15 November 2018
EMA/CHMP/62482/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

MabThera

International non-proprietary name: rituximab

Procedure No. EMEA/H/C/000165/II/0149

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AAV	ANCA-associated vasculitis
ADA	anti-drug antibody
ANCA	anti-neutrophil cytoplasmic antibodies
AZA	azathioprine
BVAS	Birmingham Vasculitis Activity Score
CL	clearance
CNS	central nervous system
CYC	cyclophosphamide
EU	European Union
EULAR	European League Against Rheumatism
EUVAS	European Vasculitis Society
GI	gastrointestinal
GPA	granulomatosis with polyangitis
IV	intravenous
PK	pharmacokinetic
MTX	methotrexate
MFM	mycophenolate mofetil
MPO	myeloperoxidase
PR3	proteinase-3
SEE	standard error of estimates
WG	Wegener’s granulomatosis

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration GmbH submitted to the European Medicines Agency on 2 March 2018 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include the maintenance of remission of polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA) for MabThera; as a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package leaflet is updated accordingly. In addition, the MAH took the opportunity to implement a terminology change in Annex II. The RMP (v. 17.1) was also updated as a consequence.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Sinan B. Sarac Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	2 March 2018
Start of procedure:	31 March 2018
CHMP Rapporteur Assessment Report	26 May 2018
PRAC Rapporteur Assessment Report	26 May 2018
PRAC members comments	6 June 2018
Updated PRAC Rapporteur Assessment Report	8 June 2018
PRAC Outcome	14 June 2018
CHMP members comments	n/a
Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 June 2018
Request for supplementary information (RSI)	28 June 2018
Submission of responses	14 September 2018
CHMP Rapporteur Assessment Report	12 Oct 2018
PRAC Rapporteur Assessment Report	12 Oct 2018
PRAC members comments	24 Oct 2018
Updated PRAC Rapporteur Assessment Report	26 Oct 2018
PRAC Outcome	31 October 2018
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	n/a
Opinion	15 Nov 2018

2. Scientific discussion

2.1. Introduction

Granulomatosis with polyangiitis (GPA) – also known as Wegener's granulomatosis (WG) – and microscopic polyangiitis (MPA) are both associated with anti-neutrophil cytoplasmic antibodies (ANCAs) and are therefore referred to collectively as ANCA-associated vasculitis (AAV). The causative role of ANCAs in generating small-vessel vasculitis has been demonstrated in several in-vitro and in-vivo models. Two types of ANCA have been identified in GPA and MPA, defined by the antigenicity against two different self –antigens which are the endogenous enzymes; MPO (myeloperoxidase) and PR3 (proteinase-3) that are present in neutrophilic lymphocytes. ANCA-serology has a different distribution between GPA and MPA. GPA is mainly associated with PR3-ANCA (95% of the cases), whereas MPA is more frequently associated with MPO-ANCA (75% of MPA patients).

AAV are rare disorders, with an estimated yearly incidence of 1 in 100,000 in Europe. The clinical features of GPA and MPA largely overlap, as necrotizing vasculitis may occur in the same organs. In GPA, crusting granulomata in the ear, nose and throat area and alveolar bleeding are the most prominent feature, and segmental, necrotizing glomerulonephritis may occur in about 50% of the cases. In MPA, glomerulonephritis is the most prominent feature present in virtual all patients, whereas the respiratory tract may be spared. In both GPA and MPA, vasculitis may be extended to other organs like the skin, nervous system, heart and gastrointestinal (GI) tract (mesenterium). CNS involvement is relatively rare for both disorders. Systemic features (fever, arthritis) are more common in MPA. The distinction between both entities is made by histology.

Until the late 1960s the prognosis of WG was poor, with mortality rate of 80% within 1 year, mainly because of renal failure and GI/alveolar bleedings. With the introduction of cyclophosphamide therapy in the 1970s, prognosis has significantly improved, with reported remission rates of flares of 70-90%, and survival rate of 80% in 5 years. Mortality is also reduced by improved supportive care of renal failure. The clinical response to induction therapy with cyclophosphamide (CYC) is reported to be similar for MPA and GPA, although the relapse-rate is reported to be higher for PR-3 ANCA positive GPA (60-80% within 2 years) than for MPA (about 30%). In general, GPA relapses are more progressive of nature (i.e. more severe symptoms and more organs involved), than for MPA.

However CYC is associated with significant toxicity, such as uro-toxicity (haemorrhagic cystitis, bladder cancer), cardio-toxicity, malignancies (lymphoma, thyroid cancer, non-melanoma skin cancer), lymphopenia and neutropenia, serious and opportunistic infections, thrombocytopenia and reduced fertility. Because of its toxicity, its use is limited to short-term induction therapy of severe flares, followed by maintenance therapy with other, in general better-tolerated immune-suppressant agents, like AZA (azathioprine), MFM (mycophenolate mofetil) or MTX (methotrexate). Mild-isolated cases of GPA granulomata may be treated with MTX alone. In a recent series, encompassing a mean follow-up of 17.8 months, 50% of participants suffered either severe or life-threatening adverse effects associated with conventional therapies. Since currently available therapies are associated with significant toxicities, as well as disease relapses when therapy is tapered or discontinued, there is a need for novel, more specific treatment approaches.

The rationale of developing B-cell targeting therapy with rituximab in AAV is that the number of activated B cells in the periphery has been shown to correlate with the extent of disease activity. Short-lived plasma cells, thought to be a major source of pathogenic autoantibodies like ANCAs, are the terminally differentiated progeny of antigen-specific B-cell precursors. Without their B-cell precursors, short-lived plasma cells disappear after about 2 weeks.

Rituximab is a monoclonal antibody against CD20, a cell surface antigen expressed on B-lymphocytes. It depletes peripheral CD19/20 positive B cells, thereby reducing the production of antibodies, including those related to autoimmune reactions. Anti-CD20 therapy effectively eliminates most circulating B cells, while allowing restoration of much of the B-cell lineage once B cell production resumes. Thus, by depleting CD20 positive B cells, rituximab may disrupt critical B-cell contributions to disease and suppress autoantibody production and could potentially contribute to the restoration of B-cell tolerance to ANCA antigens.

In the European Union (EU), rituximab intravenous (IV) infusion in combination with glucocorticoids, was approved on 22 April 2013 for the induction of remission in adult patients with severe, active GPA and MPA (EMEA/H/C/000165/II/0079). The purpose of the current application is to extend the indication to include the use of rituximab for maintenance treatment of patients with GPA and MPA who are in remission.

The other currently approved indications for Mabthera include Non-Hodgkin's Lymphoma (NHL), Chronic Lymphocytic Leukaemia (CLL) and 3rd line treatment of Rheumatoid Arthritis (RA).

The current submission was based on the results from one investigator sponsored pivotal Phase III trial (Study ML22514/MAINRITSAN I), which evaluated the efficacy and safety of rituximab versus azathioprine for the prevention of disease relapse.

The following indication was proposed:

Granulomatosis with polyangiitis and microscopic polyangiitis

MabThera, in combination with glucocorticoids, is indicated for ~~the induction of remission in~~ treatment of adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA).

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The pharmacologically active substance in MabThera, Rituximab (CAS 174722–31–7), is a recombinant immunoglobulin-G monoclonal antibody with a molecular mass of approximately 145 kD.

As an unaltered protein, Rituximab is predicted to be metabolised by regular proteinolysis in the patient and biodegraded in sewage treatment, as shown for other monoclonal antibodies. Thus, Rituximab is unlikely to result in a significant risk to the environment and therefore it is submitted that it does not need a formal ERA according to the EMA 2006 Guideline (corr. 2).

2.2.2. Conclusion on the non-clinical aspects

Based on the updated data submitted in this application Rituximab is unlikely to result in a significant risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

The claim of the indication extension is based on data from a single pivotal study, ML22514 (MAINRITSAN I) which is a multicentre, randomized, open-label study comparing rituximab treatment against azathioprine, a current standard of care treatment.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

- Tabular overview of clinical studies

Table 1 Overview of clinical studies of rituximab in AAV

Studies	Sponsor	Design	Population	Treatment Regimen	No of Patients
ML22514 MAINRITSAN I	Investigator led (Roche)	Phase III, open-label, active-controlled, multicentre, randomized	≥18 to ≤75 years of age with GPA, MPA, renal-limited ANCA associated vasculitis in remission after induction treatment with cyclophosphamide	Experimental arm: Rituximab 500 mg IV infusions on Days 1 and 15, followed by repeat doses at 6, 12 and 18 months Control arm: Aazathioprine at 2 mg/kg/day orally, with tapering after 12 months	Planned: 118 Actual: 115
ITN021AI RAVE	Investigator led (Roche)	Phase II/III, multicenter, randomized, active-controlled, double-blind, double-dummy, parallel-group	Severe AAV (147 with WG and 48 with MPA)	Experimental arm: IV 375 mg/m2 RTX wkly x 4 Control arm: oral CYC, daily for 3-6 months followed by oral AZA	197
WA27893 RaVeR	Investigator led (Roche)	Phase IV, open-label, observational study (ongoing)	Patients with GPA or MPA	Patients followed for a maximum of 4 years	97

2.3.2. Pharmacokinetics

When Study ML22514 was designed, no pharmacokinetic (PK) assessments were planned. The MAH explored the potential use of frozen serum samples from this study to determine whether they could be used retrospectively to determine rituximab concentrations. However, most of the samples were

outside the window of controlled PK stability (3.5 years) for which rituximab concentrations could be accurately quantified. Therefore, rituximab concentrations were only determined in samples used for the measurement of serum anti-drug antibody (ADA), to aid in the interpretation of the ADA data.

Although no PK data are available from Study ML22514, the ITN021AI (RAVE) study, which also enrolled patients with GPA/MPA, did provide clinical pharmacology information which is relevant to the GPA/MPA patient population that was investigated in Study ML22514.

In RAVE, rituximab treatment consisted of four weekly IV infusions of 375 mg/m2, on the first day of weeks 1, 2, 3, and 4. Rituximab levels were evaluated prior to the first and third doses, then on Days 29, 60, 120, 180, 270, and 545 from the first dose. Nonlinear mixed effects modelling (with software NONMEM) was used to analyse the PK data from a total of 97 patients in the rituximab group. The structural model that best described rituximab PK was a two-compartment linear model. The typical population estimates (% standard error of estimates [SEE]) of rituximab clearance (CL), and volume of distribution in central compartment (V1) were 0.289 L/day (4.39%), and 4.42 L (3.21%), respectively. The inter-patient variability (%SEE) for CL, and V1 were 42.1% (13.8%), and 26.8% (18.9%), respectively. The median of individual estimates of t1/2 of rituximab was 23.4 days (range: 9.38-48.7 days). Sex and ADA were the two covariates with the largest effect on inter-individual variability on CL. Men had approximately 31.4% faster CL than women. ADA-positive patients had 37% faster clearance than ADA-negative patients and ADA-positive patients were associated with shorter t1/2 than ADA-negative patients (19.0 vs. 25.6 days). Sex and body surface area (BSA) were the two covariates with the largest effect on the inter-individual variability on V1. Men had 21.6% larger V1 than women. Patients associated with larger BSA had larger V1. Volume of distribution in central compartment was 18% larger for a BSA of 2.30 m2. The estimate of t1/2, based on the final model was very similar between men and women (23.6 and 24.9 days, respectively). Mean PK parameters summarized in Table 2.

Table 2 RAVE study: Summary Statistics of Rituximab PK Parameters

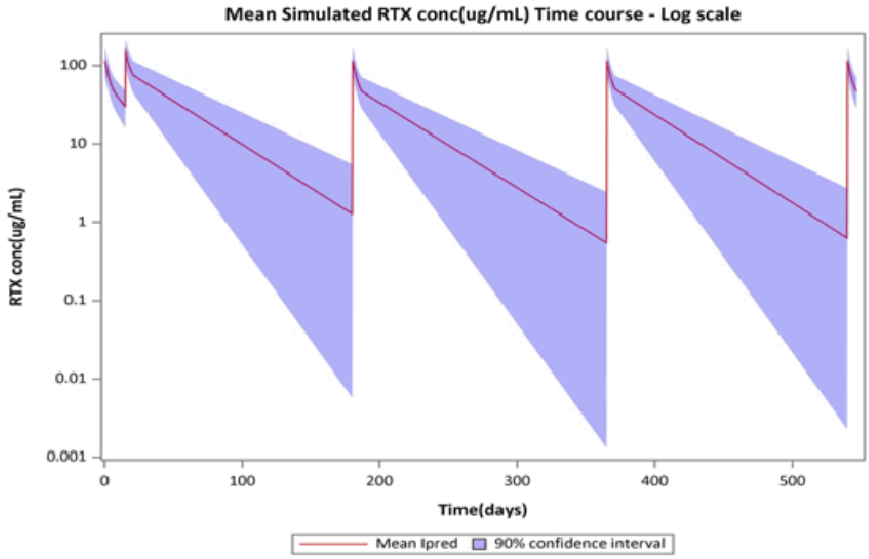
PK parameters	n	Mean	SD	Median	Range
CL, mL/day	97	313	131	281	116-725
V_1, L	97	4.50	1.08	4.40	2.25-7.39
$t_{1/2}$, day	97	24.3	8.05	23.4	9.38-48.7
$AUC_{0\text{-}inf}$, mg/mL•day	97	10.6	3.93	10.1	3.14-24.5

$AUC_{0\text{-}inf}$=area under concentration time curve from time 0 to infinity; CL=clearance; n=number of patients; PK=pharmacokinetic; SD=standard derivation; $t_{1/2}$=half-life determined by elimination phase; V_1=volume of distribution in central compartment.

Overall, the population PK parameters for rituximab in patients with GPA/MPA are similar to those estimated for other Immunoglobulin G (IgG) antibodies. Rituximab PK in the GPA/MPA patient population also appears to be similar to that observed in patients with RA. Given the moderate inter-patient variability and the moderate covariates effect on CL and V1, these findings suggest that the tested covariates (e.g., age, race, ethnicity, albumin, BSA, sex and ADA) have no clinically relevant effect on rituximab PK and that no dose adjustments based on the demographic or physiological variables are needed.

Figure 1 shows the predicted concentration-time profiles for rituximab, using the PK parameters from Study ITN021AI, and the rituximab doses from the ML22514 trial, i.e. 500 mg on Day 1 and 15 followed by a dose of 500 mg every 6 months. Simulations were conducted in 130 patients by taking into account the expected baseline characteristics (i.e. age, gender, BSA, and presence of ADA) of the patients and were run 100 times to determine the median, 5th and 95th percentile predicted PK

profiles. For the simulations, 50% of the patients were men, the median (P5-P95) BSA was 1.84 (1.46-2.28) m2, and 21% of the patients were ADA-positive. The 13000 simulated PK time courses were summarized using median concentration-time profiles and 5th and 95th percentiles (90% prediction interval) and are shown in Figure 1.



Blue area and solid red line represent the 90% prediction interval (PI) of simulated rituximab concentrations and the corresponding median among 13000 simulations with the population PK model previously developed in patients with GPA/MPA

Figure 1 Predicted PK Profiles in ML22514 Study in 130 Patients With GPA/MPA Treated With Rituximab 500 mg on Day 1, Day 15, and at Month 6, Month 12 and Month 18

With the dosing regimen used in the Study ML22154, rituximab concentrations are expected to be similar to those observed using the dosing regimen in Study ITN021AI

2.3.3. Pharmacodynamics

Mechanism of action

Rituximab is a monoclonal antibody against CD20, a cell surface antigen expressed on B-lymphocytes. The binding of rituximab to CD20 on B lymphocytes promotes B cell lysis via a number of different possible mechanisms, including antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and induction of apoptosis. The depletion of peripheral CD19/20 positive B cells reduces the production of antibodies, including those related to autoimmune reactions. Anti-CD20 therapy effectively eliminates most circulating B cells, while allowing restoration of much of the B-cell lineage once B cell production resumes. Thus, by depleting CD20 positive B cells, rituximab may disrupt critical B-cell contributions to disease and suppress autoantibody production and could potentially contribute to the restoration of B-cell tolerance to ANCA antigens.

Primary and secondary pharmacology

Immunogenicity

Study ML22514 did not have a prospective plan for immunogenicity assessment as part of the study protocol or schedule of assessments. Immunogenicity data and measurement of ADA was therefore analysed as a post-hoc evaluation by the MAH. Available stored serum samples, were requested retrospectively from the Sponsor at the following pre-dose time points: Day 1 (Infusion 1), Day 180 (Month 6, Infusion 3), Day 365 (Month 12, Infusion 4), and Day 545 (Month 18, Infusion 5). ADA data were evaluated for patients in the rituximab arm only. ADA were measured using a bridging ELISA.

Overall, samples were available for ADA analysis from 44 patients, broken down as follows:

- Baseline samples only: 10 patients
- Baseline plus at least 1 post-baseline sample: 26 patients
- Post-baseline samples only: 8 patients

Since 10 patients provided only baseline samples, a total of 34 patients were available for the immunogenicity assessment following rituximab administration. Of the 26 patients who provided a sample at baseline and at least one post-baseline sample, 4 patients developed rituximab-induced ADA at any point during the study. Of the 8 patients with post-baseline samples only (i.e. missing Day 1 baseline sample), 2 patients were found to be ADA-positive at Month 12. In summary, 6/34 evaluable patients (18%) developed treatment-induced ADA; one first occurring at Month 6, four at Month 12, and one at Month 18.

From the available data, the occurrence of ADA did not appear to have a negative effect on the efficacy of rituximab. Of the 3-rituximab treated patients who had a major relapse by month 28, none tested positive for ADA. When looking at the impact of ADA on safety, the data did not suggest a different safety profile in patients who tested positive for ADA post-baseline compared to those that tested negative. Furthermore, as expected, patients testing ADA-positive also experienced peripheral CD19 count depletion following rituximab administration.

2.3.4. Discussion on clinical pharmacology

The clinical pharmacology of rituximab used in an AAV population is relatively well established. The data primary derive from the pivotal study used for the approval of the induction therapy indication (Study ITN021AI) with participation of a total of 97 patients. Additional a PK simulation of predicted rituximab exposure is presented based on data from the pivotal study from the actual application (Study ML22154).

Overall, there is no new data with regards to the basic PK properties including absorption, distribution, metabolism, elimination and excretion. The structural model that best described rituximab PK was a two-compartment linear model. The population estimates of rituximab clearance (CL), and volume of distribution in central compartment (V1) were 0.289 L/day and 4.42 L, respectively. The median of individual estimates of t1/2 of rituximab was 23.4 days. As supplement, the simulation of predicted rituximab exposure showed that the dosing regimen of Study ML22154 is expected to be similar to those observed using the dosing regimen of Study ITN021AI. Overall, the description of the PK seems appropriate.

No new information regarding mechanism of action is presented. Rituximab mediate a depletion of CD20 positive B-cells and reduces the production of antibodies, including those related to autoimmune reactions.

Immunogenicity data were analysed as a post-hoc evaluation which is considered acceptable. A total of 34 patients were available for immunogenicity assessment following rituximab administration and 6 of 34 (18%) developed treatment-induced ADA. It appeared, that the occurrence of ADA did not have a negative effect on the efficacy of rituximab. The presented data is considered sufficient.

2.3.5. Conclusions on clinical pharmacology

The Clinical pharmacology is sufficiently covered with data from the application for MabThera on the induction treatment indication and a PK simulation study. Overall, there is no new data with regards to

the basic PK properties. From a clinical pharmacology point of view, no unexpected findings of clinical relevance have been revealed and no concerns are identified.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No dose-response studies were submitted. The 500 mg rituximab dose used in the trial (ML22514) is lower than that used for induction or maintenance of remission in other conditions, such as rheumatoid arthritis. This dose was chosen because the investigators estimated that it might be appropriate for patients in remission (already B-cell depleted) at the start of maintenance treatment and could limit the risk of infection.

2.4.2. Main study

Study ML22514 therapeutic, prospective, Phase III, multi-centre, comparative, randomized, open-label study comparing azathioprine versus rituximab in combination with low-dose corticosteroids for the maintenance treatment of GPA/MPA

Methods

Study ML22514 is a therapeutic, prospective, Phase III, multi-centre, comparative, randomized, open-label study comparing azathioprine versus rituximab in combination with low-dose corticosteroids for the maintenance treatment of GPA/MPA.

Eligible patients were randomized 1:1 to either rituximab or azathioprine; randomization was stratified by recently diagnosed or recurrent disease (Figure 2). A priori, 66% of patients were newly diagnosed and 33% were in relapse. Patients randomized to the rituximab arm received 500 mg intravenous (IV) on Day 1, Day 15, and Months 6, 12, and 18. Patients randomized to the azathioprine arm received an oral dose of 2 mg/kg/day for 12 months, followed by a dose of 1.5 mg/kg/day for 6 months, and finally 1 mg/kg/day for 4 months (treatment discontinuation after 22 months). Following the enrolment visit (Day 1) and a Day 15 visit (patients on rituximab only), patients were monitored every 3 months through Month 24, with a follow-up visit at Month 28. Hence, after the completion of maintenance treatment, patients in the rituximab arm were followed for 10 months while those in the azathioprine arm were followed for 6 months. Continuing the azathioprine maintenance treatment through Month 22, aimed to limit possible bias that could have been in favour of rituximab due to the prolonged pharmacodynamics effect (prolonged B cell depletion) anticipated to extend beyond the last infusion at Month 18.

The 6-month interval between rituximab infusions was based on reported B-cell reconstitution and relapses after a median of 1 year (range, 4 to 37 months for relapses) in early studies of patients given rituximab for induction.

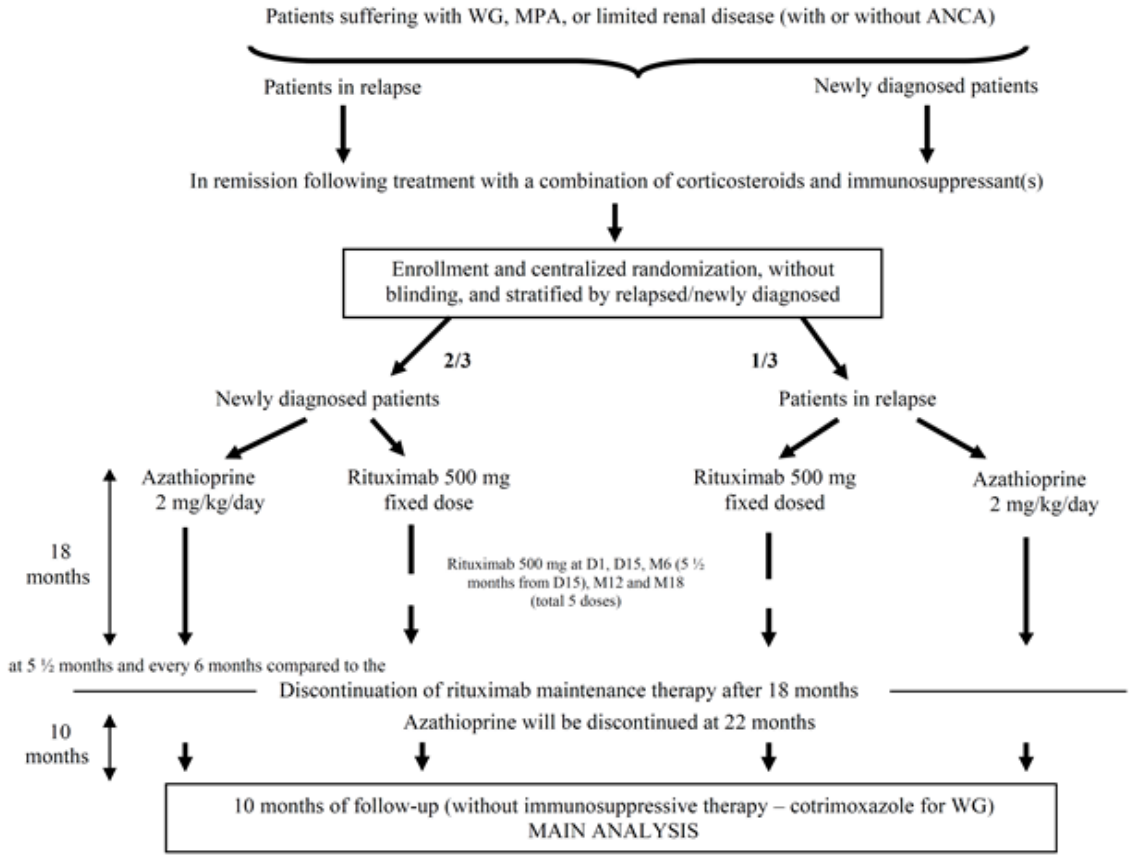


Figure 2 Study design

Study participants

Inclusion Criteria

The patients who met the following criteria were eligible for enrollment into the study:

1. Age 18 to 75 years (at the time of disease diagnosis)
2. ANCA-associated vasculitis: GPA, MPA, and limited renal forms (pauci-immune glomerulonephritis) with or without ANCA (at the time of diagnosis as well as remission). There are 4 types of ANCA-associated vasculitis: limited renal forms, GPA, MPA, and Churg-Strauss syndrome. Only the first 3 of these diseases were investigated in this study. However, ANCA are absent in certain types of vasculitis at the time of diagnosis. Absence of ANCA was not considered an exclusion criterion as long as histological confirmation of the diagnosis was obtained.

- GPA that met American College of Rheumatology 1990 criteria and/or Chapel Hill nomenclature, with either:

    a) Renal, cardiac, nervous system, and/or digestive system disorders
    b) Other general clinical manifestations (non-infectious fever >38.3°C lasting >1 week; change in overall condition with a Karnofsky score <40; weight loss >5 kg in <3 months)
    c) A massive intra-alveolar hemorrhage (drop in hemoglobin level greater than 3 g/dL; hypoxemia with O_2 saturation <90%; respiratory distress syndrome)

d) Another rare form characterized by pulmonary, ocular or otorhinolaryngological granulomatous presentations

- MPA meeting the Chapel Hill nomenclature criteria and exhibiting signs of a poor prognosis in accordance with the 5-factor score (renal failure with serum creatinine >140 µmol/L; proteinuria with >1 g per 24 hours; specific central nervous system disorders, cardiomyopathy, or gastrointestinal involvement)

3. Patients in remission following a first induction therapy or a relapse, achieved with any treatment regimen combining corticosteroids and at least 1 immunosuppressant, in accordance with the currently accepted good practice, with the exception of anti-CD20 or anti-tumor necrosis factor α (TNFα). A period of 10 to 15 days was required between the onset of remission and the start of maintenance therapy.
4. A maximum period of 1 month between the end of their previous immunosuppressive therapy and randomization into the study.
5. Patients who read and signed the informed consent form for their participation in the study

Biological criteria defining satisfactory bone marrow, liver, and kidney functions for inclusion in the study were the following:

- Bone marrow function: Bone marrow reserve was evaluated using complete blood count and platelet count.
- Liver function was evaluated by transaminase and alkaline phosphatase levels.
- Renal function was evaluated based on creatinine level and calculated clearance.

These tests were performed in the study as part of the initial testing during the enrollment visit.

Exclusion criteria

Patients who met at least 1 of the following criteria were excluded from the study:

1. Churg-Strauss syndrome
2. Other types of systemic vasculitis
3. Secondary vasculitis (particularly paraneoplastic or infectious forms)
4. Patients who had not achieved remission with corticosteroid and immunosuppressant therapy (disease still active)
5. Patients previously treated with monoclonal antibodies such as anti-CD20 or anti-TNFα
6. History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies
7. Inability or refusal to understand or sign the informed consent form to participate in the study
8. Inability or refusal to follow the treatment or undergo required follow-up examinations for the study (non-compliance)
9. Allergy, known hypersensitivity, or contraindication to the medications being used and investigated in the study (cyclophosphamide, corticosteroids, azathioprine, rituximab)
10. Patients being treated with allopurinol were not included if allopurinol treatment had to be continued (risk of increased azathioprine toxicity)

11. Pregnancy, lactation: Women of childbearing potential had to agree to use a reliable method of contraception during the entire immunosuppressive treatment period.
12. Human immunodeficiency virus, hepatitis B virus, or hepatitis C virus infection
13. Progressive, uncontrolled infection requiring long-term treatment (tuberculosis, etc.)
14. Other types of severe infection reported less than 3 months prior to randomization (cytomegalovirus, human herpesvirus-8, etc.)
15. Bacterial, viral, fungal, or mycobacterial infection (with the exception of fungal infection of the nail bed) or any other progressive infection or significant episode of infection requiring hospitalization or treatment with anti-infective medication either intravenously within 4 weeks or orally within 2 weeks prior to enrolment
16. History of deep tissue infection (fasciitis, abscess, osteomyelitis, articular septic arthritis) in the year prior to enrolment in the study
17. History of severe chronic or recurrent infection or any other underlying condition that predisposed the patient to severe infections
18. Administration of a live vaccine in the 4 weeks prior to enrolment in the study
19. Known severe chronic obstructive pulmonary disease (forced expiratory volume in 1 second <50% or grade 3 functional dyspnoea)
20. New York Heart Association Stage III or IV heart failure
21. Recent history of acute coronary syndrome
22. Progressive cancer or haematological malignancy diagnosed in the 5 years prior to the vasculitis diagnosis. Patients with non-metastatic prostate cancer or basal cell carcinoma, or patients cured from cancer or a hematologic malignancy more than 5 years ago, and who had not received any cancer treatment in the past 5 years, were permitted.
23. Patients with systemic diseases that could have rendered the effects of the study treatments (azathioprine or rituximab) unpredictable and inappropriate
24. Severe immunosuppression
25. Participation in another clinical research study within the 4 weeks prior to enrolment
26. Any medical or psychiatric condition that may have prevented the administration of the study treatments and patient follow-up according to the protocol, or which, based on the judgment of the study investigator, would have exposed the patient to an increased risk of adverse effects
27. Lack of affiliation with a social security program (beneficiary or rights-holder)

Treatments

Induction therapy

Patients who were not in remission at the time of study entry received induction therapy prior to randomization to maintenance therapy. According to standard of care in France, induction therapy included a combination of corticosteroids and an immunosuppressant, namely bolus doses of cyclophosphamide; oral cyclophosphamide and methotrexate were acceptable induction therapies. The investigator was free to define the initial treatment, provided that it did not include monoclonal antibodies such as anti-CD20 or anti-TNF-alpha. Plasma exchanges and/or immunoglobulins

administered intravenously were permitted as part of the initial treatment. Corticosteroid treatment was left to the investigator's discretion and was to be gradually tapered as the disease improved.

Patients received remission-induction therapy for approximately 4 to 6 months until remission was attained. At that time, and within a maximum of 1 month after the last cyclophosphamide dose, eligible patients were enrolled and randomly assigned in a 1:1ratio (stratified by disease characteristic: newly diagnosed or relapsing disease) to receive maintenance therapy with rituximab or azathioprine.

Maintenance therapy

Rituximab administration:

Rituximab was administered IV at a fixed dose of 500 mg in the month following discontinuation of the immunosuppressive therapy that led to remission. The first infusion occurred within 4 days after the enrolment visit. Subsequent infusions of rituximab were administered at the Day 15, Month 6, Month 12, and Month 18 visits (5 infusions total), regardless of the ANCA titer and the level of circulating CD19+ lymphocytes. Before each infusion, the patients were pre-medicated with an analgesic/antipyretic drug (paracetamol), a short IV infusion of 100 mg methylprednisolone, and 5 mg dexchlorpheniramine. To avoid any risk of hypotension related to the infusion of rituximab, antihypertensive treatments were interrupted 12 hours before the rituximab infusion. Rituximab infusions were discontinued if signs of severe infusion related reactions (especially severe dyspnoea or bronchospasms) were detected. If the patient developed an initial allergic reaction during the first infusion, the administration of the product was permanently discontinued. If a patient developed a mild-to-moderate reaction during the first infusion, an antihistamine and corticosteroid treatment was recommended at the second infusion and patient care was reinforced with closer monitoring.

Azathioprine administration:

Azathioprine was administered orally at a dose of 2 mg/kg/day for 12 months, followed by 1.5 mg/kg/day for 6 months, and finally 1 mg/kg/day for 4 months; treatment was discontinued after 22 months. The daily dose, based on body weight, was rounded to the nearest multiple of 25, without exceeding 200 mg/day. Maintenance therapy was initiated in the month following discontinuation of the immunosuppressive therapy that led to the patient's remission and no later than 8 days after the patient was included in the study.

Corticosteroid administration:

Corticosteroid treatment at study inclusion was left to the investigator's discretion. The recommended initial dose of corticosteroids was prednisone at 1 mg/kg/day. During the study, and concurrent with sustained disease remission, prednisone treatment was tapered and then kept at a low dose (approximately 5 mg per day) for at least 18 months after randomization. Prednisone dose tapering and the decision to stop prednisone treatment after Month 18 were left to each site investigator's discretion. Before each infusion of rituximab, there was a short IV infusion of 100 mg methylprednisolone. For a minor relapse (not life threatening nor involving a major organ), a modest increase in corticosteroid, up to 20 mg/day for 3 weeks, was allowed, with gradual tapering over a maximum of 6 weeks, returning to the dose level used before the minor relapse. Corticosteroid use was tracked in the patient diary.

All other immunosuppressants and immunomodulators specifically intended to control vasculitis (eg, colchicine, dapsone, hydroxychloroquine, danazol) were prohibited for the duration of the study. If the disease worsened and required more intensive treatment, the patient was withdrawn from the study (premature withdrawal) and received treatment in accordance with current standard practices for vasculitis.

Objectives

Primary objective

The primary objective of this study was to evaluate the efficacy of rituximab as maintenance therapy for patients in remission from ANCA-related systemic vasculitis after a first exacerbation or relapse.

Secondary objectives

- To evaluate rituximab tolerance compared to azathioprine
- To determine if reappearance of ANCA and/or increase in circulating levels of CD19+ B lymphocytes (CD19+ only for patients in the rituximab arm) was predictive of relapse occurrence.

Outcomes/endpoints

Primary endpoint

The primary endpoint is the percentage of patients with major relapse (reappearance or worsening of disease with Birmingham Vasculitis Activity Score (BVAS) >0, and involvement of at least one major organ, a life-threatening manifestation, or both) at month 28 (18 months of treatment + 10 months of follow-up for the rituximab arm and 22 months of treatment + 6 months of follow-up for the Azathioprine arm). The definitions of remission and relapse are based on those formulated and adopted by experts of EUVAS/EULAR

The percentages of patients with at least one major relapse in each treatment group were compared using the Pearson Chi-squared test, and the resulting p-value is reported. As part of the primary analysis, the time to first major relapse was analyzed with a Cox proportional hazards regression, comparing treatment groups, and adjusting for the stratification factor (newly diagnosed vs. relapsing disease). The probabilities of a major relapse within the 28 month study period are presented by treatment group using Kaplan-Meier plots. The survival curves, from the date the maintenance therapy was started until the date of relapse, were compared between treatment groups using the log-rank test. Patients were censored at day of death or study withdrawal if it occurred before a major relapse.

Secondary endpoints

The secondary endpoints for the ML22514 study were separated in endpoints related to efficacy and endpoints related to safety.

Secondary efficacy endpoints:

- Number of patients with detectable ANCA in each treatment group
- Number of minor relapses in each treatment group
- A minor relapse is defined as reappearance or worsening of disease with Birmingham Vasculitis Activity Score (BVAS) > 0 without involvement of at least one major organ and/or without life-threatening manifestation.
- Cumulative corticosteroid dose and duration of treatment in each group 10 months after completion of maintenance therapy

The same endpoints will be assessed 6 months after the completion of maintenance therapy (post-treatment observation phase). Patients experiencing a relapse during this phase of the study will be

treated with immunosuppressants in accordance with Good Clinical Practice (GCP), or with a new rituximab infusion (outside of the protocol) for those in the rituximab arm.

Secondary endpoints related to safety:

- Number and seriousness of side-effects in each treatment group
- Mortality in each treatment group

Additional analyses

Efficacy analyses:

- BVAS values will be summarized with descriptive statistics by visit and treatment group
- Immunological results, specifically CD19 percentage of total lymphocytes, total immunoglobin, IgG and IgM titers in each treatment group

Safety analyses:

- The number and seriousness of adverse events (related or not) in each treatment group
- Counts, descriptions and seriousness of adverse events which are infusion related reactions (IRRs) for the Rituximab arm
- Exposure to Study Medication
- Adverse Events
- Infusion Related Reactions

Sample size

The sample size calculation was based on the assumption, that the rate of major relapse at 28 months after remission was expected to be 40% for the azathioprine arm. Rituximab was hypothesized to reduce the number of major relapses at Month 28 by an absolute difference of 25 percentage points. Under the assumption of 5% exclusion or dropout rates, with 80% statistical power and a two-sided alpha risk of 0.05%, a total of 118 patients had to be enrolled in the trial.

Randomisation

At the time of enrolment, patients were randomized in a 1:1 ratio to either rituximab or azathioprine using a computer based random assignment system for balanced random assignment of patients to treatment groups. The randomization sequence was generated in fixed blocks of size 4, within each randomization stratum (relapsers versus new diagnosis). The randomization list was established by Unite de Recherche Clinique (URC) Paris Centre in collaboration with the Agence Générale des Equipements et Produits de Santé (AGEPS), then integrated into the online randomization system (CleanWeb). Randomization was stratified based on whether the patient was newly diagnosed or had relapsing disease (in each treatment arm: approximately 2/3 newly diagnosed patients and 1/3 patients with relapsing disease). The URC and AGEPS will be immediately notified of any patient enrollment/randomization through an automatic email/fax from the CleanWeb system. The AGEPS will ship the treatments (rituximab or azathioprine) to the site pharmacy (PUI) of each investigational center as soon an enrolment is confirmed and within 72 hours of receipt of the fax.

Blinding (masking)

As this was an open-label study, blinding procedures were not applicable.

Statistical methods

All randomized patients comprise the Intent-To-Treat (ITT) population, even if not actually treated. Results for ITT analyses are displayed according to the randomized treatment group. All results for study conduct is summarized by randomized group and by total patient population, and display frequencies with percentages wherever appropriate. A disposition table shows numbers and percentages of patients enrolled, completing the study and withdrawing. Numbers for different reasons of withdrawal is also shown.

All statistical testing is two-sided with 5% Type I error with 95% confidence intervals. All efficacy analyses is done for the ITT population. The testing strategy is based on the primary endpoint only and no adjustment for multiplicity has been made for any secondary or supporting endpoints, as such, any p-values should therefore be interpreted with caution.

Demographic and baseline disease characteristics is summarized by randomized group and overall, and display frequencies with percentages for non-continuous variables or the number of non-missing values, means, standard deviations, medians, quartiles, minima and maxima for continuous variables. Medical history is included in the listing of baseline demographics and characteristics.

Primary endpoint

The percentages of patients with at least one major relapse in each treatment group, were compared with the Pearson Chi-squared test (or Fisher's exact test with mid-p correction if frequencies are small), and the resulting p-value was reported.

A supportive analysis of the primary result includes a Cochran-Mantel-Haenszel (CMH) test to adjust for difference of disease flare category (new diagnosis or relapsing disease). This was added because the randomization was stratified by disease flare category.

As part of the primary analysis, the time to first major relapse were analyzed with a Cox proportional hazards regression, comparing treatment groups, and adjusting for the stratification factor (new diagnosis vs. relapsers). Kaplan-Meier graphs of the probability of remaining free of major relapse by treatment group is also be presented. The survival curves, from the date the maintenance therapy was started until the date of relapse, is compared between treatment groups using the log-rank test. Patients were censored at death or study withdrawal if it occurred before a major relapse.

Secondary endpoints

All adverse events (AEs) were collected and described as they occurred. These AEs were graded by the investigator using CTCAE v4.0 criteria. Serious AEs were captured on a separate form. All AEs and SAEs were to be coded using MedDRA v20.0. An overall summary will be prepared to show the number of events and then number and percentage of patients with events for the following event types: all AEs, related AEs (possibly or probably related to rituximab or azathioprine), AEs leading to discontinuation, deaths (fatal AEs), SAEs, and related SAEs. Adverse events will be summarized for the Safety population by actual treatment group and overall, by System Organ Class (SOC), Preferred Term (PT), severity (intensity grade), relationship to investigational product (IP), with the number and percentage of patients exhibiting each of these adverse event types by actual treatment group and overall.

The numbers and percentages of patients with detectable ANCAs at each visit were compared by treatment group with Pearson Chi-squared tests (or Fisher's exact tests with mid-p correction if frequencies are small), and the resulting p-values was reported.

Mortality in each treatment arm were summarized, if any.

The percentages of patients with at least one minor relapse at or before Month 28, without a preceding major relapse, in each treatment group, were compared with the Pearson Chi-squared test (or Fisher's exact test with mid-p correction if frequencies are small), and the resulting p-value was reported. As part of this analysis, the time to first minor or major relapse were analyzed with a Cox Proportional Hazards regression, comparing treatment groups, and adjusting for the stratification factor (new diagnosis vs. relapsers). Kaplan-Meier graphs of the probability of remaining free of minor relapse by treatment group were also be presented. The survival curves, from the date the maintenance therapy was started until the date of relapse, were compared between treatment groups using the log-rank test. Patients were censored at death or study withdrawal if it occurred before a relapse.

The cumulative dose and duration of corticosteroid treatment for each patient were summarized by treatment group.

The primary endpoints were analysed using the same methods as above but at the time point 6 months after the end of the maintenance therapy (post-treatment follow-up).

Additional endpoints

Listings of major and minor relapses are presented along with patient characteristics and BVAS calculated at relapse. BVAS values are summarized with descriptive statistics by visit and treatment group. Immunological results, specifically CD19 percentage of total lymphocytes, total immunoglobin (Ig), IgG, and IgM titers are presented for each treatment group.

Subgroup analyses

An analysis of the primary endpoint were performed by subgroups of patients with and without detectable ANCAs.

Results

Participant flow

A total of 118 patients signed informed consent forms (Table 3). Of these, 117 patients were randomized 1:1 to treatment with rituximab (58 patients) or azathioprine (59 patients). One hundred fifteen patients (57 rituximab; 58 azathioprine) received study treatment during the study. Two patients were randomized but did not receive study, one who was randomized to receive rituximab, was not in remission at the time of enrolment and did not receive study treatment, and the other, who was randomized to receive azathioprine, withdrew consent prior to the first dose of study treatment. The proportion that completed the month 28 visit was 94.8% for the rituximab group compared with 89.8% for the azathioprine group.

More patients in the azathioprine arm (45.8%) compared with the rituximab arm (17.2%) prematurely discontinued study treatment (Table 3). Relapse of vasculitis (5.2% rituximab vs. 27.1% azathioprine) and discontinuations for safety (1.7% vs. 10.2%) mainly accounted for the overall higher incidence of discontinuations in the azathioprine arm. It is stated, that patients could have discontinued for more than one reason.

Table 3 Summary of Disposition of Patients by Trial Treatment (All Patients)

	Rituximab (N = 58)	Azathioprine (N = 59)	All Patients (N = 118)
Signed Informed Consent	58	59	118
Randomized	58	59	117
Treated	57	58	115
Completed Month 28 Visit	55 (94.8%)	53 (89.8%)	108 (91.5%)
Discontinued Before Month 28 Visit	3 (5.2%)	6 (10.2%)	9 (7.6%)
Completed Planned Treatment	48 (82.8%)	32 (54.2%)	80 (67.8%)
Discontinued Planned Treatment	10 (17.2%)	27 (45.8%)	37 (31.4%)
Safety Reasons	1 (1.7%)	6 (10.2%)	7 (5.9%)
Onset of a Serious Adverse Effect	0	5 (8.5%)	5 (4.2%)
Death of the patient	0	0	0
Other	1 (1.7%)	1 (1.7%)	2 (1.7%)
Other: HEPATITIS/AZATHIOPRINE	0	1 (1.7%)	1 (0.8%)
Other: pregnancy at 6 and a half months	1 (1.7%)	0	1 (0.8%)
Non-safety Reasons	9 (15.5%)	21 (35.6%)	30 (25.4%)
Relapse of vasculitis during or after the treatment, requiring a change in or resumption of the immunosuppressive therapy	3 (5.2%)	16 (27.1%)	19 (16.1%)
Form not completed	3 (5.2%)	1 (1.7%)	4 (3.4%)
Treatment failure, which required a change in immunosuppressive therapy	0	2 (3.4%)	2 (1.7%)
Worsening of the disease, which required an intensification of the immunosuppressive therapy	0	2 (3.4%)	2 (1.7%)
Decision of the investigator	1 (1.7%)	1 (1.7%)	2 (1.7%)
Withdrawal of consent	0	1 (1.7%)	1 (0.8%)
Patient lost to follow-up	1 (1.7%)	0	1 (0.8%)
Other	2 (3.4%)	2 (3.4%)	4 (3.4%)
Other: Patient left for the United States for his studies	0	1 (1.7%)	1 (0.8%)
Other: not meeting inclusion criteria	1 (1.7%)	0	1 (0.8%)
Other: patient monitoring not compliant	0	1 (1.7%)	1 (0.8%)
Other: patient not in remission	1 (1.7%)	0	1 (0.8%)

Completed Planned Treatment - Treatment received in compliance with protocol and visits carried out until Month 28 as per CRF End of Study form.

Overall 9 patients, 3 in the rituximab group and 6 in the azathioprine group, discontinued before the Month 28 visit. The reason for the discontinuation does not appear clearly. One patient is stated to be lost to follow-up. The MAH was asked to provide more clear information on the reason(s) for the discontinuation of the 9 patients before the Month 28 visit. The MAH subsequently provided tabulated descriptions of the reasons for discontinuation of treatment for the 9 patients. The response was considered sufficient and issue was resolved.

Recruitment

Patients were recruited from 49 sites in France; most sites recruited between 1 and 3 patients with the highest recruiting site (Site 1) enrolling 19 patients. The first patient enrolled on 07 October 2008, and the last patient's last visit was 12 December 2012. A list of investigators who recruited patients and the investigator CVs is provided in the dossier.

Conduct of the study

Protocol amendments

There were a total of 6 protocol amendments. Table 4 lists major changes to the protocol. Of importance, in protocol v2, dated 22 September 2008, the definition of a major relapse was revised from BVAS > 10 to be defined as the reappearance of clinical and/or biological signs of vasculitis activity which could be life threatening or lead to organ failure or destruction.

Table 4 Summary of Major Changes to the Protocol

Document, Version, Date	Summary of Changes
Protocol, v 2 22 September 2008	• Revised the definition of major relapse (primary endpoint) from BVAS > 10 to "the reappearance of clinical and/or biological signs of vasculitis activity which could be life threatening or lead to organ failure or destruction." • Added an interim analysis, to be performed after 50% of patients were enrolled.[a]
Protocol, v 3 31 December 2008	• Added an inclusion criterion to specify that the end of immunosuppressive therapy must be less than 1 month prior to randomization. • Added an interim analysis of the primary endpoint to be performed after half of the patients were enrolled.[a]
Protocol, v 4 12 August 2009	• Extended azathioprine treatment from 18 months to 22 months.

[a] Interim analysis was not performed because study recruitment was faster than expected.

Several amendments were made to the original protocol; however, none are considered critical with regards to study design, endpoints and objectives. The changes with regard to the definition of major relapse (primary endpoint), were implemented before enrolment of the first patient.

Protocol Deviations

Protocol deviations that were considered as major were identified in a post-hoc review by the study's Scientific Director. Four patients were considered to have had major deviations as follows:

Rituximab Arm

- One patient was incorrectly enrolled because the disease was not in remission
- One patient received an additional immunosuppressant (mycophenolate mofetil as a standard anti-rejection regimen after renal transplant) as of Month 16

Azathioprine Arm

- One patient stopped taking study drug for 3 months, then resumed at the appropriate dose
- One patient had poor compliance between Month 12 and Month 18

A listing of all deviations (major and minor) identified during the study was provided by the MAH. Overall, more than 100 minor and major deviations are listed across both treatment groups involving more than 60 patients. The MAH has presented brief narratives of the patients who presented with protocol violations. The MAH has provided tabulated overview of protocol violation stratified by the categories; inclusion criteria deviations, medication deviations and study protocol violations. Further, a more detailed description with frequencies within the categories is also presented. Overall, in consideration of the nature of the disease and the treatment, the deviations do not significantly influence the integrity of the trial.

Baseline data

Demographics

Table 5 Summary of Demographic Data by ITT

	Rituximab (N = 58)	Azathioprine (N = 59)	All Patients (N = 117)
Baseline Age (years)			
n	58	59	117
Mean	52.8	55.7	54.2
SD	13.28	13.49	13.41
Median	53.5	58.0	56.0
Q1, Q3	44.0, 62.0	49.0, 67.0	48.0, 65.0
Min, Max	24, 75	21, 75	21, 75
Age Category			
n	58	59	117
<25 years	1 (1.7%)	2 (3.4%)	3 (2.6%)
25-<35 years	6 (10.3%)	4 (6.8%)	10 (8.5%)
35-<45 years	8 (13.8%)	5 (8.5%)	13 (11.1%)
45-<65 years	31 (53.4%)	30 (50.8%)	61 (52.1%)
< 65 years	46 (79.3%)	41 (69.5%)	87 (74.4%)
>=65 years	12 (20.7%)	18 (30.5%)	30 (25.6%)
Gender			
n	58	59	117
Male	37 (63.8%)	29 (49.2%)	66 (56.4%)
Female	21 (36.2%)	30 (50.8%)	51 (43.6%)
Baseline Height (cm)			
n	57	58	115
Mean	171.1	166.8	168.9
SD	9.23	8.69	9.18
Median	170.0	168.0	169.0
Q1, Q3	165.0, 177.0	161.0, 173.0	162.0, 176.0
Baseline Weight (kg)			
n	57	58	115
Mean	79.4	70.9	75.1
SD	21.75	14.95	19.03
Median	78.0	70.0	73.0
Q1, Q3	65.0, 90.0	60.0, 80.0	62.0, 85.0
Min, Max	48, 138	45, 119	45, 138
Baseline BMI (kg/m^2)			
n	57	58	115
Mean	26.99	25.48	26.23
SD	6.612	5.186	5.958
Median	26.22	25.54	26.01
Q1, Q3	22.49, 29.38	21.80, 28.39	22.14, 28.63
Min, Max	17.4, 50.7	17.3, 48.2	17.3, 50.7
Baseline BSA (m^2)			
n	57	58	115
Mean	1.91	1.79	1.85
SD	0.260	0.198	0.238
Median	1.87	1.78	1.83
Q1, Q3	1.73, 2.10	1.66, 1.93	1.68, 2.03
Min, Max	1.5, 2.6	1.4, 2.4	1.4, 2.6

Abbreviations: SD = Standard deviation, Q1, Q3 = 1st and 3rd quartiles, cm = Centimeter, kg = Kilogram, BMI = Body mass index, BSA = Body surface area, m = Meter.
BMI and BSA are calculated from weight and height.

The baseline demographics are not well-balanced between the two treatment arms with respect to gender and the age category >65 years. There are a relative larger proportion of men in the rituximab arm compared with the azathioprine arm. Further, there are a relative larger proportion of patients >65 years in the azathioprine group compared with the rituximab group.

The MAH acknowledges that some baseline differences with regards to gender were observed in the ML22514 study. At the CHMP's request, the MAH provided satisfactory analysis and discussion of the data and concluded that overall, the baseline differences in gender between the two study arms and within the RTX arm do not appear to have influenced response to rituximab or prognosis of the disease. The response on the baseline gender differences was considered sufficient by the CHMP.

Regarding the baseline differences in age category, the RTX arm indeed enrolled fewer patients ≤ 65 years (21% rituximab vs. 31% azathioprine). The baseline differences observed in the ML22514 study with regards to age are likely to be due to random chance and do not appear to have influenced response to rituximab treatment or prognosis of the disease. Data shows that rituximab consistently reduced the number of disease relapses in both age groups (above and below aged 65). The response was considered sufficient by the CHMP.

Baseline disease characteristics

Table 6 Summary of Baseline Vasculitis and Clinical Characteristics by ITT

	Rituximab (N = 58)	Azathioprine (N = 59)	All Patients (N = 117)
Disease Type			
n	58	59	117
GPA (Wegener's)	48 (82.8%)	40 (67.8%)	88 (75.2%)
Microscopic Polyangitis	8 (13.8%)	16 (27.1%)	24 (20.5%)
Renal Limited Vasculitis	2 (3.4%)	3 (5.1%)	5 (4.3%)
Classification of Recent or Recurrent Disease at Inclusion			
n	58	59	117
New Diagnosis	46 (79.3%)	47 (79.7%)	93 (79.5%)
Relapsers	12 (20.7%)	12 (20.3%)	24 (20.5%)
ANCA at Inclusion			
No	25 (43.1%)	17 (28.8%)	42 (35.9%)
Yes	32 (55.2%)	42 (71.2%)	74 (63.2%)
BVAS at Inclusion			
n	56	58	114
Mean	0.1	0.2	0.1
SD	0.53	0.78	0.67
Median	0.0	0.0	0.0
Q1, Q3	0.0, 0.0	0.0, 0.0	0.0, 0.0
Min, Max	0, 4	0, 5	0, 5
Initial Cutaneous and/or Mucosal Signs			
Purpura	13 (22.4%)	15 (25.4%)	28 (23.9%)
Urticaria	0	1 (1.7%)	1 (0.9%)
Livedo	5 (8.6%)	2 (3.4%)	7 (6.0%)
Nodosities	1 (1.7%)	2 (3.4%)	3 (2.6%)
Cutaneous Necrosis	2 (3.4%)	3 (5.1%)	5 (4.3%)
Other Types of Vasculitis-related Skin Lesions	3 (5.2%)	5 (8.5%)	8 (6.8%)
Initial Ocular Signs			
Exophthalmos	1 (1.7%)	1 (1.7%)	2 (1.7%)
Orbital Pseudotumor	0	1 (1.7%)	1 (0.9%)
Episcleritis Or Scleritis	9 (15.5%)	5 (8.5%)	14 (12.0%)
Retinal Vasculitis	1 (1.7%)	0	1 (0.9%)
Other	9 (15.5%)	8 (13.6%)	17 (14.5%)
Initial ENT Signs			
Non-Invasive Sinusitis	20 (34.5%)	16 (27.1%)	36 (30.8%)
Invasive Sinusitis	5 (8.6%)	2 (3.4%)	7 (6.0%)
Scabby Rhinitis	32 (55.2%)	18 (30.5%)	50 (42.7%)
Epistaxis	16 (27.6%)	9 (15.3%)	25 (21.4%)
Otitis	15 (25.9%)	16 (27.1%)	31 (26.5%)
Other	23 (39.7%)	22 (37.3%)	45 (38.5%)
Initial Pulmonary Signs			
Dyspnea On Exertion (> Stage 2)	10 (17.2%)	8 (13.6%)	18 (15.4%)
Asthma	3 (5.2%)	1 (1.7%)	4 (3.4%)
Nidus Pneumopathy	1 (1.7%)	4 (6.8%)	5 (4.3%)
Interstitial Pneumopathy	2 (3.4%)	2 (3.4%)	4 (3.4%)
Pulmonary Infiltrates	11 (19.0%)	16 (27.1%)	27 (23.1%)
Pulmonary Nodules	23 (39.7%)	25 (42.4%)	48 (41.0%)
Excavated Nodules	10 (17.2%)	2 (3.4%)	12 (10.3%)
Pleurisy	2 (3.4%)	3 (5.1%)	5 (4.3%)
Alveolar Hemorrhage	9 (15.5%)	11 (18.6%)	20 (17.1%)
Respiratory Distress	0	2 (3.4%)	2 (1.7%)
Other	10 (17.2%)	7 (11.9%)	17 (14.5%)
Initial Cardiovascular Signs			
Raynaud's Disease	0	1 (1.7%)	1 (0.9%)
Limb Ischemia	0	1 (1.7%)	1 (0.9%)
Phlebitis	0	0	0
Pulmonary Embolism	0	1 (1.7%)	1 (0.9%)
Disorders of Cardiac Rhythm and Conduction	0	1 (1.7%)	1 (0.9%)
Pericarditis	5 (8.6%)	2 (3.4%)	7 (6.0%)
Heart Failure	0	2 (3.4%)	2 (1.7%)
Abnormalities in the Cardiac MRI	2 (3.4%)	0	2 (1.7%)
Other	5 (8.6%)	8 (13.6%)	13 (11.1%)
Initial Digestive Signs			
Abdominal Pain	6 (10.3%)	3 (5.1%)	9 (7.7%)
Diarrhea	3 (5.2%)	2 (3.4%)	5 (4.3%)
Other	6 (10.3%)	3 (5.1%)	9 (7.7%)
Initial Renal and Urinary Signs			
Abnormalities in the Urinalysis	37 (63.8%)	36 (61.0%)	73 (62.4%)
Test Strip (CBEU)	20 (34.5%)	18 (30.5%)	38 (32.5%)
Abnormalities in the Urinalysis Test Strip			
Hematuria	35 (60.3%)	32 (54.2%)	67 (57.3%)
Proteinuria (# 1 +)	33 (56.9%)	30 (50.8%)	63 (53.8%)
Leukocyturia	6 (10.3%)	7 (11.9%)	13 (11.1%)
Nitrites	0	0	0
CBEU			
Leukocyturia > 10/mm³	8 (13.8%)	3 (5.1%)	11 (9.4%)
Hematuria > 10/mm³	18 (31.0%)	14 (23.7%)	32 (27.4%)
Infection	1 (1.7%)	0	1 (0.9%)
Normal	1 (1.7%)	3 (5.1%)	4 (3.4%)
Worsening of Renal Function (>30% of Creatinine and/or >25% of Clearance)	21 (36.2%)	31 (52.5%)	52 (44.4%)
Recent Arterial Hypertension	6 (10.3%)	8 (13.6%)	14 (12.0%)
Severe or Malignant Arterial Hypertension	1 (1.7%)	1 (1.7%)	2 (1.7%)
Other	2 (3.4%)	2 (3.4%)	4 (3.4%)

	Rituximab (N = 58)	Azathioprine (N = 59)	All Patients (N = 117)
Initial Neurological Signs			
Recent headaches	7 (12.1%)	1 (1.7%)	8 (6.8%)
Meningitis	0	0	0
Pachymeningitis	0	0	0
Peripheral nerve disease	13 (22.4%)	16 (27.1%)	29 (24.8%)
Sensory	12 (20.7%)	13 (22.0%)	25 (21.4%)
Motor	5 (8.6%)	7 (11.9%)	12 (10.3%)
Mononeuritis	1 (1.7%)	3 (5.1%)	4 (3.4%)
Mononeuritis Multiplex	4 (6.9%)	5 (8.5%)	9 (7.7%)
Polyneuritis	2 (3.4%)	2 (3.4%)	4 (3.4%)
External Popliteal Nerve	10 (17.2%)	9 (15.3%)	19 (16.2%)
Internal Popliteal Nerve	5 (8.6%)	2 (3.4%)	7 (6.0%)
Median	2 (3.4%)	2 (3.4%)	4 (3.4%)
Radial	1 (1.7%)	1 (1.7%)	2 (1.7%)
Ulnar	2 (3.4%)	2 (3.4%)	4 (3.4%)
Other Nerve	2 (3.4%)	0	2 (1.7%)
Cranial Nerve Disease	2 (3.4%)	2 (3.4%)	4 (3.4%)
Ischemic Stroke	3 (5.2%)	0	3 (2.6%)
Brain Hemorrhage	0	0	0
Other	3 (5.2%)	1 (1.7%)	4 (3.4%)

Abbreviations: SD = Standard deviation, Q1, Q3 = 1st and 3rd quartiles, mmHg = Millimeters of mercury, CBEU = Cytobacteriological examination of urine, BVAS = Birmingham vasculitis activity score.
n = number of patients with a non-missing value.
Percentages are based on N.

The treatment arms were comparable with respect to baseline disease characteristics (Table 6).

In the overall study population, the majority had GPA (75%), followed by MPA (21%) and renal limited vasculitis (4%). Compared with the azathioprine arm, more patients in the rituximab arm had GPA (83% rituximab vs 68% azathioprine) and fewer had MPA (14% vs 28%, respectively). The majority (80%) of enrolled patients were in remission after being newly diagnosed (baseline stratification factor).

A majority of patients (63%) were ANCA-positive at inclusion, with a slightly lower incidence (55%) in the rituximab arm compared with the azathioprine arm (71%).

Per protocol, the median BVAS at entry was 0.0 because all patients were expected to be in remission. Although Table 6 implies that one patient in each arm had a BVAS above 0, these were confirmed by the investigator to be data entry errors.

Numbers analysed

All 58 patients in the rituximab arm and 59 patients in the azathioprine arm were included in the ITT population; one patient signed an ICF but was not randomized, did not receive study medication, and was not included in the ITT population. Of these, 57 patients (98.3%) in the rituximab arm and 58 patients (98.3%) in the azathioprine arm received at least one dose of study medication and were included in the safety population. All patients received the assigned treatment.

Outcomes and estimation

Primary endpoint

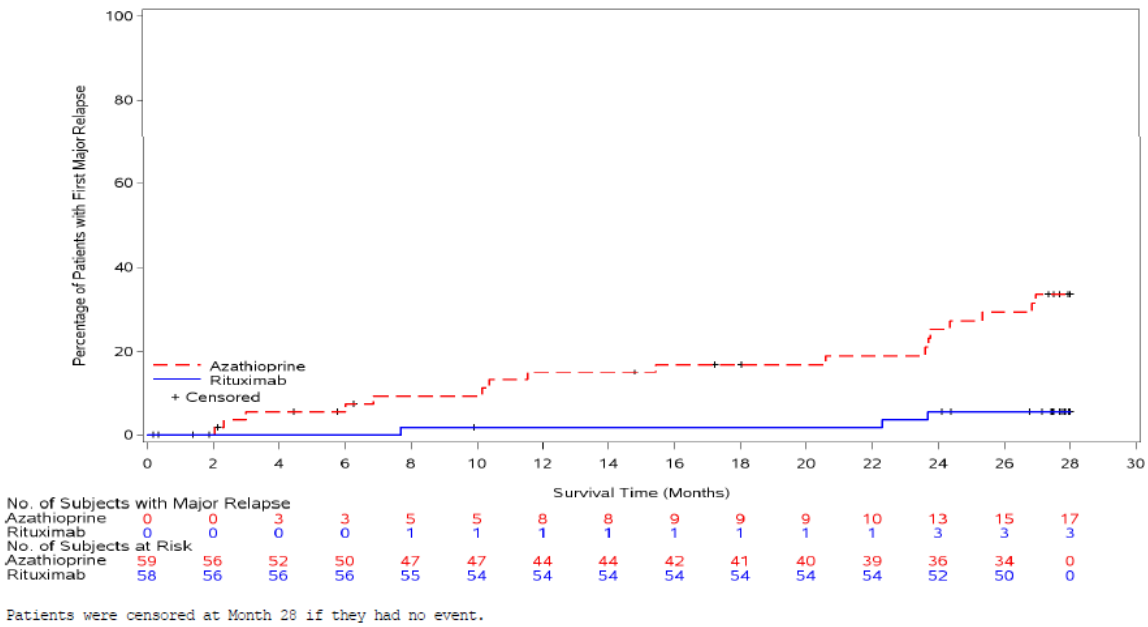
The primary endpoint of Study ML22514 was the percentage of patients with a major relapse by Month 28. Significant fewer patients in the rituximab arm had experienced a major relapse by Month 28 (5.2%), compared with the azathioprine arm (28.8%) (Table 7). The log-rank test showed that rituximab significantly reduced the incidence of major relapse (p=0.002). Adjusting for the stratification factor using Cox PH modelling, rituximab reduced the risk of major relapse by approximately 86% relative to azathioprine (HR: 0.14; 95% CI: 0.04, 0.47, p=0.0015).

Table 7 Time to First Major Relapse (Intent to Treat)

	Rituximab (N = 58)	Azathioprine (N = 59)	p-value
Time to First Major Relapse (Month) [b]			
Number of subjects in analysis	58 (100.0%)	59 (100.0%)	
Number of subjects with major relapse	3 (5.2%)	17 (28.8%)	0.0002 [a]
Q1 (95% CI)	NE (NE , NE)	23.8(10.4, NE)	
Median (95% CI)	NE (NE , NE)	NE (NE , NE)	
Q3 (95% CI)	NE (NE , NE)	NE (NE , NE)	
Min, Max [c]	0*, 28*	0*, 28*	
Percent of Patients with Major Relapse (95% CI) [d]			
By Month 6	0.0%(NE , NE)	5.4%(1.8%, 15.9%)	
By Month 12	1.8%(0.3%, 12.0%)	15.0%(7.8%, 27.9%)	
By Month 18	1.8%(0.3%, 12.0%)	17.0%(9.2%, 30.2%)	
By Month 22	1.8%(0.3%, 12.0%)	19.1%(10.7%, 32.6%)	
By Month 28	5.4%(1.8%, 15.9%)	33.6%(22.4%, 48.5%)	
Hazard Ratio of Rituximab vs. Azathioprine (95% CI) [e]	0.14(0.04 , 0.47)		0.0015

CI = Confidence interval, Q1 = 25% quartile, Q3 = 75% quartile, NE = Not estimable.
Patients were censored at Month 28 if they had no event.
[a] p-value is from a log-rank test from a Kaplan-Meier model comparing treatment groups.
[b] Time calculated from the date of randomization until the date of the first major relapse, up to Month 28.
[c] Minimum or maximum values that are a censored value are marked by a *.
[d] Estimates and 95% confidence intervals from Kaplan-Meier method.
[e] Estimated from Cox model, adjusted for sampling strata (new diagnosis vs. relapser).

The cumulative incidence rate curves showed a separation between arms in favor of rituximab that started from Month 2 and was maintained up to Month 28 (Figure 3). The taper in azathioprine dose, which started at Month 12, was not associated with an increased incidence of major relapse.



Patients were censored at Month 28 if they had no event.

Figure 3 Cumulative Incidence over Time of First Major Relapse (Intent to Treat)

Secondary endpoint: Number of Patients with Detectable ANCAs in Each Group

In the rituximab arm, the percentage of patients with detectable ANCAs decreased from 56.1% at baseline to 22.6% at Month 12 and remained relatively stable through Month 28 (27.3%). In the azathioprine arm, the percentage of patients with detectable ANCAs decreased from 71.2% at baseline to 58.0% at Month 18 and fluctuated between 73.9% and 64.4% through Month 28 (Figure 4).

Within treatment arms, the percentage of patients with detectable ANCAs was similar at baseline and at relapse (for those patients who relapsed). In the rituximab arm, 32 of 57 patients (56.1%) had detectable ANCAs at baseline, compared with 5 of 9 patients (55.6%) at relapse. In the azathioprine

arm, 42 of 59 patients (71.2%) had detectable ANCAs at baseline, compared with 17 of 24 patients (70.8%) at relapse.

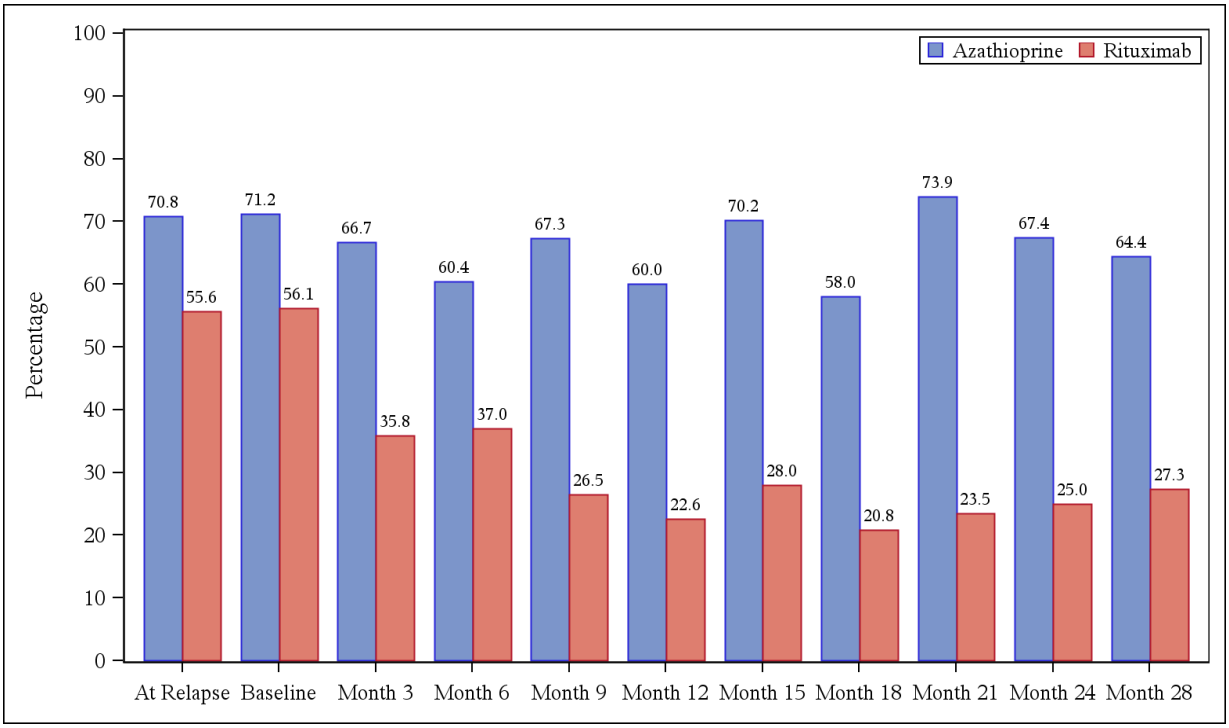


Figure 4 Patients with Detectable ANCAs (Intent to Treat)

Secondary endpoint: Major or Minor Relapses

The incidence of minor relapses (as first relapse) by Month 28 was similar between treatment arms, 12.1% for rituximab vs. 13.6% for azathioprine, p= 0.8095 (chi-squared test). The HR on the incidence of major or minor relapse was 0.31; 95% CI: 0.14, 0.70, p=0.0051.

Secondary endpoint: Cumulative Dose and Duration of the Corticosteroid Treatment

The median cumulative dose of corticosteroid treatment after the end of maintenance therapy was 1457.5 mg in the rituximab arm and 905.0 mg in the azathioprine arm. The variability among patients was high, as seen with the large standard deviations as well as the wide range of values for each treatment arm (range: 124 to 5245 mg in the rituximab arm; 68 to 9693 mg in the azathioprine arm). The median daily dose was the same for each treatment arm (5.0 mg/day).

Table 8 Cumulative Dose and Duration of Corticosteroid Treatment After the End of Maintenance Therapy

	Rituximab (N = 57)	Azathioprine (N = 58)
Total Cumulative Dose (mg)		
n	46	47
Mean	1447.4	1252.1
SD	998.44	1716.32
Median	1457.5	905.0
Q1, Q3	807.0, 1820.0	315.0, 1314.0
Min, Max	124, 5245	68, 9693
Mean Daily Dose (mg/day)		
n	46	47
Mean	5.2	7.4
SD	2.88	8.72
Median	5.0	5.0
Q1, Q3	3.2, 5.6	2.7, 8.2
Min, Max	2, 18	1, 48
Total Duration (Months) [a]		
n	46	47
Mean	8.5	5.0
SD	3.34	1.88
Median	9.9	5.8
Q1, Q3	6.0, 10.4	2.5, 6.2
Min, Max	2, 17	2, 8

Since the time period was approximately 10 months for patients in the rituximab arm, and approximately 6 months for patients in the azathioprine arm, data for the six-month period after the last dose of study treatment (Month 18 to Month 24 for rituximab and Month 22 to Month 28 for azathioprine), were also presented (Table 9). The median total cumulative dose was similar between arms (912.5 mg rituximab; 905.0 mg azathioprine) but mean values was higher in the azathioprine arm compared with the rituximab arm (1252.1 mg vs. 903.2 mg).

Table 9 Cumulative Dose and Duration of Corticosteroid Treatment up to 6 Months After the End of Maintenance Therapy

	Rituximab (N = 57)	Azathioprine (N = 58)
Total Cumulative Dose (mg)		
n	46	47
Mean	903.2	1252.1
SD	452.34	1716.32
Median	912.5	905.0
Q1, Q3	655.0, 1122.5	315.0, 1314.0
Min, Max	124, 1884	68, 9693
Mean Daily Dose (mg/day)		
n	46	47
Mean	5.1	7.4
SD	2.00	8.72
Median	5.0	5.0
Q1, Q3	3.7, 6.0	2.7, 8.2
Min, Max	2, 9	1, 48
Total Duration (Months) [a]		
n	46	47
Mean	5.6	5.0
SD	1.46	1.88
Median	6.0	5.8
Q1, Q3	5.8, 6.2	2.5, 6.2
Min, Max	2, 8	2, 8

The CHMP noted that post-maintenance treatment mean and median total cumulative dose of corticosteroid per patient was higher in the rituximab arm compared with the azathioprine arm (1447.4 mg and 1457.5 vs. 1252.1 and 905.0 mg) at Month 28. This is not surprising, since the data was collected over 10 months and 6 months in the rituximab and azathioprine arms respectively. Comparison data for the six-month period after the last dose of study treatment were also presented by the MAH. The median total cumulative dose was similar between arms (912.5 mg rituximab; 905.0 mg azathioprine), but mean values was higher in the azathioprine arm compared with the rituximab arm (1252.1 mg vs. 903.2 mg). The information provided from this comparison indicate, that the azathioprine treated patients could be more steroid demanding/sicker than the rituximab treated subjects, but the data only covers 6 of the 28 months of potential steroid treatment during the trial.

The mean total cumulative dose of prednisone is 6004.2 mg and 6988.8 mg for rituximab and azathioprine respectively. It appears that the pre-treatment 100 mg IV doses of methylprednisolone in the rituximab arm are not included in the data. The MAH was asked by the CHMP to provide data and discuss the results regarding the total cumulative corticosteroid dose over the full course of the study, including the pre-treatment methylprednisolone doses. According to the MAH, details of pre-medication and dosing were not routinely collected in the eCRF. The MAH explained, that if pre-treatment with methylprednisolone occurred as stated in the protocol, and that all patients in the RTX treatment arm received the full 100 mg IV dose of methylprednisolone prior to each infusion, the mean total cumulative corticosteroid dose would theoretically be 6611.7 mg for the RTX (compared to 6988.8 mg for the AZA arm). The MAH concluded that the pre-treatment 100 mg IV doses of methylprednisolone in the RTX arm do not appear to have had an impact on interpretation of efficacy or safety outcomes between the treatment arms. This conclusion was endorsed by the CHMP and the issue was considered resolved.

Secondary endpoint: Major relapses 6 months after the end of the respective treatment

Because the duration of follow-up "off treatment" was different between groups at month 28 (namely 6 months for the azathioprine arm vs. 10 months for the rituximab arm), an additional analysis was carried out, focusing on the number of major relapses occurring in each group up to 6 months after the end of the respective treatment. The percentage of patients with a major relapse was 5.2% and 28.8% for rituximab (at week 24) and azathioprine arms (at week 28), respectively. The HR for rituximab versus azathioprine from a Cox-PH model was 0.19 (95% CI: 0.05, 0.66), p< 0.0007, and a little higher than the HR calculated in the primary endpoint (0.14 [95% CI: 0.04, 0.47], p< 0.0015). The difference is due to four additional relapses in the azathioprine arm after week 24.

Ancillary analyses

Additional analysis: BVAS analysis

Mean BVAS remained low for patients in both treatment arms (Table 8). For patients in the rituximab arm, mean BVAS was 0.1 at Day 1 and 0.2 at Month 28; mean BVAS ranged from a low of 0.0 (Day 1, Month 21, and Month 24) to a high of 0.3 (Month 9), with the highest individual score of 9 reported at Month 28. For patients in the azathioprine arm, mean BVAS was 0.2 at Day 1 and 0.0 at Month 28; mean BVAS ranged from a low of 0.0 (Months 6, 21, and 28) to a high of 0.7 (Month 18). The highest individual score among patients in the azathioprine arm was 18, which occurred at Month 15.

Table 10 Summary of BVAS by Visit and Treatment (Intent to Treat)

	Rituximab (N = 58)	Azathioprine (N = 59)
BVAS at Day 1		
n	56	58
Mean	0.1	0.2
SD	0.53	0.78
Median	0.0	0.0
Q1, Q3	0.0, 0.0	0.0, 0.0
Min, Max	0, 4	0, 5
BVAS at Day 15		
n	51	0
Mean	0.0	
SD	0.00	
Median	0.0	
Q1, Q3	0.0, 0.0	
Min, Max	0, 0	
BVAS at Month 3		
n	55	50
Mean	0.1	0.3
SD	0.42	0.97
Median	0.0	0.0
Q1, Q3	0.0, 0.0	0.0, 0.0
Min, Max	0, 3	0, 5

BVAS at Month 6		
n	53	47
Mean	0.2	0.0
SD	0.92	0.15
Median	0.0	0.0
Q1, Q3	0.0, 0.0	0.0, 0.0
Min, Max	0, 6	0, 1
BVAS at Month 9		
n	50	54
Mean	0.3	0.1
SD	1.21	0.33
Median	0.0	0.0
Q1, Q3	0.0, 0.0	0.0, 0.0
Min, Max	0, 6	0, 2
BVAS at Month 12		
n	54	50
Mean	0.2	0.1
SD	0.72	0.58
Median	0.0	0.0
Q1, Q3	0.0, 0.0	0.0, 0.0
Min, Max	0, 4	0, 4
BVAS at Month 15		
n	53	52
Mean	0.2	0.5
SD	0.92	2.62
Median	0.0	0.0
Q1, Q3	0.0, 0.0	0.0, 0.0
Min, Max	0, 6	0, 18
BVAS at Month 18		
n	54	51
Mean	0.1	0.7
SD	0.54	2.65
Median	0.0	0.0
Q1, Q3	0.0, 0.0	0.0, 0.0
Min, Max	0, 4	0, 16
BVAS at Month 21		
n	54	50
Mean	0.0	0.0
SD	0.27	0.00
Median	0.0	0.0
Q1, Q3	0.0, 0.0	0.0, 0.0
Min, Max	0, 2	0, 0
BVAS at Month 24		
n	52	47
Mean	0.0	0.2
SD	0.14	0.97
Median	0.0	0.0
Q1, Q3	0.0, 0.0	0.0, 0.0
Min, Max	0, 1	0, 6
BVAS at Month 28		
n	50	47
Mean	0.2	0.0
SD	1.28	0.15
Median	0.0	0.0
Q1, Q3	0.0, 0.0	0.0, 0.0
Min, Max	0, 9	0, 1

BVAS = Birmingham vasculitis activity score, SD = Standard deviation, Q1, Q3 = 1st and 3rd quartiles.

At Day 15, no BVAS data were available for the Azathioprine arm.

Additional endpoint: Immunological analysis

CD19 counts decreased from Day 1 (median 38.5/mm3) to Day 15 (median 0/mm3) and remained low through Month 24. Median values had returned toward baseline by Month 28.

For two of the patients in the rituximab arm who had major relapses by Month 28, CD19 counts were 0/mm3 near the time of the major relapse. A patient, who had a major relapse a few weeks before Month 24, the patient's CD19 count was 29/mm3 at Month 18 and 0/mm3 at Month 28.

Median IgA, IgG, and IgM values were comparable between treatment arms and changes from baseline were small over the course of the study. Where ADA was present prior to an infusion, it did not appear to interfere with rituximab pharmacodynamics (CD19 counts) when this data was available. Peripheral CD19 counts depleted as normal following rituximab infusions.

Subgroup analysis:

Subgroup analyses by patients with or without detectable ANCAs at baseline were performed for the primary endpoint, the secondary endpoints of patients with minor relapse and dose and duration of corticosteroid treatment after the end of maintenance therapy, and for the additional endpoint of BVAS by visit and treatment. The number of patients in each subgroup was too small to draw conclusions.

Analysis of long-term outcomes at 60 months

A plenary session conference abstract on analysis of long term outcomes of the MAINRITSAN (Study ML22514) trial patients was submitted by the MAH.

Methods: Data on survival, relapse, cancers, cardiovascular morbidity and other adverse events were ascertained prospectively and collected from physicians. All patients were analyzed according to randomization group. Quality-adjusted time-without-symptoms-and-toxicity (Q-TWiST) analysis was computed, with the aim of better discerning the therapeutic impact and tradeoffs between treatment toxicity (severe adverse events, SAEs) and disease activity (relapse).

Results: Data from 60 months of follow-up were available for 110 (96%) of the 115 randomized participants. For the RTX- and AZA-treated groups, respectively: 0 and 4 died; 60-month overall survival rates were 100% and 93.0% [95% CI 86.7-99.9%] (P=0.045); all-relapse-free survival rates were 57.9% [95% CI 46.4-72.2%] and 37.2% [95% CI 26.5-52.2%] (P=0.012); and major relapse-free survival rates were 71.9% [95% CI 61.2-84.6%)] and 49.4% [95% CI 38.0-64.3%] (P=0.003). In contrast, no between-group differences were observed for survival without SAEs (P=0.95) and the cumulative GC dose (P=0.11) at 60 months. For RTX-treated patients, PR3-ANCA positivity or ANCA persistence 12 months after starting maintenance therapy were associated with higher major relapse rates. During the 60-month follow-up, RTX- and AZA-arm patients had similar amounts of time spent with SAEs (P=0.21), whereas the former, compared to the latter, spent 9.7 months less with major relapses (P<0.001) and 12.6 months more without relapse or toxicity (P<0.001). The threshold utility analysis at 60 months showed that the Q-TWiST period was significantly longer for RTX- than AZA-arm patients (55.2 vs. 47.95 months, respectively, P<0.001).

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 11 Summary of Efficacy for trial

Title: MAINRITSAN - A study comparing the efficacy of rituximab and azathioprine as maintenance therapy for ANCA-associated vasculitis: a prospective, multi-center, controlled, randomized study		
Study identifier	ML22514	
Design	Phase III, prospective, multi-center, controlled, randomized trial	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Approx.. 4 ¼ years, study initiated October 2008, last patient last visit December 2012. Patients treated for 18 months/22 months, then followed 10 months/6 months
Hypothesis	Superiority	
Treatments groups	Rituximab arm	IV Rituximab 500 mg fixed dose at day 1, day 15, month 6, month 12 and month 18

	Azathioprine arm		Oral tablet azathioprine 2 mg/kg/day for 12 monhs, followd by 1.5 mg/kg/day for 6 months, and finally 1 mg/kg/day for 4 months, treatment discontinued after 22 months
Endpoints and definitions	Primary endpoint	N-MAR	Number of patients with major relapse (reappearance or worsening of disease with Birmingham Vasculitis Activity Score (BVAS) > 0 and involvement of at least one major organ, a life-threatening manifestation, or both)
	Secondary endpoint	N-ANCA	Number of patients with detectable ANCA in each treatment group
	Secondary endpoint	N-MIR	Number of minor relapses in each treatment group
	Secondary endpoint		Cumulative corticosteroid dose and duration of treatment in each group 10 months after completion of maintenance therapy

Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	Rituximab arm	Azathioprine arm	
	Number of subject	58	59	
	N-MAR, patients (%)	3 (5.2)	17 (28.8)	
	N-ANCA, patients (%)	12 (27.3)	29 (64.4)	
	N-MIR, patients (%)	7 (12.1)	8 (13.6)	

Effect estimate per comparison	Primary endpoint, N-MAR	Comparison groups	Rituximab arm vs. azathioprine arm
		HR	0.14
		95% CI	(0.04, 0.47)
		P-value	0.0015
	Secondary endpoint, N-MAR + N-MIR	Comparison groups	Rituximab arm vs. azathioprine arm
		HR	0.31
		95% CI	(0.14, 0.70)
		P-value	0.0051

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

No dose response study was submitted. The rituximab dose was chosen pragmatic based on previous clinical experiences of use of the drug within approved indications (induction therapy for AAV and rheumatoid arthritis). This approach was considered acceptable to the CHMP considering the rarity of the disease.

The MAH has provided one phase III study, ML22514 and a conference abstract describing 60 month follow-up data from the mentioned study to support the proposed new indication. The phase III study is a prospective, multi-centre, comparative, randomized, open-label study including 117 patients study comparing azathioprine versus rituximab in combination with low-dose corticosteroids for the maintenance treatment of GPA/MPA. The study design is considered acceptable. The inclusion/exclusion criteria clearly define a patient diagnosed with GPA, MPA, and limited renal forms (pauci-immune glomerulonephritis) with or without ANCA is based on established criteria, and the proposed new indication clearly reflects these criteria.

Patients in remission were randomized 1:1 to maintenance treatment with rituximab or azathioprine and was stratified by recently diagnosed or recurrent disease. The rituximab arm were treated for 18 months and the azathioprine arm were treated for 22 months. The reason for the chosen differences in duration of treatment is well argued by the MAH and is due to differences in pharmacodynamics between the study drug and comparator. Corticosteroid treatment throughout the study was left to the investigator's discretion, and it is noted, that each study subject in the rituximab arm received 100 mg methylprednisolone before each rituximab infusion.

Induction therapy followed standard of care in France with "older" immunosuppressants such as cyclophosphamide or methotrexate. No patients received monoclonal antibodies as the initial treatment. The number and proportion of subjects in each treatment group that were given MTX as induction treatment was presented to the CHMP, since patients being selected to receive induction with MTX probably has a limited or less severe disease. If there is an imbalance between the groups regarding these patients, it could have affected the study results. The MAH has provided sufficient data on patients receiving MTX as induction therapy. Only one patient in the AZA arm (1.7%) and no patients in the RTX arm received induction therapy with MTX, which in the CHMP's opinion has no impact on the primary analyses.

For azathioprine, the EULAR guideline recommends a dose of 2 mg/kg/day; it is recommended to continue remission-maintenance therapy for at least 24 months following induction of sustained remission and no recommendation to gradually taper the dose is given. In ML22514, azathioprine was started at 2mg/kg/day for 12 months, followed by 1.5 mg/kg/day for 6 months, and finally 1 mg/kg/day for 4 months; treatment was discontinued after 22 months. Although it was noted that the major-relapse rate after azathioprine dose reduction was not higher than before dose reduction, the MAH was asked to discuss if the azathioprine dose could have been suboptimal and how this could affect the interpretation of the efficacy results from the study. The MAH responded, that the dosing schedule for the comparator, AZA, was selected based on previous experiences from clinical study and on the warning in the product label due to the increased risk of malignancy and other side effects of continuous treatment. Further, it was argued, that the occurrence of major relapse was similar before and after AZA tapering until the primary endpoint at Month 28. The issue was considered resolved by the CHMP.

The objectives are clearly described. The primary objective was to evaluate the efficacy of rituximab as maintenance therapy for patients in remission from ANCA-related systemic vasculitis after a first exacerbation or relapse. Clinically meaningful secondary objectives are also defined including comparison of tolerance to treatments.

The primary endpoint is clearly defined, clinically relevant and fully acceptable in this setting. The secondary endpoints are overall acceptable.

With regard to sample size, the power and alpha are as to be expected for a phase III study. With regard to statistics all randomized patients comprise the Intent-To-Treat (ITT) population, and all

statistical testing is two-sided with 5% Type I error with 95% CI. The statistical methods proposed was endorsed by the CHMP.

The CHMP noted that the baseline disease characteristics were not well balanced with respect to gender disease type, where more patients in the rituximab arm had GPA compared with the azathioprine arm and fewer had MPA. Further, more patients were ANCA positive in the azathioprine arm compared with the rituximab am.

The MAH was asked to discuss if these differences were of importance with respect to the duration and prognosis of the GPA/MPA disease. The MAH provided elaborated and satisfactory discussions on the mentioned differences. With respect to GPA and MPA, it was argued, that due to the overlapping features (and symptoms), there is little clinical distinction between the two vasculitides and they are considered to form part of the same disease spectrum. Subgroup analysis of patients with GPA showed fewer relapses by month 28 in favour of rituximab. Further, analysis of the baseline differences in gender between the two study arms did not appear to have influenced response to rituximab or prognosis of the disease. The issue was considered resolved by the CHMP. With regards to ANCA status at baseline, the majority of patients (63%) were ANCA positive at study entry (55% and 71% in the RTX and AZA arm, respectively). Subgroup analyses based on ANCA status were previously performed for the primary analysis of number of patients with a major relapse by Month 28, and no obvious relationship was demonstrated in either treatment arm, between the ANCA status at baseline or at the time of relapse and the occurrence of relapse. The MAH concluded that the baseline ANCA appeared to have no impact on the effect of rituximab in preventing relapse. This was endorsed by the CHMP.

Efficacy data and additional analyses

The study met its primary endpoint, showing both a statistically significant and clinically relevant difference in terms of risk of major relapse in advantage of rituximab at Month 28. Adjusting for the stratification factor using Cox PH modelling, rituximab reduced the risk of major relapse by approximately 86% relative to azathioprine (HR: 0.14; 95% CI: 0.04, 0.47, p=0.0015). Risk estimate of major relapses 6 months after the end of treatment in both arms were presented as a secondary endpoint (HR for rituximab versus azathioprine arms 0.19, 95% CI: 0.05, 0.66, p< 0.0007, and was due to four fewer events in the azathioprine arm).

With regard to the secondary endpoint on the percentage of patients with detectable ANCAs, the baseline difference between the two groups clearly appears. In the rituximab arm, a tendency of decreasing detectable ANCAs is seen from baseline to Month 12. Then a stable period from Month 12 to 18 is seen, followed by a slow increase up to Month 28. In the azathioprine arm, a more fluctuating course is observed.

The secondary endpoint on incidence of minor relapse by Month 28, a small numeric, but statistically non-significant, difference between the two treatment arms was observed.

As expected, a near-complete depletion of peripheral CD19 was observed following rituximab treatment. Two patients had major relapses despite complete CD19 depression near the time of relapse. Relapse of disease appears not to be related to presence of CD19+ B-cells, but data are too sparse for further and more safe conclusions.

The secondary endpoint on cumulative corticosteroid dose and duration of treatment at Month 10 after end of maintenance treatment appears to be of limited value due to the differences in follow-up time, and since only post-treatment data was presented (10 months in the rituximab arm vs. 6 months in the azathioprine arm). The MAH subsequently provided data for the total cumulative corticosteroid dose which overall showed a lower value for the rituximab arm compared with the azathioprine arm.

Of additional analysis, no difference was observed between the two arms with respect to mean BVAS. Subgroup analyses were performed, but the number of patients in each subgroup was too small to draw conclusions. However, the MAH satisfactory complemented the subgroup analysis with additional data and discussion.

Patients enrolled in the study ML22514 had achieved disease control after induction of remission with cyclophosphamide only. Indeed, the indication in the induction of remission therapy of granulomatosis with polyangiitis and microscopic polyangiitis was not approved for Mabthera at the time when the study was conducted. However, the MAH proposed to extend the indication in maintenance treatment to patients who received Mabthera for the induction of remission. The rituximab dosing regimen in patients who received Mabthera for the induction of remission was chosen pragmatically based on previous clinical experiences of use of the drug within approved indications. This approach was considered acceptable to the CHMP considering the rarity of the disease.

As recommended in the pre-submission meeting, data on the analysis of long-term outcomes at 60 months were submitted in form of a plenary session conference abstract. The major relapse-free survival rates at 60 months after initiation of maintenance treatment were 71.9% (95% CI 61.2-84.6%) and 49.4% (95% CI 38.0-64.3%), P=0.003 for the rituximab arm and azathioprine arm respectively. The conclusion was that the long-term analysis showed that, despite late relapses after the 28-month initial follow-up period, maintenance therapy with rituximab remained significantly superior to azathioprine to maintain remission at 60 months and was associated with better survival.

2.4.4. Conclusions on the clinical efficacy

Study ML22514 comparing rituximab to azathioprine is overall a well-designed and well-conducted phase III study demonstrating the effect of reducing relapse of AAV disease, showing both a statistically significant and clinically relevant difference in terms of time to first major relapse in advantage of rituximab. The results from secondary endpoints and additional endpoints seem consistent with the primary endpoint.

The CHMP considered that the clinical efficacy satisfactorily supports the new indication.

2.5. Clinical safety

Introduction

The safety evidence for the use of rituximab as maintenance therapy in patients with GPA/MPA after achieving remission, was primarily obtained from the phase III trial (Study ML22514) with 115 patients (57 of them exposed to rituximab). Data obtained from these patients was recorded regularly on e-CRFs at least every 3 months, until the Month 28 visit. The investigators continuously kept the study coordinators informed of the health status and progress of the patients. For subjects who were lost to follow-up, the e-CRF was to be completed until the last visit performed.

Additional supportive safety evidence were included from an interim report available for a phase IV, open-label, observational study (Study WA27893, RaVeR), which is still ongoing, as well as from literature and post marketing safety data from the Applicant's safety database.

Patient exposure

Rituximab and azathioprine exposure:

In the safety population there were 115 patients who received at least one dose of any study drug; 57 patients received rituximab and 58 patients received azathioprine.

The median cumulative dose of rituximab was 2500 mg (range: 500 mg to 2500 mg), suggesting that most patients received the full set of five 500-mg doses over the course of the study (Table 12).

The median cumulative dose of azathioprine was 71,625 mg (range: 6,000 to 122,350 mg). Because dosing was done on a mg/kg basis that decreased stepwise (2 mg/kg/day for Months 1 to 12, 1.5 mg/kg/day for Months 12 to 18, and 1.0 mg/kg/day for Months 18 to 22), daily doses of azathioprine varied among patients and over the course of the study.

Table 12 Summary of Extent of Exposure to Rituximab and Azathioprine During Maintenance Period by Trial Treatment (Safety)

	Rituximab (N = 57)	Azathioprine (N = 58)
Total Cumulative Dose (mg) [a]		
n	57	58
Mean	2429.8	65949.1
SD	319.58	27582.42
Median	2500.0	71625.0
Q1, Q3	2500.0, 2500.0	56725.0, 83450.0
Min, Max	500, 2500	6000, 122350

Abbreviations: mg = Milligrams, SD = Standard deviation, Q1, Q3 = 1st and 3rd quartiles.
[a] Rituximab: Up to month 18. Azathioprine: Up to month 22.
Relapse from Months 2 to 12 was treated with rituximab for 4 patients in the Azathioprine arm. Dosage was recorded for only one of those (700mg).

Corticosteroid exposure:

Corticosteroid dosing was left to the investigator's discretion during the study; however, the protocol recommended that doses be tapered and maintained at a low dose through Month 18. The median cumulative doses of corticosteroid over time were similar between treatment arms (see table below).

Table 13 Summary of Extent of Exposure to Corticosteroid by Trial Treatment (Safety)

_	Rituximab (N = 57)	Azathioprine (N = 58)
Total Cumulative Dose (mg) [a]		
n	57	58
Mean	6004.2	6988.8
SD	2099.34	3443.10
Median	6007.0	5973.0
Q1, Q3	4450.0, 7506.0	4562.5, 8244.8
Min, Max	1189, 11290	2470, 17197

Abbreviations: mg = Milligrams, SD = Standard deviation, Q1, Q3 = 1st and 3rd quartiles.
Not included are 100 mg doses of IV methylprednisolone taken with each infusion of rituximab.
[a] Up to month 28.

Adverse events

Table 14 Overview of Adverse Events from Study ML22514 (Safety)

	Rituximab N=57	**Azathioprine N=58**
Mean Duration in Study (Months)	28.2	27.5
Any Adverse Event		
Total No. of patients with one or more events	51 (89.5%)	53 (91.4%)
Total No. of events	252	290
Any Related Adverse Event		
Total No. of patients with one or more events	29 (50.9%)	34 (58.6%)
Total No. of events	85	87
Any Serious Adverse Event		
Total No. of patients with one or more events	26 (45.6%)	32 (55.2%)
Total No. of events	64	62
Any Related Serious Adverse Event		
Total No. of patients with one or more events	5 (8.8%)	5 (8.6%)
Total No. of events	13	7
Any Adverse Event Leading to Discontinuation from Study Treatment		
Total No. of patients with one or more events	2 (3.5%)	9 (15.5%)
Total No. of events	2	11
Total No. of All Cause Deaths	0 (0%)	3 (5.2%)

Duration in study is from the first study drug dose date to the study day of the last safety assessment or safety assessment visit or before Month 28, divided by 30.43.

Included are 7 adverse events beyond Month 28, at study days 855, 857, 858, 876, 949, 960 and 1056.

Percentages are based on N.

Common AEs

Table 15 AEs Occuring in at Least 5% of Patients by System Organ Class and Preferred Term (Safety)

System Organ Class/ Patients Preferred Term	Rituximab N=57)	Azathioprine (N=58)	All (N=115)
Any System Organ Classes			
Total No. of patients with one or more events	51 (89.5%)	53 (91.4%)	104 (90.4%)
Total No. of events	252	290	542
Infections and infestations			
Total No. of patients with one or more events	30 (52.6%)	33 (56.9%)	63 (54.8%)
Bronchitis	8 (14.0%)	6 (10.3%)	14 (12.2%)
Nasopharyngitis	6 (10.5%)	7 (12.1%)	13 (11.3%)
Gastroenteritis	4 (7.0%)	4 (6.9%)	8 (7.0%)
Urinary tract infection	2 (3.5%)	6 (10.3%)	8 (7.0%)
Herpes zoster	2 (3.5%)	3 (5.2%)	5 (4.3%)
Rhinitis	3 (5.3%)	2 (3.4%)	5 (4.3%)
Lung infection	0 (0.0%)	3 (5.2%)	3 (2.6%)
Total No. of events	71	72	143
General disorders and administration site conditions			
Total No. of patients with one or more events	17 (29.8%)	17 (29.3%)	34 (29.6%)
Asthenia	3 (5.3%)	6 (10.3%)	9 (7.8%)
Pyrexia	5 (8.8%)	4 (6.9%)	9 (7.8%)
Fatigue	2 (3.5%)	4 (6.9%)	6 (5.2%)
Influenza like illness	3 (5.3%)	1 (1.7%)	4 (3.5%)
Oedema peripheral	3 (5.3%)	1 (1.7%)	4 (3.5%)
Total No. of events	24	23	47
Gastrointestinal disorders			
Total No. of patients with one or more events	12 (21.1%)	20 (34.5%)	32 (27.8%)
Diarrhoea	4 (7.0%)	2 (3.4%)	6 (5.2%)
Vomiting	1 (1.8%)	5 (8.6%)	6 (5.2%)
Nausea	1 (1.8%)	4 (6.9%)	5 (4.3%)
Abdominal pain upper	1 (1.8%)	3 (5.2%)	4 (3.5%)
Gastrointestinal disorder	0 (0.0%)	3 (5.2%)	3 (2.6%)
Total No. of events	13	29	42
Musculoskeletal and connective tissue disorders			
Total No. of patients with one or more events	15 (26.3%)	16 (27.6%)	31 (27.0%)
Arthralgia	2 (3.5%)	4 (6.9%)	6 (5.2%)
Myalgia	1 (1.8%)	4 (6.9%)	5 (4.3%)
Total No. of events	24	22	46

Respiratory, thoracic and mediastinal disorders			
Total No. of patients with one or more events	13 (22.8%)	11 (19.0%)	24 (20.9%)
Dyspnoea	5 (8.8%)	2 (3.4%)	7 (6.1%)
Cough	1 (1.8%)	3 (5.2%)	4 (3.5%)
Total No. of events	18	14	32
Skin and subcutaneous tissue disorders			
Total No. of patients with one or more events	12 (21.1%)	10 (17.2%)	22 (19.1%)
Alopecia	2 (3.5%)	3 (5.2%)	5 (4.3%)
Total No. of events	12	14	26
Nervous system disorders			
Total No. of patients with one or more events	10 (17.5%)	9 (15.5%)	19 (16.5%)
Headache	3 (5.3%)	3 (5.2%)	6 (5.2%)
Paraesthesia	0 (0.0%)	3 (5.2%)	3 (2.6%)
Total No. of events	13	16	29
Injury, poisoning and procedural complications			
Total No. of patients with one or more events	10 (17.5%)	6 (10.3%)	16 (13.9%)
Infusion related reaction*	7 (12.3%)	0 (0.0%)	7 (6.1%)
Total No. of events	15	6	21
Metabolism and nutrition disorders			
Total No. of patients with one or more events	8 (14.0%)	7 (12.1%)	15 (13.0%)
Diabetes mellitus	6 (10.5%)	3 (5.2%)	9 (7.8%)
Diabetes mellitus inadequate control	1 (1.8%)	0 (0.0%)	1 (0.9%)
Total No. of events	14	8	22
Eye disorders			
Total No. of patients with one or more events	7 (12.3%)	6 (10.3%)	13 (11.3%)
Cataract	3 (5.3%)	5 (8.6%)	8 (7.0%)
Total No. of events	11	9	20
Blood and lymphatic system disorders			
Total No. of patients with one or more events	2 (3.5%)	7 (12.1%)	9 (7.8%)
Neutropenia	0 (0.0%)	3 (5.2%)	3 (2.6%)
Total No. of events	2	15	17
Ear and labyrinth disorders			
Total No. of patients with one or more events	2 (3.5%)	6 (10.3%)	8 (7.0%)
Vertigo	1 (1.8%)	5 (8.6%)	6 (5.2%)
Total No. of events	2	6	8
Hepatobiliary disorders			
Total No. of patients with one or more events	0 (0.0%)	7 (12.1%)	7 (6.1%)
Cholestasis	0 (0.0%)	3 (5.2%)	3 (2.6%)
Total No. of events	0	12	12

Investigator text for adverse events is encoded using MedDRA version 20.0.
Included are 7 AEs beyond Month 28, at study days 855, 857, 858, 876, 949, 960 and 1056.
Each patient is counted only once for each SOC, and each patient is counted only once for each preferred term.
'Uncoded' means 'Uncodable'.
*AEs reported as infusion related reactions on exposure CRF were compared against the Roche AEGT basket, and only those matching Roche's
AEGT basket and occurring on the visit day or the next day were retained and summarized.
Percentages are based on N.

Treatment-Related AEs

Table 16 Summary of Treatment Related Adverse Events With an Incidence Rate of at Least 5% by System Organ Class, Preferred Term, and Trial Treatment (Safety)

System Organ Class/ Patients Preferred Term	Rituximab (N=57)	Azathioprine (N=58)	All (N=115)
Any System Organ Classes			
Total No. of patients with one or more events	29 (50.9%)	34 (58.6%)	63 (54.8%)
Total No. of events	85	87	172
Infections and infestations			
Total No. of patients with one or more events	15 (26.3%)	22 (37.9%)	37 (32.2%)
Bronchitis	5 (8.8%)	2 (3.4%)	7 (6.1%)
Nasopharyngitis	1 (1.8%)	4 (6.9%)	5 (4.3%)
Urinary tract infection	2 (3.5%)	3 (5.2%)	5 (4.3%)
Total No. of events	33	33	66
Gastrointestinal disorders			

Total No. of patients with one or more events	5 (8.8%)	10 (17.2%)	15 (13.0%)
Nausea	1 (1.8%)	4 (6.9%)	5 (4.3%)
Diarrhoea	3 (5.3%)	0 (0.0%)	3 (2.6%)
Total No. of events	5	10	15
General disorders and administration site conditions			
Total No. of patients with one or more events	5 (8.8%)	4 (6.9%)	9 (7.8%)
Pyrexia	3 (5.3%)	1 (1.7%)	4 (3.5%)
Total No. of events	7	4	11
Skin and subcutaneous tissue disorders			
Total No. of patients with one or more events	3 (5.3%)	5 (8.6%)	8 (7.0%)
Alopecia	2 (3.5%)	3 (5.2%)	5 (4.3%)
Total No. of events	3	6	9
Metabolism and nutrition disorders			
Total No. of patients with one or more events	3 (5.3%)	2 (3.4%)	5 (4.3%)
Diabetes mellitus	3 (5.3%)	2 (3.4%)	5 (4.3%)
Total No. of events	4	3	7
Injury, poisoning and procedural complications			
Total No. of patients with one or more events	8 (14.0%)	0 (0.0%)	8 (7.0%)
Infusion related reaction*	7 (12.3%)	0 (0.0%)	7 (6.1%)
Total No. of events	12	0	12

Investigator text for adverse events is encoded using MedDRA version 20.0.
Each patient is counted only once for each SOC, and each patient is counted only once for each preferred term.
*AEs reported as infusion reactions on exposure CRF were compared against the Roche AEGT basket, and only those matching Roche's AEGT basket and occurring on the visit day or the next day were retained and summarized.
Percentages are based on N.

AEs by intensity

AEs by intensity from the ML22514 study was presented detailed in tabular. In summary, in both arms, the majority of patients experienced adverse events that were mild (35% rituximab vs. 16% azathioprine) or moderate (40% vs. 47%) in intensity. However, more patients on azathioprine (29%) compared with rituximab (14%) experienced severe events. In the rituximab arm, severe events were most frequently reported in the SOC of Infections and infestations (5% rituximab vs. 3% azathioprine) whereas General disorders and administration site conditions were more common in the azathioprine arm (2% vs. 7%, respectively). Infections were predominantly mild or moderate in intensity.

Serious adverse event/deaths/other significant events

Deaths

Three patients (2.6%), all in the azathioprine arm, died during the study (1 event occurred after Month 28) (Table 17). The narratives for these patients were provided in details. In summary:

- 1 patient enrolled in the study with a new diagnosis of MPA and was randomized to receive azathioprine. The patient had a major relapse at study day 305 and withdrew from the study five days later. The patient had a fatal event of ischemic colitis on Study Day 855. Relatedness of this event to study drug was not provided.
- 1 patient enrolled in the study with a new diagnosis of GPA and was randomized to receive azathioprine. The patient had minor relapses on study days 512 and 588. The patient withdrew from the study during month 18 due to the adverse event of metastatic pancreatic carcinoma. The patient died at home (no cause of death provided) on study day 726. Relatedness of this event to study drug was not provided.

- 1 patient enrolled in the study with a new diagnosis of GPA and was randomized to receive azathioprine. The patient had a major relapse during study day 203 and withdrew from the study the same day. The patient died from septic shock on study day 218. Relatedness of this event to study drug was not provided.

Table 17 Summary of Deaths by System Organ Class and Preferred Term (Safety)

System Organ Class/ Patients Preferred Term (N=115)	Rituximab (N=57)	Azathioprine (N=58)	All
Any System Organ Classes			
Total No. of patients with one or more events	0 (0.0%)	3 (5.2%)	3 (2.6%)
Total No. of events	0	3	3
Gastrointestinal disorders			
Total No. of patients with one or more events	0 (0.0%)	1 (1.7%)	1 (0.9%)
Colitis ischaemic	0 (0.0%)	1 (1.7%)	1 (0.9%)
Total No. of events	0	1	1
General disorders and administration site conditions			
Total No. of patients with one or more events	0 (0.0%)	1 (1.7%)	1 (0.9%)
Death	0 (0.0%)	1 (1.7%)	1 (0.9%)
Total No. of events	0	1	1
Infections and infestations			
Total No. of patients with one or more events	0 (0.0%)	1 (1.7%)	1 (0.9%)
Septic shock	0 (0.0%)	1 (1.7%)	1 (0.9%)
Total No. of events	0	1	1

Investigator text for adverse events is encoded using MedDRA version 20.0.
Adverse events with death as outcome are described.
Included is 1 Death beyond Month 28, at study day 855.
Percentages are based on N.

Other SAEs

Table 18 Summary of Serious Adverse Events by System Organ Class and Preferred Term (Safety)

System Organ Class/ Patients Preferred Term	Rituximab (N=57)	Azathioprine (N=58)	All (N=115)
Any System Organ Classes			
Total No. of patients with one or more events	26 (45.6%)	32 (55.2%)	58 (50.4%)
Total No. of events	64	62	126
Infections and infestations			
Total No. of patients with one or more events	7 (12.3%)	7 (12.1%)	14 (12.2%)
Bronchitis	3 (5.3%)	0 (0.0%)	3 (2.6%)
Atypical mycobacterial pneumonia	0 (0.0%)	1 (1.7%)	1 (0.9%)
Bacteraemia	1 (1.8%)	0 (0.0%)	1 (0.9%)
Campylobacter gastroenteritis	0 (0.0%)	1 (1.7%)	1 (0.9%)
Gastroenteritis	0 (0.0%)	1 (1.7%)	1 (0.9%)
Genitourinary tract infection	0 (0.0%)	1 (1.7%)	1 (0.9%)
Herpes zoster	0 (0.0%)	1 (1.7%)	1 (0.9%)
Lung infection	0 (0.0%)	1 (1.7%)	1 (0.9%)
Oesophageal candidiasis	1 (1.8%)	0 (0.0%)	1 (0.9%)
Pneumocystis jirovecii pneumonia	1 (1.8%)	0 (0.0%)	1 (0.9%)

Pneumonia	1 (1.8%)	0 (0.0%)	1 (0.9%)
Pulmonary tuberculosis	1 (1.8%)	0 (0.0%)	1 (0.9%)
Respiratory tract infection	1 (1.8%)	0 (0.0%)	1 (0.9%)
Septic shock	0 (0.0%)	1 (1.7%)	1 (0.9%)
Urosepsis	0 (0.0%)	1 (1.7%)	1 (0.9%)
Total No. of events	14	8	22
General disorders and administration site conditions			
Total No. of patients with one or more events	7 (12.3%)	6 (10.3%)	13 (11.3%)
Pyrexia	5 (8.8%)	1 (1.7%)	6 (5.2%)
Asthenia	1 (1.8%)	1 (1.7%)	2 (1.7%)
Chest pain	1 (1.8%)	1 (1.7%)	2 (1.7%)
Adverse drug reaction	0 (0.0%)	1 (1.7%)	1 (0.9%)
Death	0 (0.0%)	1 (1.7%)	1 (0.9%)
Inflammation	1 (1.8%)	0 (0.0%)	1 (0.9%)
Systemic inflammatory response syndrome	0 (0.0%)	1 (1.7%)	1 (0.9%)
Total No. of events	8	6	14
Respiratory, thoracic and mediastinal disorders			
Total No. of patients with one or more events	5 (8.8%)	4 (6.9%)	9 (7.8%)
Dyspnoea	2 (3.5%)	0 (0.0%)	2 (1.7%)
Pulmonary embolism	1 (1.8%)	1 (1.7%)	2 (1.7%)
Acute respiratory distress syndrome	1 (1.8%)	0 (0.0%)	1 (0.9%)
Cough	0 (0.0%)	1 (1.7%)	1 (0.9%)
Laryngeal stenosis	0 (0.0%)	1 (1.7%)	1 (0.9%)
Lung disorder	0 (0.0%)	1 (1.7%)	1 (0.9%)
Sleep apnoea syndrome	1 (1.8%)	0 (0.0%)	1 (0.9%)
Total No. of events	6	5	11
Eye disorders			
Total No. of patients with one or more events	3 (5.3%)	4 (6.9%)	7 (6.1%)
Cataract	3 (5.3%)	4 (6.9%)	7 (6.1%)
Total No. of events	5	5	10
Vascular disorders			
Total No. of patients with one or more events	2 (3.5%)	5 (8.6%)	7 (6.1%)
Phlebitis	2 (3.5%)	2 (3.4%)	4 (3.5%)
Granulomatosis with polyangiitis	0 (0.0%)	2 (3.4%)	2 (1.7%)
Aortic dissection	0 (0.0%)	1 (1.7%)	1 (0.9%)
Haematoma	1 (1.8%)	0 (0.0%)	1 (0.9%)
Total No. of events	4	5	9
Gastrointestinal disorders			
Total No. of patients with one or more events	4 (7.0%)	2 (3.4%)	6 (5.2%)
Diarrhoea	2 (3.5%)	0 (0.0%)	2 (1.7%)
Inguinal hernia	2 (3.5%)	0 (0.0%)	2 (1.7%)
Colitis ischaemic	0 (0.0%)	1 (1.7%)	1 (0.9%)
Large intestine polyp	0 (0.0%)	1 (1.7%)	1 (0.9%)
Lower gastrointestinal haemorrhage	0 (0.0%)	1 (1.7%)	1 (0.9%)
Total No. of events	4	3	7
Musculoskeletal and connective tissue disorders			
Total No. of patients with one or more events	2 (3.5%)	3 (5.2%)	5 (4.3%)
Osteonecrosis	1 (1.8%)	2 (3.4%)	3 (2.6%)
Intervertebral disc protrusion	0 (0.0%)	1 (1.7%)	1 (0.9%)

Osteoarthritis	1 (1.8%)	0 (0.0%)	1 (0.9%)
Total No. of events	4	3	7
Nervous system disorders			
Total No. of patients with one or more events	2 (3.5%)	2 (3.4%)	4 (3.5%)
Facial paralysis	1 (1.8%)	0 (0.0%)	1 (0.9%)
Monoparesis	1 (1.8%)	0 (0.0%)	1 (0.9%)
Neuromyopathy	0 (0.0%)	1 (1.7%)	1 (0.9%)
Syncope	0 (0.0%)	1 (1.7%)	1 (0.9%)
Trigeminal neuralgia	1 (1.8%)	0 (0.0%)	1 (0.9%)
Total No. of events	3	3	6
Blood and lymphatic system disorders			
Total No. of patients with one or more events	0 (0.0%)	4 (6.9%)	4 (3.5%)
Anaemia	0 (0.0%)	2 (3.4%)	2 (1.7%)
Haemorrhagic anaemia	0 (0.0%)	1 (1.7%)	1 (0.9%)
Neutropenia	0 (0.0%)	1 (1.7%)	1 (0.9%)
Total No. of events	0	5	5
Renal and urinary disorders			
Total No. of patients with one or more events	2 (3.5%)	2 (3.4%)	4 (3.5%)
Acute kidney injury	0 (0.0%)	1 (1.7%)	1 (0.9%)
Proteinuria	1 (1.8%)	0 (0.0%)	1 (0.9%)
Renal colic	1 (1.8%)	0 (0.0%)	1 (0.9%)
Renal failure	0 (0.0%)	1 (1.7%)	1 (0.9%)
Total No. of events	2	3	5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Total No. of patients with one or more events	1 (1.8%)	3 (5.2%)	4 (3.5%)
Basal cell carcinoma	0 (0.0%)	2 (3.4%)	2 (1.7%)
Pancreatic carcinoma metastatic	0 (0.0%)	1 (1.7%)	1 (0.9%)
Prostate cancer recurrent	1 (1.8%)	0 (0.0%)	1 (0.9%)
Total No. of events	1	3	4
Hepatobiliary disorders			
Total No. of patients with one or more events	0 (0.0%)	3 (5.2%)	3 (2.6%)
Cholangitis	0 (0.0%)	1 (1.7%)	1 (0.9%)
Cholelithiasis	0 (0.0%)	1 (1.7%)	1 (0.9%)
Cholestasis	0 (0.0%)	1 (1.7%)	1 (0.9%)
Drug-induced liver injury	0 (0.0%)	1 (1.7%)	1 (0.9%)
Hepatitis	0 (0.0%)	1 (1.7%)	1 (0.9%)
Hepatocellular injury	0 (0.0%)	1 (1.7%)	1 (0.9%)
Jaundice	0 (0.0%)	1 (1.7%)	1 (0.9%)
Total No. of events	0	7	7
Investigations			
Total No. of patients with one or more events	0 (0.0%)	3 (5.2%)	3 (2.6%)
Colonoscopy	0 (0.0%)	1 (1.7%)	1 (0.9%)
Endoscopy gastrointestinal	0 (0.0%)	1 (1.7%)	1 (0.9%)
Laboratory test abnormal	0 (0.0%)	1 (1.7%)	1 (0.9%)
Total No. of events	0	3	3
Pregnancy, puerperium and perinatal conditions			
Total No. of patients with one or more events	3 (5.3%)	0 (0.0%)	3 (2.6%)
Abortion spontaneous	1 (1.8%)	0 (0.0%)	1 (0.9%)
Foetal death	1 (1.8%)	0 (0.0%)	1 (0.9%)
Pregnancy	1 (1.8%)	0 (0.0%)	1 (0.9%)

Total No. of events	3	0	3
Cardiac disorders			
Total No. of patients with one or more events	1 (1.8%)	0 (0.0%)	1 (0.9%)
Acute coronary syndrome	1 (1.8%)	0 (0.0%)	1 (0.9%)
Total No. of events	1	0	1
Metabolism and nutrition disorders			
Total No. of patients with one or more events	1 (1.8%)	0 (0.0%)	1 (0.9%)
Diabetes mellitus inadequate control	1 (1.8%)	0 (0.0%)	1 (0.9%)
Total No. of events	1	0	1
Psychiatric disorders			
Total No. of patients with one or more events	1 (1.8%)	0 (0.0%)	1 (0.9%)
Confusional state	1 (1.8%)	0 (0.0%)	1 (0.9%)
Total No. of events	1	0	1
Reproductive system and breast disorders			
Total No. of patients with one or more events	0 (0.0%)	1 (1.7%)	1 (0.9%)
Prostatitis	0 (0.0%)	1 (1.7%)	1 (0.9%)
Total No. of events	0	1	1
Surgical and medical procedures			
Total No. of patients with one or more events	0 (0.0%)	1 (1.7%)	1 (0.9%)
Renal transplant	0 (0.0%)	1 (1.7%)	1 (0.9%)
Total No. of events	0	1	1
Uncoded			
Total No. of patients with one or more events	1 (1.8%)	0 (0.0%)	1 (0.9%)
Uncoded	1 (1.8%)	0 (0.0%)	1 (0.9%)
Total No. of events	1	0	1
Injury, poisoning and procedural complications			
Total No. of patients with one or more events	2 (3.5%)	1 (1.7%)	3 (2.6%)
Ankle fracture	1 (1.8%)	0 (0.0%)	1 (0.9%)
Hand fracture	1 (1.8%)	0 (0.0%)	1 (0.9%)
Infusion related reaction*	1 (1.8%)	0 (0.0%)	1 (0.9%)
Injury	0 (0.0%)	1 (1.7%)	1 (0.9%)
Total No. of events	6	1	7

Investigator text for serious adverse events is encoded using MedDRA version 20.0.
Included are 2 SAEs beyond Month 28, at study days 855 and 857.
Each patient is counted only once for each SOC, and each patient is counted only once for each preferred term.
'Uncoded' means 'Uncodable'.
*AEs reported as infusion related reactions on exposure CRF were compared against the Roche AEGT basket, and only those matching Roche's
AEGT basket and occurring on the visit day or the next day were retained and summarized.
'Uncoded' means 'Uncodable'. Percentages are based on N.

Other significant AEs

Infections

The overall incidence of infections was lower in the rituximab arm compared to the azathioprine arm (53% vs 57%); infections were predominantly mild to moderate in intensity. In the rituximab arm, the most commonly reported events were upper respiratory tract infections, gastroenteritis, urinary tract infection and herpes zoster.

The incidence of serious infections was similar between the two treatment arms (approx. 12%); the most commonly reported serious infection in the rituximab arm was bronchitis. One patient in the azathioprine arm died due to an infection (septic shock) A total of three opportunistic infections were reported in Study ML22514 (all serious); two patients in rituximab arm experienced one event each of severe oesophageal candidiasis and moderate pneumocystis jirovecii pneumonia; and one patient in

azathioprine arm experienced moderate atypical mycobacterial pneumonia. One patient in the rituximab arm experienced tuberculosis.

Infusion related reactions (IRR)

Table 19 Summary of Infusion-Related Reactions by Visit (Safety)

	Rituximab (N=57)				
Preferred Term/ Investigator Text	Day 1 Infusion	Day 15 Infusion	Month 6 Infusion	Month 12 Infusion	Month 18 Infusion
Number of patients who had an infusion (n)	57	56	56	54	54
Infusion related reaction*					
Total No. of patients with events	5 (8.8%)	1 (1.8%)	2 (3.6%)	1 (1.9%)	0
bronchospasm	1 (1.8%)	0	0	0	0
cough	1 (1.8%)	0	0	0	0
exanthema	0	0	0	1 (1.9%)	0
metallic taste, tingling at the back of the throat	0	1 (1.8%)	0	0	0
pruritus	1 (1.8%)	0	0	0	0
skin rash	1 (1.8%)	0	0	0	0
tightness in the throat	0	0	1 (1.8%)	0	0
tingling at the back of the throat during the infusion, high blood pressure	0	0	1 (1.8%)	0	0
transient rash at first infusion	1 (1.8%)	0	0	0	0
Total No. of events	5	2	3	1	0

Abbreviations: AEGT = Adverse event grouped terms, CRF = Case report form.
*AEs reported as infusion reactions on exposure CRF were compared against the Roche AEGT basket, and only those matching Roche's AEGT basket and occurring on the visit day or the next day were retained and summarized.
Investigator text for serious adverse events is encoded using MedDRA version 20.0.
Percentages are based on n.

Pregnancy

Three patients in the rituximab arm became pregnant during the study:

- 1 patient was reported to be 6.5 months pregnant on Day 299, and the patient withdrew from the study on the same day. The patient, who enrolled with a new diagnosis of GPA, received her last dose of rituximab prior to the event at Study Day 173, approximately 4 months prior to the pregnancy being reported.
- 1 patient had an early spontaneous abortion (Week 3) on Study Day 505 (approximately Month 16). The patient, who enrolled with a new diagnosis of GPA, received her last dose of rituximab prior to the event at Month 12. The patient completed the study.
- 1 patient had a serious adverse event of fetal death on Study Day 181. The patient, who enrolled with a new diagnosis of GPA, received her last dose of rituximab prior to the event at Study Day 15. The event was considered by the investigator to be unrelated to rituximab. The patient completed the study.

The CHMP noted that two cases of abortion/foetal death was reported in the rituximab arm. Causality cannot be excluded albeit it appears quite unlikely. Indeed, AAV disease may per se be a risk factor of abortion/foetal death.

Laboratory findings

Laboratory data were collected locally and were not analyzed or presented in the CSR for Study ML22514.

Safety in special populations

The MAH argued that it was not meaningful to perform any subgroup analysis in special populations due to a very small number of patients within each subgroup. This approach was endorsed by the CHMP.

Discontinuation due to adverse events

Table 20 Summary of Adverse Events Leading to Discontinuation of Study Treatment by System Organ Class, Preferred Term, and Trial Treatment (Safety)

System Organ Class/ Patients Preferred Term	Rituximab (N=57)	Azathioprine (N=58)	All (N=115)
Any System Organ Classes			
Total No. of patients with one or more events	2 (3.5%)	9 (15.5%)	11 (9.6%)
Total No. of events	2	11	13
Blood and lymphatic system disorders			
Total No. of patients with one or more events	0 (0.0%)	2 (3.4%)	2 (1.7%)
Neutropenia	0 (0.0%)	1 (1.7%)	1 (0.9%)
Pancytopenia	0 (0.0%)	1 (1.7%)	1 (0.9%)
Total No. of events	0	2	2
Infections and infestations			
Total No. of patients with one or more events	0 (0.0%)	2 (3.4%)	2 (1.7%)
Bronchitis	0 (0.0%)	1 (1.7%)	1 (0.9%)
Urosepsis	0 (0.0%)	1 (1.7%)	1 (0.9%)
Total No. of events	0	2	2
Vascular disorders			
Total No. of patients with one or more events	0 (0.0%)	2 (3.4%)	2 (1.7%)
Vasculitis	0 (0.0%)	2 (3.4%)	2 (1.7%)
Total No. of events	0	2	2
Gastrointestinal disorders			
Total No. of patients with one or more events	0 (0.0%)	1 (1.7%)	1 (0.9%)
Gastrointestinal disorder	0 (0.0%)	1 (1.7%)	1 (0.9%)
Total No. of events	0	1	1
Hepatobiliary disorders			
Total No. of patients with one or more events	0 (0.0%)	1 (1.7%)	1 (0.9%)
Drug-induced liver injury	0 (0.0%)	1 (1.7%)	1 (0.9%)
Total No. of events	0	1	1
Nervous system disorders			
Total No. of patients with one or more events	1 (1.8%)	0 (0.0%)	1 (0.9%)
Carpal tunnel syndrome	1 (1.8%)	0 (0.0%)	1 (0.9%)
Total No. of events	1	0	1
Pregnancy, puerperium and perinatal conditions			
Total No. of patients with one or more events	1 (1.8%)	0 (0.0%)	1 (0.9%)
Pregnancy	1 (1.8%)	0 (0.0%)	1 (0.9%)
Total No. of events	1	0	1
Renal and urinary disorders			
Total No. of patients with one or more events	0 (0.0%)	1 (1.7%)	1 (0.9%)
Renal failure	0 (0.0%)	1 (1.7%)	1 (0.9%)
Total No. of events	0	1	1
Total No. of patients with one or more events	0 (0.0%)	1 (1.7%)	1 (0.9%)
Cough	0 (0.0%)	1 (1.7%)	1 (0.9%)
Total No. of events	0	1	1
Injury, poisoning and procedural complications			
Total No. of patients with one or more events	0 (0.0%)	1 (1.7%)	1 (0.9%)
Ligament sprain	0 (0.0%)	1 (1.7%)	1 (0.9%)
Total No. of events	0	1	1

Investigator text for adverse events is encoded using MedDRA version 20.0.
Adverse events leading to discontinuation of study treatment are described.

Each patient is counted only once for each SOC, and each patient is counted only once for each preferred term. Percentages are based on N.

Post marketing experience

Post-marketing exposure

Since the IBD (26 November 1997) until 30 September 2016 (data lock point for exposure calculation of the most recent Periodic Benefit Risk Evaluation Report), approximately 5,378,160 patient-market exposures have been estimated for rituximab. The primary market research data prior to 2009 and the available syndicated market research data (i.e., the US claims data) do not contain sufficient information for exact calculation of exposure of AAV patients to rituximab.

Post-marketing safety data from the MAH

Post-marketing safety data reported in the MAH global safety database and the literature, aiming to investigate the safety profile of rituximab maintenance therapy in patients with GPA/MPA, in support of the planned application were reviewed and summarized (Report No: 1081144).

The results from the safety database analysis, despite potential methodological limitations, showed consistency with the results from Study ML22514, and with the well-established safety profile of the approved GPA/MPA and RA indications. The long-term exposure data available on rituximab in RA and GPA/MPA clinical trial patients showed no new safety signals or increased reporting rates of AEs with increasing duration of exposure or courses of treatment.

The review of the published literature on rituximab maintenance therapy reported overall a satisfactory safety profile, and a clear interest could be seen in the literature for the use of rituximab in the maintenance indication. Most of the relevant references investigated specific concerns related to the safety profile of rituximab in GPA/MPA maintenance, such as infections, low Ig levels, and rituximab long term exposure.

Study WA27893 (RaVeR)

Study WA27893 is a Phase IV, open-label, observational study designed to examine the long-term safety profile of rituximab treatment in patients with GPA or MPA in a prospective observational setting, outside of a controlled clinical trial.

Patients received either fixed doses or body surface area (BSA)-based doses of rituximab at the discretion of the investigator. One hundred patients were enrolled in this study, including 3 patients who were not included in the safety population because their safety data could not be verified. All 97 patients in the safety population received at least one course of rituximab, and 68 patients received more than one course. As of the data cut-off date of the interim report, the median duration on study was 2.4 years (range: 0.05 to 3.2 years).

Table 21 Safety Summary (Safety Population)

	Rituximab (N=97)
Total number of patients with at least one AE	48 (49.5%)
Total number of AEs	131
Total number of deaths	6 (6.2%)
Total number of patients withdrawn from study due to an AE	0
Total number of patients with at least one	
AE with fatal outcome	6 (6.2%)
Serious AE	33 (34.0%)
Serious AE leading to withdrawal from treatment	1 (1.0%)
Serious AE leading to dose modification/interruption	2 (2.1%)
Related Serious AE	5 (5.2%)
AE leading to withdrawal from treatment	1 (1.0%)
AE leading to dose modification/interruption	9 (9.3%)
Related AE	17 (17.5%)
Related AE leading to withdrawal from treatment	0
Related AE leading to dose modification/interruption	8 (8.2%)
Severe AE (at greatest toxicity grade)	30 (30.9%)
Medical concepts: patients with	
Serious Cardiac events	7 (7.2%)
Serious Vascular events	5 (5.2%)
Serious Infections	11 (11.3%)
Malignancies excluding non-melanoma skin cancer	2 (2.1%)
Serious Events within 24hr of Infusion	0

Investigator text for AEs encoded using MedDRA version 18.0.
Percentages are based on N in the column headings.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
Severe AE is defined as any AE with NCI-CTCAE toxicity grade greater or equal to 3.

2.5.1. Discussion on clinical safety

The majority of patients experienced an AE, however the total number of patients with one or more related AE was lower in the rituximab arm compared with the azathioprine arm. The absolute total number of related events were similar between the two groups.

The most common AEs are related to infections, general disorders and administration site condition, gastrointestinal disorders and musculoskeletal/connective tissue disorders. A majority of the patients had AEs that were mild or moderate in intensity, and more patients on azathioprine compared with rituximab experienced severe events.

Overall, the incidence of patients any SAE was lower in the rituximab group, but the total number of patients with any related SAE were comparable with the azathioprine treated patients. The most frequent reported SAE was infections/infestations, which was similar between the two groups (approx. 12%). However, the number of total events was a little higher in the rituximab arm compared with the azathioprine arm (14 vs. 8). The reported SAE reflects the known safety profile of rituximab.

There were 3 patients who died in the AZA arm vs. 0 in the RTX arm. No deaths were related to treatment with rituximab.

Two patients in the rituximab arm discontinued from study treatment due to an AE vs. 9 in the azathioprine arm which indicates better tolerability in favour of rituximab.

Overall, the incidence of infections was comparable between the two arms. Opportunistic infections (candidiasis, pneumocystis jirovecii) and tuberculosis were reported in the rituximab group. The most frequent reported SAE was infections/infestations, and the incidence was identical in the two groups. However, the number of total events was a little higher in the rituximab arm. (14 vs. 8). The second most common SAE was General Disorders and Administration Site Condition was comparable between the two groups (total numbers of patients 12.3% vs. 10.3%, total numbers of events 8 vs. 6). The reported SAE reflects the known safety profile of rituximab.

Fewer gastrointestinal AEs were seen in the rituximab group in terms of no. of patients and number of events. It is noted, that markedly fewer AEs related to blood and lymphatic system appeared among the RTX treated patients.

The incidence of IRR symptoms was highest during the first infusion and decreased with subsequent infusions. The IRRs were mild or moderate and no patients withdrew from the study due to IRR. The incidence of IRR is as expected for this type of drug.

Two cases of abortion/fetal death was reported in the rituximab arm. Causality cannot be excluded albeit it appears unlikely. AAV disease may per se be a risk factor of abortion/fetal death.

Two patients in the rituximab arm discontinued the study treatment due to AEs compared with 9 patients in the azathioprine arm. The events that lead to discontinuation in the rituximab arm was carpal tunnel syndrome and pregnancy which was deemed unrelated by the investigator

No new or unexpected safety findings were identified in the post-marketing exposure- and safety data, but the conclusion should be interpreted with caution due to methodological limitations. Overall, the presentation of the post-marketing exposure and safety data was considered acceptable by the CHMP.

In study WA27893 (RaVeR), at cut-off, a total of 48 patients (49.5%) experienced at least one AE, and 33 patients (34.0%) had SAE. Six patients died during the study; none of these events were considered by the investigator to be related to study treatment. Two patients were diagnosed with

malignancy, which also was deemed unrelated to the treatment by the investigator. The number of patients with serious infections was 11 (11.3%). Overall, the interim analysis showed no unexpected safety findings and is consistent with the short-term data and the known safety profile in the RA population.

However, there is missing information on the long term use in GPA/MPA patients. This was added in the safety concerns in the RMP and the MAH should provide additional information to further address this concern. See section 2.6.

2.5.2. Conclusions on clinical safety

Overall, maintenance treatment with rituximab over 18 months is well-tolerated. The observed safety profile is as expected and in line with the known safety profile of rituximab used in other patient population with autoimmune and lympho-proliferative diseases. Discontinuation rate due to AEs was generally low.

In conclusion, there are no major concerns with regard to the safety profile of rituximab used as maintenance therapy.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The PRAC considered that the risk management plan version 17.0 could be acceptable if the applicant implements the changes to the RMP to update the approved T.II/144 RMP version 16.1 related changes and delete the previous included changes of the ongoing to variation T. II 150.

The CHMP endorsed the Risk Management Plan version 17.1 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	• Infusion-related reactions (All Indications) • Infections, including serious infections (All Indications) • Progressive multifocal leukoencephalopathy (All Indications) • Hepatitis B reactivation (All Indications) • Hypogammaglobulinemia (RA and GPA/MPA)

Summary of safety concerns	
Important potential risks	• Prolonged B-cell depletion (All Indications) • Malignant events (RA and GPA/MPA) • Impact on cardiovascular disease (RA and GPA/MPA) • Relapses (GPA/MPA only) • Off label use in pediatric patients (All Indications) • Off-label use of the subcutaneous formulation (NHL/CLL, SC formulations) • Administration route error (NHL/CLL, SC formulations) • Off label use in autoimmune disease (RA and GPA/MPA)
Missing information	• Use in pregnancy and lactation (All Indications) • Long term use in GPA/MPA patients (GPA/MPA only) • Immunogenicity Associated With The Subcutaneous Formulation (NHL/CLL, SC formulations)

Pharmacovigilance plan

Study **Status**	**Summary of Objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
BO25341/SAWYER: An adaptive, comparative, randomized, parallel-group, multi-center, Phase Ib study of subcutaneous (SC) rituximab versus intravenous (IV) rituximab both in combination with chemotherapy (fludarabine and cyclophosphamide), in patients with previously untreated CLL. Ongoing	To compare the safety profiles of rituximab subcutaneous and rituximab intravenous formulations, including, comparing the immunogenicity of rituximab subcutaneous and rituximab intravenous	Prolonged B-cell depletion; Immunogenicity Associated With The Subcutaneous Formulation (NHL and CLL Subcutaneous [SC] Formulations Only)	Primary Clinical Study Report(CSR)	September 2014 (Commitment fulfilled)
			Immunogenicity report(both parts)	Q4 2016 (Commitment fulfilled)
			Final CSR	Q4 2018

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
BO22334/SABRINA: A two-stage Phase III, international, multi-center, randomized, controlled, open-label study to investigate the pharmacokinetics, efficacy and safety of rituximab SC in combination with CHOP or CVP versus rituximab IV in combination with CHOP or CVP in patients with previously untreated follicular lymphoma followed by maintenance treatment with either rituximab SC or rituximab IV Ongoing	To compare the safety profiles of rituximab subcutaneous and rituximab intravenous formulations, including, comparing the immunogenicity of rituximab subcutaneous and rituximab intravenous	Prolonged B-cell depletion; Immunogenicity Associated With The Subcutaneous Formulation (NHL and CLL Subcutaneous [SC] Formulations Only)	Primary CSR	June 2014 (Commitment fulfilled)
			Immunogenicity report (both parts)	Q4 2016 (Commitment fulfilled)
			Final CSR	Q3 2018
Category 3 - Required additional pharmacovigilance activities				
WA25615/PePRS Phase IIa, international, multicenter, open-label, single-arm study in pediatric GPA/MPA patients Ongoing	Evaluate the safety and tolerability of rituximab in pediatric patients with severe GPA/MPA	Off-label use in pediatric patients	FPFV	23 May 2013
			LPLV	May 2018
			Study End	The common closeout date will occur 18 months after the enrollment of the last patient
BA28478 (MabThera Autoimmune Drug Utilization Study) Ongoing NI-PASS	Designed to address EMA follow-up measures (FUMs) 068 and 071.1 to evaluate off-label use and usage of the patient alert cards in the 5EU countries	Off-label use in autoimmune disease	Final report submission	May 2018

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Plasma exchange and glucocorticoid dosing in the treatment of ANCA-associated vasculitis (PEXIVAS) Ongoing	Capture long-term safety data in order to further evaluate dose regimen of rituximab in relation to infection's frequency, seriousness and severity	Infections including serious infections	Final CSR	Expected in April 2019
Intergroup B-NHL-2010 Open-label, randomized, controlled, parallel-group, multicenter trial to evaluate the pharmacokinetics, pharmacodynamics, safety and efficacy or rituximab add-on to standard chemotherapy in children from 6 months to less than 18 years of age with advanced stage B-cell lymphoma (excluding primary mediastinal B-cell lymphoma), Burkitt and Burkitt-like lymphoma/Leukemia conducted in accordance with the approved PIP Ongoing	Evaluate the safety and tolerability of rituximab in pediatric patients with advanced stage B-cell lymphoma (excluding primary mediastinal B-cell lymphoma), Burkitt and Burkitt-like lymphoma/Leukemia	Off-label use in pediatric patients	Study Start	November 2011
			Study End	June 2019
Maintenance of remission using rituximab in systemic Anti-Neutrophil Cytoplasm Antibody (ANCA) Associated Vasculitis II Phase III, interventional, randomized, open-label, comparative trial. Ongoing	Number of relapses / Number of relapses (BVAS >0) majors and minors in each group at the end of the maintenance treatment (18 months treatment $+16$ months follow-up)	Relapses	Estimated study completion date	February 2018
			Final data collection date for primary outcome measure Estimated completion date	August 2017. February 2018

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
An international, open label, randomized controlled trial comparing rituximab with azathioprine as maintenance therapy in relapsing ANCA-associated vasculitis (RITAZAREM)-Phase III, interventional, randomized, open-label, comparative trial Ongoing	Time to relapse / the primary endpoint is the time to disease relapse (either minor or major relapse) from randomization. Proportion of patients who maintain remission at 24 and 48 months	Relapses	Estimated study completion date	January 2019
BE29950 (RIVAS): Prospective, single center, secondary data use, long-term surveillance, non-interventional study. Ongoing NI-PASS	Registry to collect serious adverse event data over 5 years to determine the long-term safety of rituximab for the treatment of GPA/MPA.	Long term use in GPA/MPA patients	Study start: Interim analyses: Interim report: Final report:	Q4 2016 Annual reporting of cumulative data in PBRER 3 years after study start 5 years after study start
Category 4: Stated additional pharmacovigilance activities				
WA27893/RaAVeR: A multi-centre (US-based), prospective, observational study designed to follow 100 rituximab treated patients with granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) for a maximum of 4 years. Ongoing NI-PASS	*Primary objective* of this study is to characterize the long-term safety of rituximab in the treatment of *GPA* or MPA. *Secondary objective* of this study is to collect data on the safety of re-treatment with rituximab in patients with *GPA* or MPA.	Infusion-related reactions (All Indications) Infections, including serious infections (All Indications) Hepatitis B reactivation (All Indications) Malignant events (RA and GPA/MPA) Impact on cardiovascular disease (RA and GPA/MPA) Relapses (GPA/MPA) Use in pregnancy and lactation (All Indications)	First patient in Last patient in Last Patient Last Visit Interim Clinical Study Report Final Report expected	20 Jun 2012 19 May 2013 19 May 2017 April 2016 April 2018

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Anti Rheumatic Therapy in Sweden (ARTIS)- Nation-wide safety monitoring of MabThera treatment in patients with rheumatic Diseases in Sweden Ongoing NI-PASS	To initiate a nationwide post-marketing inception cohort of patients treated with rituximab (MabThera), including all patients with rheumatoid arthritis (RA)	Infections, including serious infections (All Indications) Malignant events (RA and GPA/MPA) Impact on cardiovascular disease (RA and GPA/MPA) Use in pregnancy and lactation (All Indications)	First patient in 3-year report 5-year report Final report expected	Q2 2007 Dec 2011 Dec 2013 Annual updates in PBRERs
British Society of Rheumatology Biologics Registry (BSRBR) Ongoing NI-PASS	Evaluate the safety profile of rituximab in Rheumatoid arthritis patients in comparison to RA patients treated with anti- tumor necrosis factor (TNF)α agents and standard disease-modifying anti rheumatic drugs (DMARD) medicines	Infections, including serious infections (All Indications) Malignant events (RA and GPA/MPA) Impact on cardiovascular disease (RA and GPA/MPA) Use in pregnancy and lactation (All Indications)	First patient in 3-year report 5-year report Final report expected	Q2 2008 August 2013 Q1 2015 Q3 2019 Annual updates in PBRERs

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
RABBIT(Rheumatoid arthritis observation of biologic therapy) Ongoing NI-PASS	Evaluate long term effectiveness of treatment with biological agents with regard to treatment continuation and clinical outcomes, and to study the long term safety of treatment with biologic therapy in RA.	Infections, including serious infections (All Indications) Malignant events (RA and GPA/MPA) Impact on cardiovascular disease (RA and GPA/MPA) Use in pregnancy and lactation (All Indications)	First Patient In Planned submission of final data	Q2 2007 Q4 2022 Annual updates in PBRERs

ANCA= Anti-Neutrophil Cytoplasmic Antibody, BVAS= Birmingham Vasculitis Activity Score, CLL= Chronic Lymphocytic Leukemia, CSR=Clinical study report, GPA= Granulomatosis with polyangiitis, SC =Subcutaneous

Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
Infusion Related Reactions **All Indications**	**Routine risk communication:** EU SmPC section 4.4: Special warnings and precautions for use EU SmPC section 4.8: Undesirable Effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** *Medicine's legal status*: Medicinal product subject to restricted medical prescription	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities:** RAVeR (WA27893)

	Additional risk minimization measures: None	
Infections, including serious infections **All Indications**	**Routine risk communication:** EU SmPC section 4.4: Special warnings and precautions for use EU SmPC Section 4.8: Undesirable Effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** *Medicine's legal status:* Medicinal product subject to restricted medical prescription **Additional risk minimization measures:** Patient Alert Card (RA and GPA/MPA) Educational Material for Healthcare Professionals and Patients (RA and GPA/MPA)	**Routine pharmacovigilance activities beyond adverse reactions reporting and** **signal detection** None **Additional pharmacovigilance activities:** Evaluate results from PEXIVAS study in GPA/MPA Study RaVeR (WA27893) Anti Rheumatic Therapy in Sweden (ARTIS) British Society of Rheumatology Biologics Registry (BSRBR) RABBIT (Rheumatoid arthritis observation of biologic therapy)
Progressive Multifocal Leukoencephalopathy (RA and GPA/MPA [non-oncology indications] only)	**Routine risk communication:** EU SmPC section 4.4: Special warnings and precautions for use **Routine risk minimization activities recommending specific clinical measures to address the risk:** Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded. Further evaluations, including Magnetic Resonance Imaging scan preferably with contrast, cerebrospinal fluid (CSF)	**Routine pharmacovigilance activities beyond adverse reactions reporting and** **signal detection:** Guided Questionnaires **Additional pharmacovigilance activities:** None

	testing for JC Viral DNA and repeat neurological assessments, should be considered. If a patient develops PML, the dosing of MabThera must be permanently discontinued. **Other risk minimization measures beyond the Product Information:** *Medicine's legal status:* Medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** • Patient Alert Card (RA and GPA/MPA) • Educational Material for Healthcare Professionals and Patients (RA and GPA/MPA)	
Hepatitis B Reactivation All Indications	**Routine risk communication:** EU SmPC section 4.4: Special warnings and precautions for use **Routine risk minimization activities recommending specific clinical measures to address the risk:** Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with MabThera. At minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guidelines. Patients with active hepatitis B disease should not be treated with MabThera. Patients with positive hepatitis B serology (either HBsAg or HBcAb) should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation. **Other risk minimization measures beyond the Product Information:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and** **signal detection:** Guided Questionnaires **Additional pharmacovigilance activities:** RaVeR (WA27893)

	Medicine's legal status: Medicinal product subject to restricted medical prescription **Additional risk minimization measures:** None	
Hypogammaglobulinemia **Indication: RA and GPA/MPA**	**Routine risk communication:** EU SmPC section 4.4: Special warnings and precautions for use **RA** EU SmPC Section 4.8: Undesirable effects **GPA/MPA** EU SmPC Section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Immunoglobulin levels are recommended to be determined prior to initiating treatment with MabThera **Other risk minimization measures beyond the Product Information:** *Medicine's legal status:* Medicinal product subject to restricted medical prescription **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and** **signal detection:** None **Additional pharmacovigilance activities:** None
Prolonged B-cell depletion	**Routine risk communication:** EU SmPC Section 5.1: Pharmacodynamic properties **Routine risk minimization activities recommending specific clinical measures to address the risk:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and** **signal detection:** None **Additional pharmacovigilance activities:**

	Other risk minimization measures beyond the Product Information: *Medicine's legal status:* Medicinal product subject to restricted medical prescription **Additional risk minimization measures:** None	Provision of long term pharmacodynamics data on B-cell depletion from Study BO22334 (SABRINA) Provision of long term pharmacodynamics data on B-cell depletion from Study BO25341 (SAWYER)
Malignant Events **Indication: RA and GPA/MPA**	**Routine risk communication:** EU SmPC Section 4.4: Special warnings and precautions for use **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** *Medicine's legal status:* Medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and** **signal detection:** Guided questionnaires **Additional pharmacovigilance activities:** RAVeR (WA27893) Anti Rheumatic Therapy in Sweden (ARTIS) British Society of Rheumatology Biologics Registry (BSRBR) RABBIT (Rheumatoid arthritis observation of biologic therapy)
Impact on Cardiovascular Disease **Indication: RA and GPA/MPA**	**Routine risk communication:** EU SmPC section 4.4: Special warnings and precautions for use **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** *Medicine's legal status:* Medicinal product subject to restricted medical prescription	**Routine pharmacovigilance activities beyond adverse reactions reporting and** **signal detection** None **Additional pharmacovigilance activities:** Study RaVeR (WA27893) Anti Rheumatic Therapy in Sweden (ARTIS) British Society of Rheumatology Biologics Registry (BSRBR)

	Additional risk minimization measures: None	RABBIT (Rheumatoid arthritis observation of biologic therapy)
Relapses (GPA/MPA only)	**Routine risk communication:** EU SmPC Section 5.1: Pharmacodynamic properties **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** *Medicine's legal status:* Medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and** **signal detection:** None **Additional pharmacovigilance activities:** Observation and evaluation of data from ongoing studies on maintenance therapy (MAINRITSAN II and RITAZAREM). RaVeR (WA27893)
Off Label Use in Pediatric Patients **All Indications**	**Routine risk communication:** SmPC section 4.1 Therapeutic indications SmPC section 4.2: Posology and method of administration, Special populations, Paediatric population **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** *Medicine's legal status:* Medicinal product subject to restricted medical prescription **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and** **signal detection:** Guided Questionnaires **Additional pharmacovigilance activities** Study WA25615 (an interventional PASS) Intergroup trial (Inter-B-NHL 2010)

Off-label Use of the Subcutaneous Formulation **Indication:** **NHL/CLL, SC formulations**	**Routine risk communication:** EU SmPC section 4.1 Therapeutic indications Separate EU SmPCs are available for the IV (100 mg and 500 mg) and SC formulations (1400 mg for NHL and 1600 mg for CLL). EU SmPC (for SC formulation) section 4.4: Special warnings and precautions for use EU SmPC (IV and SC) section 4.2: Posology and method of administration **Routine risk minimization activities recommending specific clinical measures to address the risk:** Separate SmPCs are available for the IV (100 mg and 500 mg) and SC formulations (1400 mg for NHL and 1600 mg for CLL). **Other risk minimization measures beyond the Product Information:** *Medicine's legal status:* Medicinal product subject to restricted medical prescription **Additional risk minimization measures:** Educational Material for Healthcare Professionals	**Routine pharmacovigilance activities beyond adverse reactions reporting and** **signal detection** None **Additional pharmacovigilance activities** None
Administration route error (NHL/CLL, SC formulations)	**Routine risk communication:** The IV and SC formulations are covered by separate EU SmPCs to reinforce the difference between the IV and SC formulations. EU SmPC (IV and SC) section 1: Name of the Medicinal Product EU SmPC (IV and SC) section 4.2: Posology and method of administration	**Routine pharmacovigilance activities beyond adverse reactions reporting and** **signal detection** None **Additional pharmacovigilance activities** None

	Routine risk minimization activities recommending specific clinical measures to address the risk: The IV and SC formulations are covered by separate SmPCs to reinforce the difference between the IV and SC formulations. **Other risk minimization measures beyond the Product Information:** **Packaging: Clear package differentiation** • Color differentiation (distinct colored bands) • Unique cap colors for the vials matching the colored bands • Clear statements on both the primary and secondary packaging i.e., words "*subcutaneous*", "*solution for subcutaneous injection*" and "Only *for subcutaneous use*" in red font. Peel-off sticker is included on the individual vials of the subcutaneous formulations specifying the strength, the route of administration and the indication. SC and IV formulations are covered by separate SmPCs, which include specific warning against incorrect route of administration. *Medicine's legal status*: Medicinal product subject to restricted medical prescription **Additional risk minimization measures:** Educational Material for Healthcare Professionals	
Off label Use in Autoimmune Disease	**Routine risk communication:** EU SmPC Section 4.1 Therapeutic indications	**Routine pharmacovigilance activities beyond adverse reactions reporting and**

Indication: RA and GPA/MPA	**Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** *Medicine's legal status:* Medicinal product subject to restricted medical prescription **Additional risk minimization measures:** None	**signal detection:** None **Additional pharmacovigilance activities:** BA28478 - Drug Utilization Study (DUS – 5EU [five EU countries]) - PASS
Use in Pregnancy and Lactation **All Indications**	**Routine risk communication:** EU SmPC section 4.6 Fertility, pregnancy and lactation **Routine risk minimization activities recommending specific clinical measures to address the risk**: None **Other risk minimization measures beyond the Product Information**: *Medicine's legal status:* Medicinal product subject to restricted medical prescription **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and** **signal detection** Standard pregnancy report form for follow-up. **Additional pharmacovigilance activities** Study RaVeR (WA27893) Anti Rheumatic Therapy in Sweden (ARTIS) British Society of Rheumatology Biologics Registry (BSRBR) RABBIT (Rheumatoid arthritis observation of biologic therapy)
Long term use in GPA/MPA patients (GPA/MPA only)	**Routine risk communication:** None **Routine risk minimization activities recommending specific clinical measures to address the risk**: None **Other risk minimization measures beyond the Product Information**:	**Routine pharmacovigilance activities beyond adverse reactions reporting and** **signal detection:** None **Additional pharmacovigilance activities:**

	Medicine's legal status: MabThera is a prescription only medicine. **Additional risk minimization measures:** None	WA27893 (RaVeR) RIVAS (BE29950) registry
Immunogenicity Associated With The Subcutaneous Formulation (NHL/CLL, SC formulations)	**Routine risk communication:** Section 5.1 Pharmacodynamic properties of the Eu SmPC states: The clinical relevance of development of anti-rituximab or anti-rHuPH20 antibodies after treatment with MabThera subcutaneous formulation is not known **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** *Medicine's legal status* Medicinal product subject to restricted medical prescription **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and** **signal detection:** None **Additional pharmacovigilance activities:** SABRINA/BO22334 (NHL) and SAWYER/BO25431 (CLL)

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to implement a terminology change in Annex II.D.

The "induction of remission in adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA)" was already approved for Mabthera. With this new indication in the "maintenance of treatment in adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA)", the wording of the indication was modified to "treatment of adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA)":

MabThera, in combination with glucocorticoids, is indicated for the ~~induction of remission in~~ treatment of adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA).

The other parts of the SmPC present the data in the "induction of remission" and the "maintenance treatment". Please refer to the approved PI.

2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed indication for MabThera is, in combination with glucocorticoids, the maintenance treatment of adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA).

Granulomatosis with polyangiitis (GPA) – also known as Wegener's granulomatosis (WG) – and microscopic polyangiitis (MPA) are both associated with anti-neutrophil cytoplasmic antibodies (ANCAs) and are therefore referred to collectively as ANCA-associated vasculitis (AAV). The clinical features of GPA and MPA largely overlap, as necrotizing vasculitis may occur in the same organs. In GPA, crusting granulomata in the ear, nose and throat area and alveolar bleeding are the most prominent feature, and segmental, necrotizing glomerulonephritis may occur in about 50% of the cases. In MPA, glomerulonephritis is the most prominent feature present in virtual all patients, whereas the respiratory tract may be spared. In both GPA and MPA, vasculitis may be extended to other organs like the skin, nervous system, heart and gastrointestinal (GI) tract (mesenterium). CNS involvement is relatively rare for both disorders. Systemic features (fever, arthritis) are more common in MPA. The distinction between both entities is made by histology.

3.1.2. Available therapies and unmet medical need

Historically, induction therapy with cyclophosphamide (CYC) was used. CYC is associated with significant toxicity, such as uro-toxicity (haemorrhagic cystitis, bladder cancer), cardio-toxicity, malignancies (lymphoma, thyroid cancer, non-melanoma skin cancer), lymphopenia and neutropenia, serious and opportunistic infections, thrombocytopenia and reduced fertility. Because of its toxicity, its use is limited to short-term induction therapy of severe flares, followed by maintenance therapy with other, in general better-tolerated immune-suppressant agents, like AZA (azathioprine), MFM (mycophenolate mofetil) or MTX (methotrexate). Mild-isolated cases of GPA granulomata may be treated with MTX alone.

In the European Union (EU), rituximab intravenous (IV) infusion in combination with glucocorticoids, was approved on 22 April 2013 for the induction of remission in adult patients with severe, active GPA and MPA.

3.1.3. Main clinical studies

The current submission supporting the approval of Mabthera for maintenance treatment of patients with GPA and MPA who are in remission, is based on the results from one investigator sponsored pivotal Phase III trial (Study ML22514/MAINRITSAN I), which evaluated the efficacy and safety of

rituximab versus azathioprine for the prevention of disease relapse. The study was a therapeutic, prospective, Phase III, multi-centre, comparative, randomized, open-label study comparing azathioprine versus rituximab in combination with low-dose corticosteroids for the maintenance treatment of GPA/MPA.

3.2. Favourable effects

Study ML22514 showed both a statistically significant and clinically relevant difference in terms of time to first major relapse in advantage of rituximab at Month 28. Adjusting for the stratification factor using Cox PH modelling, rituximab reduced the risk of major relapse by approximately 86% relative to azathioprine (HR: 0.14; 95% CI: 0.04, 0.47, p=0.0015). The results from secondary endpoints and additional endpoints are all consistent with the primary endpoint.

3.3. Uncertainties and limitations about favourable effects

The baseline demographics and disease characteristics were not well balanced with respect to gender, distribution of GPA and MPA between the treatment arms and occurrence of ANCA. With respect to GPA and MPA, there is little clinical distinction between the two vasuclitides due to the overlapping features (and symptoms) and they are considered to form part of the same disease spectrum. Further, analysis of the baseline differences in gender between the two study arms did not appear to have influenced response to rituximab or prognosis of the disease. With regards to ANCA, the baseline ANCA appeared to have no impact on the effect of rituximab in preventing relapse. In conclusion, those uncertainties were adequately addressed by the MAH and considered solved by the CHMP.

3.4. Unfavourable effects

The most common AEs were related to infections, general disorders and administration site condition, gastrointestinal disorders and musculoskeletal/connective tissue disorders. A majority of the patients had AEs that were classified as mild or moderate in intensity, and more patients on azathioprine compared with rituximab experienced severe events, which is reassuring in view of rituximab.

The incidence of infusion related reactions (IRR) were as expected for this type of drug, and symptoms were higher after the first infusion and decreased with subsequent infusions. Two patients treated with rituximab discontinued the treatment due to carpal tunnel syndrome and pregnancy.

No new or unexpected safety findings were identified in the post-marketing exposure- and safety data. However, conclusions on the post-marketing exposure- and safety data should be interpreted with caution due to methodological limitations. Overall, the presentation of the post-marketing exposure and safety data was considered acceptable by the CHMP.

3.5. Uncertainties and limitations about unfavourable effects

There are no major uncertainties or concerns with regard to the safety profile of rituximab in the proposed patient population. The safety profile of rituximab is as expected. However, there is missing information on the long term use in GPA/MPA patients. This was added in the safety concerns in the RMP and the MAH should provide additional information to further address this concern. See section 2.6.

3.6. Effects Table

Table 22 Effects Table for Mabthera in the maintenance treatment of patients with GPA and MPA

Effect	Unit	Rituximab	Azathioprine	Uncertainties / Strength of evidence
Favourable Effects				
N-MAR	N(%)	3 (5.2%)	17 (28.8%)	HR = 0.14, p=0.015
N-MIN	N(%)	7 (12.1%)	8 (13.6%)	
N-ANCA	N(%)	12 (27.3%)	29 (64.4%)	
Unfavourable Effects				
SAEs	N(%)	26 (45.6%)	32 (55.2%)	
IRR	N(%)	5 (8.8%)	-	

Abbreviations: ACS = Acute coronary syndrome, ARD = Acute respiratory distress syndrome, IRR = Infusion Related Reactions, N-ANCA = Number of patients with detectable ANCA, N-MAR = Number of patients with major relapse, N-MIN = Number of patients with minor relapse,

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Study ML55214 comparing rituximab to azathioprine is a well-designed and well-conducted phase III study, demonstrating value of rituximab used as maintenance treatment for AAV compared with azathioprine. The risk of major relapse of AAV was reduced by approximately 86% 28 months after initiation of maintenance treatment with rituximab as compared to azathioprine. Analysis of long-term outcomes at 60 months seemed to substantiate the superior efficacy of rituximab. The rituximab dosing regimen in patients who received Mabthera for the induction of remission was chosen pragmatically based on previous clinical experiences of use of the drug within approved indications. This approach was considered acceptable to the CHMP considering the rarity of the disease.

The observed safety profile of rituximab in this setting is favourable compared with azathioprine, and is in line with the known safety profile of rituximab used in other autoimmune disease populations (e.g. rheumatoid arthritis).

3.7.2. Balance of benefits and risks

The "induction of remission in adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA)" was already approved for Mabthera. With this new indication in the "maintenance of treatment in adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA)", the wording of the indication was modified to "treatment of adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA)":

MabThera, in combination with glucocorticoids, is indicated for the ~~induction of remission in~~ treatment of adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA).

3.8. Conclusions

The overall benefit risk balance of Mabthera in the treatment of adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA) is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication in the treatment of adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA) for MabThera; as a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package leaflet is updated accordingly. In addition, the MAH took the opportunity to implement a terminology change in Annex II.D.

The RMP (v17.1) has also been agreed.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication in the treatment of adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA) for MabThera; as a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package leaflet is updated accordingly. In addition, the MAH took the opportunity to implement a terminology change in Annex II.D.

Summary

Please refer to Scientific Discussion MabThera-H-C-165-II-0149