluded that the lower inflammatory activity at baseline in the RTM-mono group might have skewed the outcome particularly in relation to the ACR criteria. The ACR outcome criteria, which are based on relative measures, are less suitable when baseline values are not completely balanced. The DAS score in this situation is more appropriate.

Supportive Phase IIb Study 17043.
This study was designed to refine the RTM dose and determine the role of concomitant steroid use during the treatment period. Both RF-positive and RF negative patients were enrolled and the study comprised 9 possible combinations. Placebo and two doses of RTM were used, 500 mg x 2 and 1000 mg x 2 combined with steroid (total 250 mg or 820 mg prednisone equivalent). Patients were allowed background steroid (less than 10 mg per day). Primary endpoint was ACR20 at week 24 for RF positive patients. After week 24 all patients were followed for 18 months, giving an overall study duration of 24 months. After week 24 eligible patients could receive further courses of RTM under a separate protocol or in case of placebo receive a first treatment. Efficacy-measures were the same as for study 16291.
At baseline 380 patients were RF positive and 85 were RF negative. The demographic and baseline characteristics were adequately balanced between treatment groups.
The results showed virtually identical ACR20/50responses in the two RTM-arms (both were significantly superior to placebo). However, ACR70 responses were numerically more frequent in the RTM 1000 mgX2 arm. At some time-points the 500 mg RTM group performed better than the higher RTM group in the ACR20 score. The DAS score over time was almost identical between the two RTM groups.
At week 24 there were significantly more EULAR good responders in the 1000 mg RTM arm compared to the 500 mg RTM arm, whereas at week 16 more low-dose RTM patients were good responders.

This study could be viewed as a dose-finding study.

Extension study WA 16855 and WA 17531
Patients randomized to RTM in the initial treatment protocol and who required repeat treatment were enrolled into one of two open-label extension studies.
Protocol WA1685 provided eligible patients from the two Phase II studies WA16291 and WA17043 with the opportunity to receive further courses of RTM treatment from week 24 onwards. In addition, patients initially randomized to RTM-placebo in the randomized comparative portion of the original protocol were eligible to receive open label RTM in the extension study WA16855.
Another similar study (WA17531) was initiated to allow eligible patients from the phase III study (WA17042) to receive further courses of treatment with RTM 2 x 1000 mg + MTX under the same conditions. The objective of the study was to assess the long-term safety and explore response to repeated treatment with RTM.

Approximately 600 patients with active RA who had participated in one of the Phase II studies (WA16291 and WA17043), and approx 500 patients from the phase III study (WA17042), were potentially eligible to enter the extension studies.

The duration of response was explored by assessing the longest period of uninterrupted ACR20 response (defined as consecutive assessments showing an ACR20 response) for given patient.
The mean [median] duration of response (i.e. longest period of consecutive assessments with a defined ACR response), after the first course of treatment with RTM 2 x 1000 mg + MTX treatment, is currently 13 [10], 9 [4] and 6 [4] weeks for ACR20, ACR50 and ACR70 responses, respectively, in

the population of patients who had received prior anti-TNF therapy. The longest duration of an uninterrupted ACR20 response was 61 weeks at the point of data cut-off.
In contrast, patients who had no previous anti-TNF exposure and were included in the phase II studies began treatment a considerable time prior to the start of study WA17042 and the data are less subject to censoring. The mean [median] duration of response in this population is currently 23 [20], 16 [8], and 9 [4] weeks for ACR20, ACR50, and ACR70 respectively. The longest duration of uninterrupted ACR20 response was 118 weeks at the point of data cut-off.

Discussion on Clinical Efficacy

The nonclinical program for rituximab has demonstrated pharmacologic activity (B cell depletion), that rituximab has PK consistent with other well-characterized monoclonal antibodies, and that toxicological findings related to rituximab are predictable, reversible, and related to the pharmacology of CD20+ B-cell depletion. Overall, rituximab-related findings in nonclinical safety studies are considered to be acceptable for the proposed patient population.
In general the studies do substantiate that the 1000 mg x 2 dose of Rituximab is the optimal dose in RA. The lower dose (500 mg x 2) seems to be less effective, however it seems associated with fewer side effects.
On the basis of presented data it can be concluded that rituximab 2 x 1000 mg given concomitantly with MTX is more effective than MTX alone in RA patients who had an inadequate response to MTX and one or more anti TNF therapies. The lower dose regimen 2x 500 mg plus MTX regimen tested only in a small Phase II study (WA17043) seems to be less effective.
Overall, the provided evidence of efficacy and safety of MabThera with the recommended dosage in the sought indication is supportive of approval of the product in a restricted (salvage therapy) indication reflecting better the present experience (from the pivotal study) in patients with severe RA who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs including one or more tumour necrosis factor (TNF) inhibitor therapies.

The following indication has been agreed with the CHMP:

"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 including one or more tumour necrosis factor (TNF) inhibitor therapies".

The MAH committed to provide results from the following clinical trials:

Protocol WA17045
A randomized, placebo controlled, double-blind, parallel group, international study to evaluate the safety and efficacy of rituximab (MabThera/Rituxan) in combination with methotrexate, compared to methotrexate monotherapy, in patients with active rheumatoid arthritis.
Submission of a) pharmacokinetic data and repeated infusions and b) final study report (primary endpoint evaluation) exploring the efficacy and safety of the 2 x 0.5g regimen and the 2 x 1g regimen in patients who are not responding adequately to treatment with methotrexate.

Protocol WA17047
A randomized, phase 3, controlled, double-blind, parallel-group, multicenter study to evaluate the safety and efficacy of rituximab in combination with methotrexate (MTX) compared to MTX alone, in methotrexate-naïve patients with active rheumatoid arthritis.
Submission of a) pharmacokinetic data and repeated infusions and b) final study report (primary endpoint evaluation) exploring the efficacy and safety of the 2 x 0.5g regimen and the 2 x 1g regimen in methotrexate treatment naive patients.

Clinical safety
AE's associated with skin, respiratory and general disorders were more frequent in the arms receiving RTM whereas the control groups had more musculoskeletal complaints probably due to more RA disease exacerbation in these groups.

In study **16291** there were 14 serious adverse events with the highest incidence in the RTM+cyclophosphamide group. The most common type of SAE was infection. One patient (RTM-mono-therapy) died from pneumonia
Events considered expected with RTM treatment (i.e. transient hypo/hypertension, nausea, rash, pruritus, cough, dyspnoea, and pyrexia) occurred more frequently in the RTM regimens. It is of concern that severe infections were more frequently seen in the RTM groups. A statistical significant difference was observed in the "pathogen unspecified group" i.e. 11 cases in RTM+MTX vs. 3 cases in the MTX group; p=0.039. Of particularly importance was the observation of 2 cases of septic arthritis (1 in RTM group and 1 in the RTM+cyclo group) and a case of pseudomonal pneumonia (RTM+cyclo) – altogether potentially life-threatening infections.
One patient in the RTM monotherapy died 5 months after commencing the study program. Routine ECG performed during the study revealed slight abnormalities, which could indicate silent ischemic heart disease. The patient was admitted to hospital with signs of acute pneumonia and though treated with antibiotics the patient succumbed due to sudden cardiac arrest. No specific pathogens were isolated from blood or sputum.
Of the 5 patients with serious infections 4 were in the RTM treatment arms. One patient in the MTX arm had a corneal abscess and was admitted to an ophthalmologic department and stayed for 3 days.

In the extension arm of study 16291, 7 individuals developed severe infections 5 of whom were in the RTM treatment arms.

Study 17043 showed that the incidence of AE's were highest in the 1000 mg x 2 dose RTM group. Two percent in the low RTM group and 4% in the high dose RTM group were withdrawn due to AE's respectively. Pre-medication with steroids seemed to decrease the incidence of AE's to some extent.
Acute infusion related AE's occurred with a higher frequency in the 1000 mg RTM group. Five patients were withdrawn in the 1000 mg RTM vs. 0 patients in the 500 mg RTM arm due to AE's related to infusion. Three patients developed serious allergic reaction with dyspnoea and hypotension in the 1000 mg RTM group.
Combining the RTM groups, the overall incidence of cardiac disorders was higher (10%) than in the RTM placebo group (four patients, 3%). This imbalance is mainly accounted for by non-serious cardiac events associated with infusion reactions, including tachycardia, palpitations and bradycardia.
Cardiac arrhythmias were experienced by 19 (15%) and 15 (7.8%) subjects in the 500 mg and 1000 g RTM groups respectively compared to 4 (2.6%) in the placebo arm.

Severe infections (grade 3) were reported by 1% of patients in the RTM placebo group, < 1% of patients in the 2 x 500 mg RTM group and 4% of patients in the 2 x 1000 mg RTM group. No opportunitistic infections associated with RTM treatment were observed in this study, although one RTM-treated patient developed cutaneous blastomycosis. One patient in the 1000 mg x 2 RTM arm developed epiglottitis – a serious life-threatening infection.

A total of 26 patients had 26 SAEs. More patients had SAEs in the RTM groups (7% in both the 2 x 500 mg and 2 x 1000 mg dose groups) compared with the RTM placebo group (3% of patients). The most common types of SAE were infections.

Study 17042.
A slightly higher frequency of serious adverse events was observed in the placebo + MTX group (10%) than in the RTM + MTX group (7%). Nine patients (one in the placebo + MTX group and 8 in the RTM + MTX group) were withdrawn from the study as a result of an adverse event, of whom six RTM + MTX patients were withdrawn within the first two weeks of the study. There were no deaths during the 24-week study period.
More severe infections were recorded in the RTM + MTX group (10 patients, 3.2%) than in the placebo + MTX group (4 patients, 1.9%).

Seven percent of patients in the RTM + MTX group experienced vascular disorders (mostly hyper- and hypotension, and flushing/hot flush) compared to 4% of patients in the placebo + MTX group within the 24 hours post-infusion.

Respiratory disorders, including throat irritation or tightness, pharyngeal swelling or pain, and laryngeal oedema, were also more common in the RTM + MTX group (5% of patients, compared to 1% of placebo + MTX patients). Skin disorders (such as pruritus and urticaria) and gastrointestinal disorders (mainly nausea and diarrhoea) were each recorded in 5% of patients treated with RTM + MTX compared to 2% of placebo + MTX patients.

Taken together these studies have shown that treatment with RTM imposes a significant risk of serious AE's to the patients with RA. Infusion-related AE's were common and several cases of dramatic potentially life-threatening allergic reactions occurred with urticarial rash, hypotension and laryngeal oedema. It is not clear from these studies to what extent the occurrence of HACA contributes to these reactions.
Infections were common and severe life-threatening infections even with fatal outcome were observed. Of particular concern are the cases of septic arthritis, a rare condition even in RA patients.

Cardiac conduction disturbances were observed in a number of subjects. It is not unlikely that these events can be connected to RTM treatment, either indirectly through effect on the cardiovascular system (hypertension/hypotension) or as a direct consequence of cytokine release affecting the cardiac conduction system. Of importance, no cases of latent or overt tuberculosis were observed.

RISK MANAGEMENT PROGRAM

The proposed Risk Management Plan (RMP) included in Module 1 supports the application for the approval of rituximab, in conjunction with methotrexate, for the treatment of rheumatoid arthritis (RA), in patients who have had an inadequate response to one or more anti-TNF agents.
From analyses of safety data from the RA clinical trials the applicant has indicated one identified risk (acute infusion reaction/cytokine release syndrome) and six potential risks for further evaluation and/or minimization.
There are currently no safety signals identified by the applicant for rituximab related to the potential risks. The six potential risks are: Infection, immunogenicity, neoplasm, immunization response, pregnancy/lactation and drug interactions. Infection, immunogenicity and neoplasm are included because they are issues of concern in the RA patient population. Immunization response is included as a potential risk because of the mechanism of action of rituximab (B cell depletion). Pregnancy/lactation and drug interactions are included because they are areas of concern for all therapeutics.

The safety database for rituximab in rheumatoid arthritis contains 990 patients who received at least part of one infusion of rituximab as part of placebo-controlled Phase II or Phase III trials, and/or open-label extensions to these trials. Individual patient follow-up time ranges from 6 months to over 3 years, with a total of 1001 patient-years of follow-up; 306 patients received two or more courses of treatment.
However, it is estimated that approximately 730,000 patients had been exposed to rituximab worldwide by 31 May 2005, the majority of whom were treated in the oncology setting. Most patients received rituximab 375 mg/m^2 IV for 4 cycles. Thus, the safety profile of rituximab in the lymphoma indications is well-established.
The safety experience in the RA clinical trials was compared with that in the NHL clinical trials. With the exception of acute infusion reactions, which are generally less frequent and less severe in the RA population, it appears that the safety profile of rituximab in patients with RA is generally similar in pattern to that in patients with malignancy.

The actions proposed by the applicant to address the identified and potential risks are so far considered as appropriate. However, several safety issues are to be discussed within the context of the RMP, such as; the increased risk (beyond the background treatment including MTX) of serious infections, cardiac events, malignancies, serious allergic reactions especially in HACA patients, a concern of the slightly increased proportion of patients with ANA positive measurements. Thus, a final conclusion as to whether all safety concerns are adequately covered in this RMP awaits further assessment.

Discussion on Clinical Safety

The frequency of interfering antibody is therefore very low (1/1039 patients exposed). The applicant continues to study the emergence of interfering antibody. At present, as there is no practical assay for HACA in use in clinical practice, failure to deplete B cells in the peripheral blood following a second or later courses of treatment may be a bioassay which demonstrates the presence of antibody in the plasma sufficient to interfere with the biological mechanism of action of the product. Whether a HACA response has any impact on safety is not known. Based on the limited amount of data on patients treated with DMARDs including anti-TNF treatment after rituximab treatment there seems not to be an increased incidence of serious infections at least if the incidence is compared to reported rates among patients treated with anti-TNF for the first time or among patients treated with rituximab + MTX alone. The information for other DMARDs after rituximab exposure is even more limited.

From a practical clinical perspective most patients requiring another DMARD after rituximab will be B cell depleted to some extent simply because of the prolonged effect of the antibody on B-cells. These patients cannot be left untreated until complete repletion of their peripheral B-cells. Therefore, the Rapporteur is of the opinion that the information on infections in the draft SPC is acceptable. Section 4.4 states that infections were most commonly observed within 1 month of initiating MabThera and similarly to the experience in lymphoma patients the prolonged B-cell depletion seems not to be associated with a high risk of severe infections in following months. Any patient with RA requiring a DMARD including anti-TNF and rituximab should not receive such treatment in case of active infection. Patients reporting signs and symptoms of infection following DMARD therapy should be promptly evaluated and treated appropriately. Physicians should exercise caution when considering the use of most DMARDs in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection. In conclusion, this common knowledge for rheumatologists is included in sections 4.3, 4.4, and 4.8 of the SPC.
Data on myocardial infarction among the placebo-treated patients for comparison (all study population) were presented. It is important to bear in mind the significantly longer period of observation in the rituximab treated population than in the placebo group. Of the 1039 patients included in the all exposure population, 359 had pre-existing cardiovascular disease (12% 43/359 of whom had ischaemic heart disease). The rate of myocardial infarction observed in the rituximab treated group is similar to that observed in published cohort studies (Solomon DH, Karlson EW, Rimm EB et al. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. Circulation 2003;107:1303-1307 Turesson C, Jarenros A , Jacobsson L. Increased incidence of cardiovascular disease in rheumatoid arthritis. Ann Rheum 2004;63:952-955)

In the pivotal study the used corticosteroid regimen consisted of glucocorticosteroid pre-medication and oral coverage between the two infusions should follow as described in section 5.1.However, since there are some safety concerns about the oral coverage between the two infusions of Mabthera it is proposed that supplementary oral coverage should be given to patients who are not on background corticosteroid therapy for their RA. The MAH has provided a rationale for the steroid doses chosen. The use of oral corticosteroids for several days following I.V pre-medication is not recommended.

The MAH will provide a safety review and company position for MabThera following recent USPI updates for Rituxan.

The MAH should provide an updated risk management plan. PSURs will be submitted every 6 months during the first 2 years after approval of the rheumatoid arthritis indication.

3. CONCLUSION

On 1 June 2006 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet**.**

Follow-up measures undertaken by the Marketing Authorisation Holder

As requested by the CHMP, the MAH agreed to submit the follow-up measures as listed below and to submit any variation application which would be necessary in the light of compliance with these commitments (see Letter of Undertaking attached to this report):

Area[1]	**Description**	**Due date**[2]
Clinical	Protocol WA17045 A randomized, placebo controlled, double-blind, parallel group, international study to evaluate the safety and efficacy of rituximab (MabThera/Rituxan) in combination with methotrexate, compared to methotrexate monotherapy, in patients with active rheumatoid arthritis. Submission of a) pharmacokinetic data and repeated infusions and b) final study report (primary endpoint evaluation) exploring the efficacy and safety of the 2 x 0.5g regimen and the 2 x 1g regimen in patients who are not responding adequately to treatment with methotrexate.	30/06/2008
Clinical	Protocol WA17047 A randomized, phase 3, controlled, double-blind, parallel-group, multicenter study to evaluate the safety and efficacy of rituximab in combination with methotrexate (MTX) compared to MTX alone, in methotrexate-naïve patients with active rheumatoid arthritis. Submission of a) pharmacokinetic data and repeated infusions and b) final study report (primary endpoint evaluation) exploring the efficacy and safety of the 2 x 0.5g regimen and the 2 x 1g regimen in methotrexate treatment naive patients.	end 2009
PhV	Provide updated risk management plan	30/06/2006
PhV	PSURs will be submitted every 6 months during the first 2 years after approval of the rheumatoid arthritis indication.	
PhV	Provide a safety review and company position for MabThera following recent USPI updates for Rituxan	July 2006

1. Areas: Quality, Non-clinical, Clinical, Pharmacovigilance
2. Due date for the follow-up measure or for the first interim report if a precise date cannot be committed to.