21 March 2013
EMA/462277/2013
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

MabThera

Procedure no. EMEA/H/C/000165/II/0079

Marketing authorisation holder (MAH): Roche Registration Ltd.

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
ADR	Adverse Drug Reaction
AE	Adverse Event
ANCA	Anti-neutrophil cytoplasmic antibodies
AZA	Azathioprine
BMJ	Best Medical Judgement
BSA	Body Surface Area
BVAS-WG	Birmingham Vasculitis Activity Score for Wegener's Granulomatosis
CHCC	Chapel-Hill Consensus Conference
CI	Confidence interval
CLL	Chronic Lymphocytic Leukaemia
CYC	cyclophosphamide
ELISA	Enzyme Linked Immunosorbent Assay
EULAR	European League against rheumatism
GPA	Granulomatosis with polyangiitis
HACA	Human anti–chimeric antibody
IRR	Infusion Related Reactions
LLOQ	lower limit of quantitation
MPA	Microscopic polyangiitis
MPO	myeloperoxidase
NHL	Non-Hodgkin's Lymphoma
NONMEM	Non-linear mixed effects software
PML	Progressive Multifocal Leukoencephalopathy
PR-3	Proteinase 3
RA	Rheumatoid arthritis
RCT	Randomised-controlled trial
RTX	Rituximab

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 for single variation of Commission Regulation (EC) No 1234/2008, Roche Registration Ltd. submitted to the European Medicines Agency on 13 April 2012 an application for an extension of indication variation.

This application concerns the following medicinal product:

Medicinal product:	International non-proprietary name:	Presentations:
Mabthera	rituximab	See Annex A

The following variation was requested:

Variation(s) requested		**Type**
C.1.6 a)	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH applied for a new indication for the treatment of severe active Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA) in combination with glucocorticoids. Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.4, 4.8, 5.1 of the SmPC.

The Package Leaflet was proposed to be updated in accordance.

The variation proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA decision (P/0068/2012) on the agreement of a paediatric investigation plan (PIP) for the treatment of microscopic polyangiitis and treatment of microscopic polyangiitis.

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

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 from the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP:

Rapporteur: Jens Ersbøll Co-Rapporteur: Barbara van Zwieten-Boot

Submission date:	13 April 2012
Start of procedure:	22 April 2012
Rapporteur's preliminary assessment report circulated on:	22 June 2012
CoRapporteur's preliminary assessment report circulated on:	18 June 2012
Request for supplementary information and extension of timetable adopted by the CHMP on:	19 July 2012
MAH's responses submitted to the CHMP on:	15 October 2012
Joint Rapporteur's assessment report on the MAH's responses circulated on:	26 November 2012
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	13 December 2012
MAH's responses submitted to the CHMP on:	25 January 2013
Joint Rapporteur's assessment report on the MAH's responses circulated on:	5 February 2013
3rd Request for supplementary information and extension of timetable adopted by the CHMP on:	21 February 2013
MAH's responses submitted to the CHMP on:	11 March 2013
Joint Rapporteur's assessment report on the MAH's responses circulated on:	15 March 2013
CHMP opinion:	21 March 2013

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. This concept is confirmed in patients by the fact that systemic disease flares did not occur unless ANCAs persisted or returned in patients in remission of AAV [Boomsma et al. 2000]. 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 (specifically vaso nervorum of peripheral nerves), 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 (Chapel-Hill Concensus Conference criteria, see table 1 below).

Table 1 Chapel-Hill Consensus Conference (CHCC) criteria for GPA and MPA: source EUVAS (European Vasculitis Study Group)

	GPA	MPA
Histologic features	granulomatous inflammation in respiratory tract	necrotizing vasculitis, with few or no immune deposits
Vessels involved	Small-medium	Mainly small vessels (Pulmonary capillaritis)
Necrotizing glomerulonephritis	common	Very common

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+ 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 signicant 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 (WG etanercept trial -WGET). 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 (Popa

et al. 1999). 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+ -B cells, thereby reducing the production of antibodies, including those related to auto-immune 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 $CD20^{+}$ 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.

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

The MAH proposes to extend the indications to include severely active GPA (granulomatosis with polyangiitis, also called Wegener's disease) and MPA (microscopic polyangiitis), in combination therapy with high-doses of glucocorticoids.

The proposed posology of the GPA/MPA indications is the same as proposed for the NHL indications, i.e. 375 mg/m^2 body surface area, administered as an intravenous infusion once weekly for 4 sequential weeks. Specific guidance for concurrent therapy with corticosteroids is provided in Section 4.2 of the SPC. Sections 4.8, 5.1, and 5.2 of the SPC are also updated with the clinical trial outcomes in the sought indications.

2.2. Quality aspects

Not applicable for this procedure.

2.3. Non-clinical aspects

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

2.3.1. Ecotoxicity/environmental risk assessment

Since the pharmacologically active substance in MabThera, rituximab, is a monoclonal antibody, a non-conjugated protein, it is exempted from the requirement of providing an ERA as in accordance with the Guideline on the Environmental Risk Assessment (ERA) of Medicinal Products for Human Use (CHMP/SWP/4447/00), it is unlikely to result in significant risk to the environment.

2.4. Clinical aspects

2.4.1. Introduction

The indication claim is based on data from a single pivotal study, ITN021AI (RAVE), a multicenter study comparing rituximab treatment against the current standard of care (CYC) and against a historical control.

In addition, published data from RITUXVAS, a Phase II, open-label, two-group, randomized study of 44 patients from 8 centers in Europe and Australia were provided as supportive. The study was sponsored and conducted by the Cambridge University Hospitals NHS Foundation Trust (United Kingdom) and the European Vasculitis Study Group (EUVAS).

The MAH did not seek Scientific Advice from the CHMP on the clinical development.

GCP

RAVE Clinical trial was performed in accordance with GCP.

Table 2 Tabular overview of clinical studies of rituximab in AAV

Study	No. of Patients	Patient Population	Study Design and Treatment arms	Concomitant Therapies	Primary Endpoint
Pivotal, NIAID-sponsored, randomized, controlled study					
ITN021AI/ RAVE	197	Severe AAV (147 with WG and 48 with MPA)	Phase II/III, multicenter, randomized, active-controlled, double-blind, double-dummy, parallel-group, international study Experimental arm: IV 375 mg/m^2 RTX wkly x 4 Control arm: oral CYC, daily for 3-6 months followed by oral AZA	GC	Complete remission (BVAS/WG = 0) and successful taper of glucocorticoid treatment, at 6 months after randomization
Investigator-initiated, randomized, controlled study					
RITUXVAS	44	Newly diagnosed AAV with renal involvement	Open-label, two group, parallel arm, randomized trial Experimental arm: IV RTX wkly x 4 and 2 × IV CYC pulses Control arm: IV CYC and AZA	GC	Sustained remission (BVAS 2003 = 0) at 12 months after randomization
Uncontrolled Studies and case series					
Aries et al. 2006	8	WG with granulomatous manifestations refractory to standard therapy	RTX 375 mg/m^2 every 4 weeks × 4	CYC, MMF, MTX, GC	Remission defined as BVAS=0 indicating absence of signs of new / worse disease activity + persistent activity for ≤ 1 item
Brihaye et al. 2007	8	Refractory WG	RTX 375 mg/m^2 weekly × 4	GC, IS	Remission defined as BVAS 2003 = 0
Eriksson et al. 2005	9	Therapy-resistant or frequently relapsing ANCA-positive vasculitis (7 with WG and 2 with MPA)	RTX 500 mg weekly × 4 (n = 6) RTX 500 mg weekly × 2 (n = 3)	MMF, AZA, CYC	Complete remission (BVAS 1994 = 0) at 6 months after start of RTX
Jones et al. 2009	65	Refractory AAV (46 with WG, 10 with MPA, 5 with CSS and 4 unclassified)	RTX 1 g × 2, 2 weeks apart (n = 32) RTX 375 mg/m2 weekly × 4 (n = 26)	GC, Anti-TNF, AZA, MTX, MMF, CYC	Complete remission defined as absence of disease signs and symptoms, using the DEI, with reduction in GC.
Keogh et al. 2005	11	Severe, refractory, active AAV (10 with WG and 1 with MPA)	RTX 375 mg/m2 weekly × 4	Plasma exchange for nephritis, GC	Complete remission defined as BVAS/WG = 0
Keogh et al. 2006	10	Severe, active AAV refractory to CYC	RTX 375 mg/m2 weekly × 4	GC	Complete remission defined as

Study	No. of Pa-tients	Patient Population	Study Design and Treatment arms	Concomi-tant Therapies	Primary Endpoint
					BVAS/WG = 0 Stable remission defined as BVAS/WG for > 6 months a
Lovric et al. 2009	15	Refractory and relapsing AAV (13 with WG, 1 with MPA, 1 with CSS)	RTX 375 mg/m2 weekly × 4	AZA, MMF, CYC, CsA, MTX, IFX, GC	Partial remission (reduction in BVAS 1994 > 50%) or Complete remission (BVAS 1994 = 0) a
Omdal et al. 2005	3	Refractory WG	RTX 375 mg/m2 weekly × 4	GC, MTX	Remission assessed via chest radiographs, lab parameters (proteinuria, ANCA, ESR) a
Sanchez-Cano et al. 2008	4	Refractory WG	RTX 375 mg/m2 weekly × 4	CYC, GC, MTX	Remission monitored using BVAS/WG a
Seo et al. 2008	8	Refractory, limited WG	RTX 375 mg/m2 weekly × 4	CYC, GC	Remission monitored through sign and symptom resolution a
Smith et al. 2006	11	Refractory AAV (5 with WG and 5 with MPA)	RTX 375 mg/m2 weekly × 4	MMF, GC, AZA, CYC	Complete remission defined as BVAS = 0. Partial remission defined as reduction in baseline BVAS by 50% a
Stasi et al. 2006	10	Refractory AAV (8 with WG and 2 with MPA)	RTX 375 mg/m2 weekly × 4	GC	Complete remission defined as BVAS/WG = 0 a

ANCA = anti-neutrophil cytoplasmic antibodies; AZA = azathioprine, BVAS = Birmingham Vasculitis Activity Score; CsA = cyclosporine; CYC = cyclophosphamide; DEI = Disease Extent Index; ESR = erythrocyte sedimentation rate; GC = glucocorticosteroids; IS = immunosuppressants; MMF = mycophenolate mofetil; IFX = infliximab; IVIG = intravenous immunoglobulin; MPA = microscopic polyangiitis; MTX = methotrexate; RTX = rituximab; TNF = tumor necrosis factor; URI = upper respiratory infection; WG = Wegener's granulomatosis.

[a] Some of the investigator-initiated trials do not clearly define primary efficacy endpoints.

2.4.2. Pharmacokinetics

Pharmacokinetic data were derived from 487 serum samples from 97 patients treated with rituximab at the pivotal study RAVE. Rituximab (375 mg/m^2) was administered to patients by IV infusion 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. The primary goals for this analysis were to evaluate the PK characteristics of rituximab in AAV patients by quantifying the PK as well as the relationship between PK parameters and covariates in this study.

The population PK analysis encompassed a total of 487 rituximab serum samples from 97 patients who received multiple infusions of rituximab in combination with a glucocorticoid.

The study population consisted of 45 males and 52 females with age ranging from 16 to 92 years and BSA ranging from 1.43 to 2.45 m^2. The subject population was predominantly white (91.820 (20.6%) study subjects out of 97 were HACA-positive.

The typical population 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 for 97 patients with GPA and MPA was 23.4 days (range: 9.38−48.7 days) (Table 2.4.2.1). Sex and HACA were important covariates explaining inter-

individual variability on CL. The estimate of t1/2, based on the final model was very similar between male patients and female patients (23.6 and 24.9 days, respectively). The HACA-positive patients were associated with shorter t1/2 than HACA-negative patients (19.0 vs. 25.6 days).

Table 3 Mean PK parameters.

PK parameters	N	Mean	SD	Median	Range
CL, mL/day	97	313	131	281	116-726
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.

The individual AUC0-inf were similar between patients who achieved a complete remission and those who failed the primary endpoint at Month 6 (Table 2.4.1.2).

Table 4 AUC0–inf for Rituximab Patients with and without Complete Remission at 6 Months (Per-Protocol Population)

Complete Remission[a] At 6 months	n	Mean	SD	Median	Min	Max
Failure	32	10.64	4.38	9.92	4.74	24.49
Success	62	10.73	3.60	10.43	3.88	19.17

[a] Defined as BVAS/WG = 0 with successful completion of glucocorticoid taper at Month 6.
Source :Appendix 2 .

In addition, there was no correlation between the achievement of complete remission at Month 6 and the individual AUC0-inf as indicated by a Spearman coefficient of correlation of 0.01.

2.4.3. Pharmacodynamics

No clinical pharmacodynamics studies were submitted.

2.4.4. Discussion on clinical pharmacology

Overall the PK parameters of rituximab in AAV patients were similar to those previously observed in RA patients and typical for IgG antibodies (Frazer 1999). Sex and presence of HACA antibodies were important covariates explaining inter-individual variability in clearance, however, no dose adjustment according to sex or HACA status is necessary.

2.4.5. Conclusion on clinical pharmacology

Overall the PK parameters were similar to what was seen previously for rituximab and other monoclonal antibodies.

2.5. Clinical efficacy

This application for an extension of indication of Mabthera for the treatment of GPA/MPA is based on data from a single pivotal study, ITN021AI (RAVE). In addition, a summary based on the published

Phase II RITUXVAS trial was provided in this submission as supportive data. A number of publications of small uncontrolled investigator initiated studies involving rituximab in AAV (see table 5) was submitted. Most studies are small including only few patients treated with rituximab due to intolerance or treatment failure on conventional therapy with CYC. These studies will not be discussed as supportive of efficacy.

2.5.1. Dose response study

No specific dose response study was performed. The dose selection was based on the experience with the use of Mabthera in the approved heamatology indications and an investigator-sponsored, open-label study of patients with refractory AAV. In this study, rituximab 375 mg/m2 weekly for 4 weeks was used and induction of remission was achieved. The study assessed the clinical effects of rituximab 375 mg/m^2 once weekly for 4 weeks in combination with glucocorticoid in 11 patients with antineutrophil cytoplasmatic antibody (ANCA) associated vasculitis (AAV). Disease remission was induced in all 11 patients and glucocorticoids were tapered successfully in all patients. Ten patients achieved BWAS/WG scores of 0 within 6 months. Remission was maintained in all patients as long as B lymphocytes were undetectable. It was shown in the above mentioned study by Keough et al, that the rituximab dose chosen was able to induce remission in patients with AAV.

2.5.2. Main study

RAVE (Rituximab Therapy for the Induction of Remission and Tolerance in ANCA-Associated Vasculitis)

This was a Phase II/III, multicenter, randomized, active-controlled, double-blind, double-dummy, parallel-group, international trial of rituximab (375 mg/m^2 × 4 weekly doses) in patients with severe AAV.

Methods

Table 5. Study RAVE

Title	**RAVE (Rituximab Therapy for the Induction of Remission and Tolerance in ANCA-Associated Vasculitis)**
Design Center: US (8), NL (1)	Randomised, double-blind, 18-months, active-control, non-inferiority, multi-centre parallel group study. Blinding was maintained till End-of-Study at 18 months.
Induction treatment phase (Month 1-6)	Experimental: RTX 375 mg/m^2 at Week 1,2,3,4 Control: Oral CYC 2 mg/kg/day for 3-6 months@ (+ placebo -rituximab) Add on to both Experimental/Control: 1 gram IV pulse methylprednisolone Patients could switch to the other study arm in case of treatment failure
Maintenance treatment phase (Month 7-18)	Experimental: AZA-PLACEBO (from Week 4 on) Control: AZA 2 mg/kg/day (from Month 3-6 on) Patients were treated with RTX in case of relapse, in each study arm.
Inclusion criteria	Patients > 15 y, with GPA/MPA diagnosed according CHCC-criteria, with severe active disease requiring CYC (BVAS-WG ≥ 3). Both naïve/relapsing patients were eligible.
Stratification factor	Clinical study center and ANCA type (PR3 or MPO)
Number of subjects	200 aimed (ITT Experimental arm :99, Control-arm: 98)
Primary endpoint	Complete remission (BVAS-WG =0) without GC co-treatment at 6 months
Main secondary endpoint	Remission (BVAS-WG =0) at low level GC treatment (< 10 mg day)

BVAS/WG: Birmingham Vasculitis Activity Score for Wegener's Granulomatosis, GC=glucocorticosteroids, NL= Netherlands, y=year, @, duration dependent on clinical response, #followed by an oral prednisone down-taper. Depending on the patient's response, the investigator could repeat the IV GC administration for up to 3 times in the first 6 months. Prednisone tapering was to be completed by the Month 6 Visit in order to meet the definition of complete remission.

Study participants

Main Inclusion criteria:

Diagnosis type: had a diagnosis of WG or MPA according to the definitions of the Chapel Hill Consensus Conference.

Screening diagnosis: had newly diagnosed disease or must have had a disease flare

Disease activity: had active disease with a BVAS/WG ≥ 3 that would normally have required treatment with CYC.

Disease severity: had severe disease (i.e., one or more of the major BVAS/WG items listed in Table 2 of the protocol), or disease severe enough to require treatment with CYC.

ANCA status: was positive for either proteinase 3 (PR3)-ANCA or myeloperoxidase (MPO)-ANCA at the Screening Visit.

Patients with biopsy-proven, pauci-immune glomerulonephritis who did not have evidence of disease in non-renal organ systems were also eligible, provided that they were positive for PR3-ANCA or MPO-ANCA antibodies.

Main Exclusion Criteria:

Diagnosis: had a diagnosis of Churg Strauss syndrome as defined by the Chapel Hill Consensus Conference

Disease severity:

a. Limited disease: limited disease that would not normally be treated with CYC.

b. Severe disease: required mechanical ventilation because of alveolar hemorrhage. - Co-morbidities, such as allergies, infections, liver disease, renal disease, malignancies.

Treatments

Patients in both arms received 1 g intravenous (IV) pulse methylprednisolone (or an equivalent IV dose of another glucocorticoid preparation), followed by protocol-mandated oral prednisone taper (starting at 1 mg/kg/day, not exceeding 80 mg/day). Depending on the patient's presenting clinical and disease state, the investigator could repeat the IV glucocorticoid administration for up to, but not exceeding, 3 days of therapy (total of 3g methylprednisolone or dose-equivalent of another glucocorticoid preparation). Prednisone tapering was to be completed by the Month 6 Visit in order to meet the definition of complete remission.

The study consisted of two phases:

- a 6-month remission-induction phase followed by
- a 12-month remission-maintenance phase.

During the remission-induction phase, patients in the control arm received oral prednisone daily, rituximab placebo infusions once weekly for 4 weeks, and oral CYC daily (2 mg/kg/day) for 3 to

6 months. Patients in the experimental arm received oral prednisone daily, rituximab (375 mg/m^2) infusions once weekly for 4 weeks, and CYC placebo daily for 3 to 6 months.

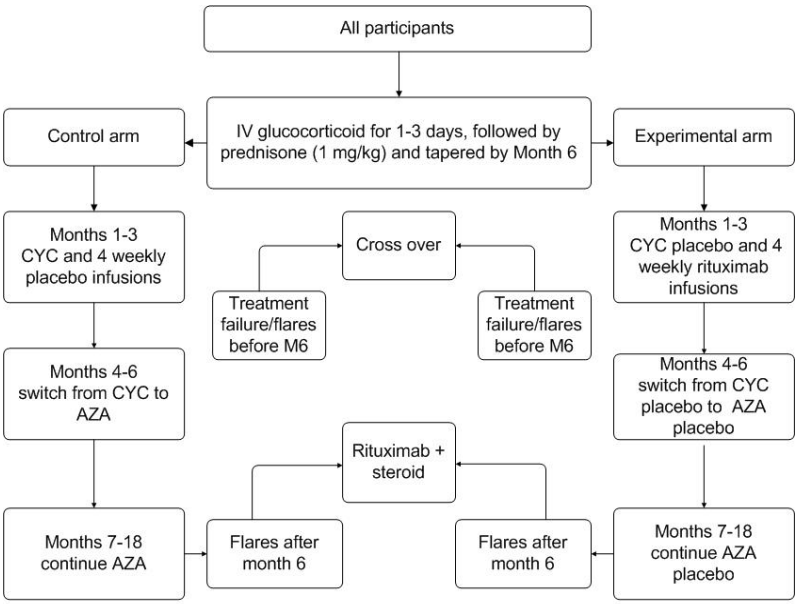
During the remission-maintenance phase, patients in the control arm discontinued CYC and started oral azathioprine (AZA) (2 mg/kg/day), and patients in the experimental arm discontinued CYC placebo and started oral AZA placebo daily. Both arms continued oral AZA/AZA placebo daily up to Month 18.

Upon achievement of remission in the RTX group, no additional maintenance therapy was to be provided to these patients. Patients in either group who achieved remission, defined as a BVAS/WG of 0 before completing 6 months of therapy, could stop induction therapy and start maintenance therapy after completing 3 months of induction therapy. An exception was that any patient who was in remission (BVAS/WG = 0) and developed hemorrhagic cystitis before Month 3 after his or her most recent rituximab/rituximab placebo infusion could start maintenance therapy.

Patients who experienced severe disease flares or treatment failure between Visit V5 (1 week after the last rituximab/rituximab placebo infusion) and Visit V8 (i.e., the Month 6 Visit) switched to the alternative treatment in a blinded manner (see Figure 1), unless specifically contraindicated. Patients who experienced severe flares during months 6 to 18 could be treated with open-label rituximab or according to best medical judgment if rituximab was contraindicated per the investigator's assessment.

An overview of study design is presented in Figure1.

Figure 1: Overview of design for RAVE



Objectives

The primary objective of RAVE was to demonstrate non-inferiority of rituximab efficacy as compared with conventional therapy (CYC/AZA) and superiority to historical control.

The secondary objective was superiority of rituximab to CYC for the percentage of patients who had a BVAS/WG of 0 and successfully completed the glucocorticoid taper by 6 months after randomization.

Outcomes/endpoints

The primary endpoint was the percentage of patients who achieved complete remission at Month 6, defined as a BVAS/WG of 0 and successful completion of the glucocorticoid taper at Month 6 (i.e., completely off glucocorticoids).

The secondary efficacy endpoint was testing of superiority of rituximab treatment at month 6.

The tertiary efficacy endpoints for RAVE were as follows:

- The cumulative BVAS/WG area under the curve (AUC) during the 6 months after randomization
- The percentage of patients who achieved and maintained partial remission as defined by having BVAS $\leq$ 2 and off glucocorticoids at Month 6
- The percentage of patients who achieved a BVAS/WG of 0 on prednisone $<$ 10 mg/day at 6 months
- The cumulative glucocorticoid dose at 6 months
- The number of severe flares (i.e., increase in BVAS/WG to $\geq$ 3 or experiencing one major BVAS/WG item requiring treatment with CYC) at 6 months
- The number of limited flares (new occurrence or worsening of one or more minor BVAS/WG items) at 6 months
- Laboratory markers of inflammation (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]) at 6 months

The endpoints for the assessment of long-term efficacy, assessed out to 18 months, included the duration of complete remission, and the time to limited and/or severe flare after complete remission in the two treatment groups.

The studies mentioned in this application used the BVAS or BVAS/WG and the Disease Extent Index (DEI).

Sample size

Based on the data from the WGET trial (Stone 2002), the sample size was calculated assuming that 70% of the patients receiving CYC or rituximab would attain complete remission during the first 6 months after randomization and that the non-inferiority limit for the difference in percentage complete remission between rituximab and CYC would be 20%. If the dropout rate was 10% and equally distributed between treatment groups, a sample size of 100 patients per arm would yield 83% power to conclude non-inferiority using a one-sided 0.025 level test. The sample size was to be re-evaluated if the assumptions (e.g., dropout rate) changed markedly during the study.

Randomisation

Two-hundred patients were to be randomized in a blinded way in a 1:1 ratio to the experimental (rituximab) or control arm (conventional therapy). Differences in organ involvement, prognosis, and relapse rate have been documented between proteinase 3 (PR3)-ANCA and myeloperoxidase (MPO)-ANCA and, thus, the randomization was stratified by clinical study center and type of ANCA (PR3 or MPO). Because the clinical types of AAV in RAVE have many overlapping features, and no data show a different response to medical interventions, the randomization was not further stratified by the type of AAV (WG or MPA). However, to ensure that the proportions of WG and MPA patients were similar to those in the AAV population, the maximum percentage of MPA patients was to be 50% of all AAV patients.

Blinding (masking)

This was a double blind study.

Follow-up

All patients were to be followed until 18 months after the enrolment of the last patient. After the Month 18 Visit, patients were to be treated according to best medical judgment (BMJ).

Statistical methods

Primary analyses were performed in the ITT population which included all randomised and treated patients. Two-sample comparisons were performed with the use of Student's t-test or a Wilcoxon rank-sum test for continuous measures and a chi-square test or Fisher's exact test for binary measures. Patients with missing data at Month 6 and patients who experienced early treatment failures -defined as failure to achieve disease response at Month 1, or inability to complete at least 3 infusions of rituximab or rituximab-placebo-, were considered as non-responders. As a secondary supportive analysis, PP (per=protocol) analyses and "as-treated" analysis was performed. The PP analysis population was a subset of the ITT analysis population that excluded patients without any BVAS/WG observation post randomization, patients with less than 75% of total 375 mg/m2 x 4 rituximab/placebo infusions and Patients with major protocol deviations. The "as-treated" population includes patients who fulfilled the protocol definition of early treatment failure but continued their initial treatment (under best medical judgment).

As a sensitivity analysis, the primary endpoint was also determined using Worst-Case Imputation for ITT patients who discontinued permanently from study treatment or withdrew from study before Month 6, beyond meeting the criteria of the definition of early treatment failures as stated above.

To assess the consistency of the study results, subgroup analyses were performed based on the following baseline variables: type of AAV (GPA or MPA), type of ANCA, newly diagnosed disease, relapsing disease, alveolar hemorrhage, and severe renal disease. There was no correction for multiplicity because they were pre-specified and had biologically plausible bases.

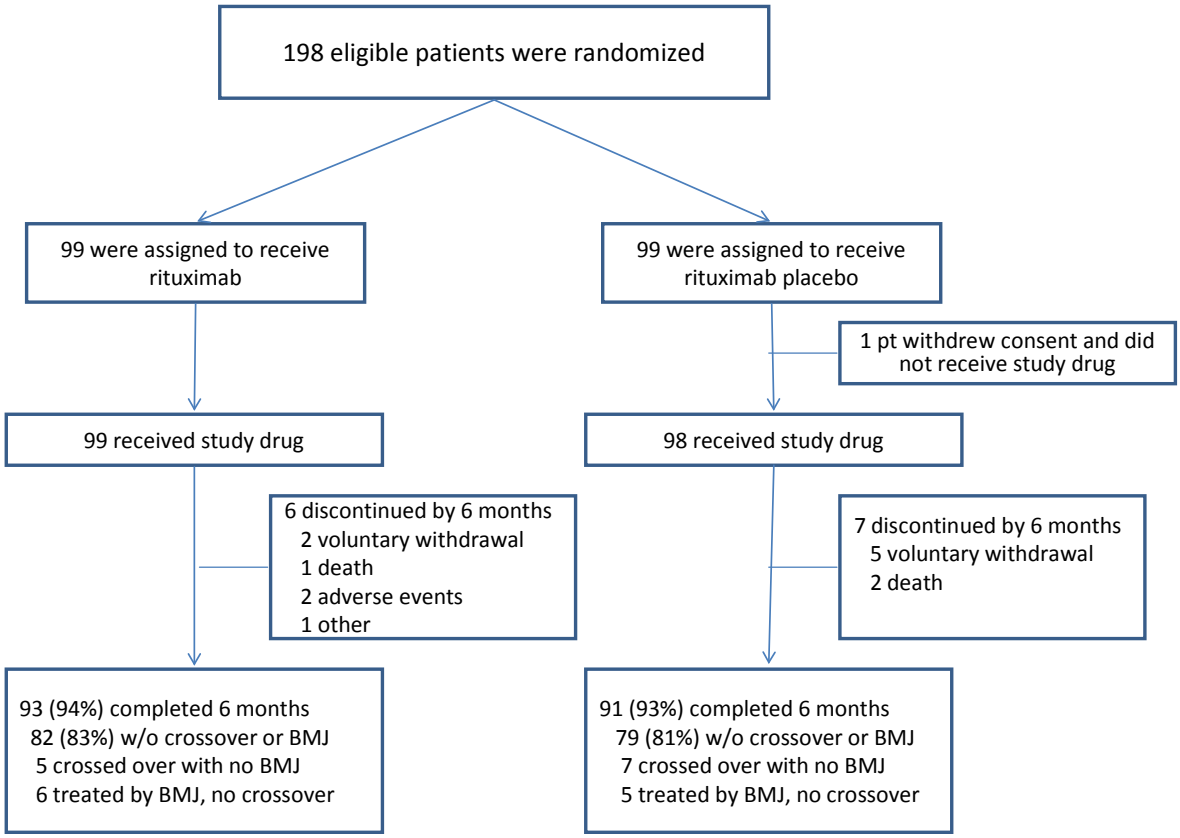
Non-Inferiority margin was predefined at -20% with an expected response rate of 80%. A 0.049 level of significance was used for the analysis of non-inferiority, to account for an interim efficacy analysis performed for the DSMB when half of the patients completed the 6-month' evaluation. As secondary analyses, superiority was tested for the primary and main secondary endpoint with X^2 test, after testing for non-inferiority.

Results

Participant flow

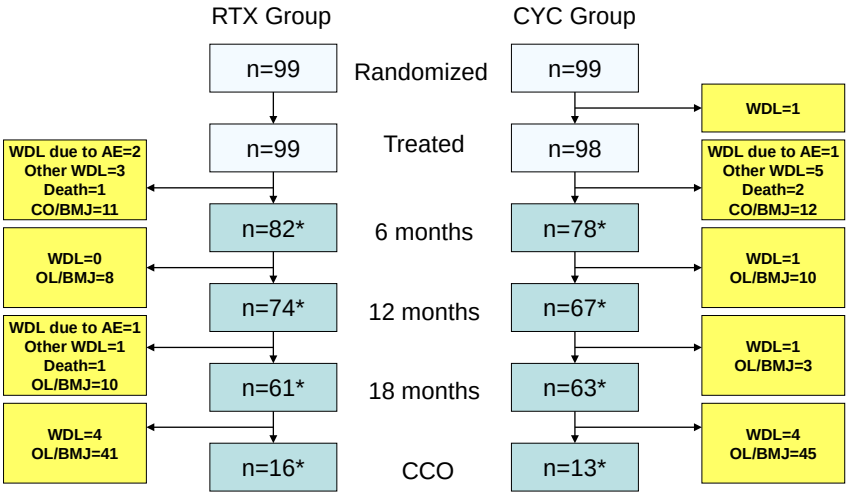
Eighty-two (83%) patients in the RTX group and 79 (81%) patients in the CYC group completed 6 months of the study without switching treatment or change to BMJ. During the maintenance phase of the study, patients in RAVE were followed up to a common closeout (CCO) date, corresponding to the last patient's 18-month visit. In total, 123 completed 18 months on their randomized treatment (61 of 99 [62%] on rituximab and 62 of 98 [63%] on CYC).

Figure 2 **RAVE: Patient Disposition During 6-Month Remission Induction Phase**



BMJ = best medical judgment.

Figure 3 **RAVE: Patient Disposition Until Common Closeout of the Study**



AE = adverse event; BMJ = best medical judgment; CCO = common closeout; CO = crossover; CYC = cyclophosphamide; OL = open-label rituximab; RTX = rituximab; WDL = withdrawal.
Notes: Patients may have switched therapy multiple times. Only the first switch (or withdrawal) is captured here.
Sixteen patients from the RTX group had repeat treatment with open-label rituximab (15 prior to 18 months and 1 after 18 months).
Thirteen patients from the CYC group received open-label rituximab (11 prior to 18 months and 2 after 18 months).
Mean follow-up times from randomization through CCO were 3.0 years in the RTX group and 2.8 years in the CYC group. *Completed as randomized.

Recruitment

The study was initially estimated to recruit 200 patients over an accrual period of 30 months. The study was initiated on 21 December 2004 and completed on 9 January 2009 for the 6 month analyses cut-off.

Conduct of the study

The original protocol version 1.0 issued on 1 July 2004, was amended 7 times. Main amendments were implemented in version 2 to add a secondary objective to demonstrate superiority of rituximab to conventional therapy, 2 tertiary objectives and 11 tertiary endpoints, including changing the secondary endpoint of percentage of patients in complete remission at 12 and 18 months to a tertiary endpoint. Other points added in this version were: secondary endpoints on treatment arm difference, duration of remission (combined with time to limited or severe flare after remission), percentage of patients who met criteria for clinical tolerance, risks associated with AZA. Amendments 6 and 7 occurred after the lock for the 6-month analysis. All amendments occurred before the final database closure which included the follow-up data for all patients.

Baseline data

Baseline demographic characteristics are presented in the following table.

Table 6 RAVE: Baseline Demographic Characteristics (ITT Population)

	Rituximab n = 99	Cyclophosphamide n = 98	Total n = 197
Age at screening, years			
Mean (SD)	54.0 (16.76)	51.5 (14.07)	52.8 (15.49)
Gender (%)			
Male	46.5	54.1	50.3
Female	53.5	45.9	49.7
Primary Race (%)			
White	91.9	94.9	93.4
Black or African-American	3.0	3.1	3.0
Asian	1.0	0.0	0.5
Other	4.0	2.0	3.0
Ethnicity (%)			
Not Hispanic or Latino	91.9	94.9	93.4
Hispanic or Latino	6.1	3.1	4.6
Unknown	2.0	2.0	2.0

Source: RAVE CSR, Table 14.1/7.1

Baseline Disease Characteristics

The majority of patients (74.6%) in RAVE had a diagnosis of WG, and 24.4% had a diagnosis of microscopic polyangiitis (MPA). One percent of the patients had an unknown AAV type.

Table 7 New/Relapsing Disease by AAV Type (ITT Population)

	MPA	WG	Indeterminate/ Missing	Total
All Patients	N=48	N=147	N=2	N=197
New Disease n (%)	39 (81.3)	56 (38.1)	1	96 (48.7)
Relapsing Disease n (%)	9 (18.8)	91 (61.9)	1	101 (51.3)
Rituximab Patients	N=24	N=73	N=2	N=99
New Disease n (%)	21 (87.5)	26 (35.6)	1	48 (48.5)
Relapsing Disease n (%)	3 (12.5)	47 (64.4)	1	51 (51.5)
Cyclophosphamide Patients	N=24	N=74		N=98
New Disease n (%)	18 (75.0)	30 (40.5)		48 (49.0)
Relapsing Disease n (%)	6 (25.0)	44 (59.5)		50 (51.0)

AAV = ANCA-associated vasculitis; ITT = intent to treat; MPA = microscopic polyangiitis; WG = Wegener's granulomatosis.

Renal involvement was almost identical in both groups (RTX 65.7% and CYC 66.3%). However, renal function expressed by creatinine clearance was markedly different with a mean clearance of 76.5 (RTX group) vs.91.4 (CYC group).

Approximately two-thirds of the patients in each arm were positive for classical ANCA (c-ANCA) by immunofluorescence, and the remaining one-third was positive for perinuclear-staining ANCA (p-ANCA)). Similarly, approximately two-thirds of the patients were positive for PR3-specific antibodies, and one-third was positive for MPO-specific antibodies.

Numbers analysed

Both the ITT and Safety populations included all 197 treated patients. The PP population included 188 (95.4%) patients and excluded 4 and 5 patients from the rituximab and CYC arms, respectively.

Outcomes and Estimation

- **Primary endpoint**

The following tables summarise the efficacy results of the primary endpoint.

Table 8 RAVE: Complete Remission at 6 Months after Randomization (ITT Population)

	Rituximab n = 99 n (%)	**Cyclophosphamide n = 98 n (%)**	**Difference in Rate**	**Two-sided 95.1% CI of Difference**
n [a]	98	95		
Complete remission	63 (64.3)	52 (54.7)	9.5	– 4.3, 23.4 [b]
95.1% CI	54.8, 73.8	44.7, 64.8		p = 0.177, χ^2 test

CI = confidence interval.

[a] Patients with non-missing results for complete remission at 6 months after randomization.

[b] The lower limit of the 95.1% CI for the difference, –4.3, was greater than –20 and thus met the protocol-specified non-inferiority criterion.

Source: RAVE CSR

After worst case imputation of missing Month 6 complete remission status, the results were similar, with a treatment difference of 10.6 (95.1%: – 3.2, 24.3) (Table 9).

Table 9 RAVE: Complete Remission (WCI) at 6 Months after Randomization (ITT Population)

	Rituximab n = 99 n (%)	Cyclophosphamid n = 98 n (%)	Difference in Rate	Two-sided 95.1% CI of Difference
n	99	98		
Complete remission (WCI)	63 (63.6)	52 (53.1)	10.6	– 3.2, 24.3 [a] p = 0.132, χ^2 test
95.1% CI	54.1, 73.2	43.1, 63.0		

CI = confidence interval; ITT = intent-to-treat; WCI = worst case imputation
[a] The lower limit of the 95.1% CI for the difference, –3.2, was greater than –20 and thus met the protocol-specified non-inferiority criterion.
Source: RAVE CSR

Similar results were obtained with the "as-treated" analysis (under which early treatment failures continuing on the initial treatment were not classified as primary endpoint failures but were instead assessed at Month 6) with either the ITT or PP populations; all analyses showed a treatment difference of approximately 10%, with a lower bound of the 95.1% CI for the difference exceeding – 5.

Complete Remission by Amount of Planned CYC dose Received

Table 10 below shows the primary endpoint of complete remission at Month 6 by subgroups of patients based on the CYC dose received.

Table 10 Patients Who Had Complete Remission at 6 Months, by Percentage of Protocol-Defined Initial Dose Received

Percentage of Protocol-Defined Dose Received	N	No (%) Patients who had Complete Remission at Month 6
≥ 80%	37	20 (54.1%)
65-80%	31	18 (58.1%)
<65%	29	14 (48.3%)

Note: the protocol-defined initial dose was adjusted for baseline weight and renal function only. WBC count and other lab tests were not taken into account.
source: t_comremw6_bycycdose

- **Secondary endpoints**

Cumulative BVAS/WG AUC during the First 6 Months

Using worst case imputation, the mean (SD) BVAS/WG AUC/month over the first 6 months was 1.29 (1.331) points for the RTX group and 1.25 (1.030) points for the CYC group. No significant difference was observed between the treatment arms.

Remission on < 10 mg/day Prednisone at 6 Months

Using worst case imputation, 70 patients (70.7%) in the RTX group achieved a BVAS/WG of 0 at 6 months while on < 10 mg prednisone per day. Fewer patients (61, 62.2%) in the CYC group achieved this outcome; however, the resulting treatment difference (8.5%) was not statistically significant).

Partial Remission

Using worst case imputation, 70 patients (70.7%) in the RTX group and 61 patients (62.2%) in the CYC group achieved a BVAS/WG ≤ 2 while off glucocorticoids at 6 months.

Exploratory Analysis—Remission

An exploratory analysis was conducted to determine the rate of remission (BVAS\WG = 0) regardless of prednisone use. Using worst-case imputation, 80 patients (80.8%) in the RTX arm achieved a BVAS/WG of 0 compared with 65 (66.3%) patients in the CYC arm, resulting in a treatment difference of 14.5 (95% CI: 2.3, 26.6), p = 0.021.

Severe and Limited Flares During the Remission Induction Phase

In the first 6 months after randomization, no significant difference in severe or limited flares was observed between the two treatment arms. In this analysis, flares that occurred after switching treatment were excluded. Five (5.1%) patients in the RTX group experienced a total of six severe flares, and 10 (10.2%) patients in the CYC group experienced a total of 10 severe flares. These events translated to a rate of 0.011 and 0.019 severe flares per patient-month in the RTX and CYC treatment groups, respectively (p = 0.293). Limited flares occurred at an equal rate of 0.026 per patient-month for both arms.

Cumulative Glucocorticoid Dose

During the 2 weeks prior to randomization, the median cumulative dose of methylprednisolone was 0 mg in both treatment arms. The median cumulative dose of prednisone was 240.0 mg in the RTX group and 270.0 mg in the CYC group.

From randomization through 6 months after randomization, IV administration of methylprednisolone was similar across treatment arms, with a median dose of 1000 mg for both arms.

The median cumulative dose of prednisone from randomization to 6 months was lower in the RTX group (3310.0 mg) compared with the CYC group (3450.0 mg; p = 0.055).

Ancillary analyses

RAVE Subgroup Analyses of Primary Endpoint

Complete Remission at Month 6 by Demographic Factors

Table 11 RAVE: Complete Remission at 6 Months by Demographic Factors (ITT Population)

	Rituximab Group n = 99	CYC Group n = 98	Difference 95.1% CI
Age			
< 52[a]	28/43 (65.1%)	25/48 (52.1%)	13.0 (– 7.1, 33.2)
≥ 52[a]	35/56 (62.5%)	27/50 (54.0%)	8.5 (– 10.3, 27.3)
< 65	43/63 (68.3%)	44/79 (55.7%)	12.6 (– 3.4, 28.5)
≥ 65	20/36 (55.6%)	8/19 (42.1%)	13.5 (– 14.2, 41.1)
Gender			
Male	28/46 (60.9%)	27/53 (50.9%)	9.9 (– 9.7, 29.5)
Female	35/53 (66.0%)	25/45 (55.6%)	10.5 (– 8.9, 29.9)

[a] Median age at screening.

Complete Remission at Month 6 by Baseline Disease Characteristics

Table 12 RAVE: Complete Remission at 6 Months by Baseline Characteristic Subgroups (ITT Population)

	Rituximab n = 99	CYC n = 98	Absolute Difference 95.1% CI	p-value [a]
Disease status				
New	29/48 (60.4%)	31/48 (64.6%)	−4.2% −23.6, 15.3	0.673
Relapsing	34/51 (66.7%)	21/50 (42.0%)	24.7% 5.8, 43.6	0.013
Renal Involvement				
≥ 1 major renal item on BVAS/WG	31/51 (60.8%)	32/51 (62.7%)	−2.0% −20.9, 17.0	0.839
No major renal item on BVAS/WG	32/48 (66.7%)	20/47 (42.6%)	24.1% 4.6, 43.6	0.018
Creatinine clearance, mL/min				
Cr Cl < 60	25/45 (55.6%)	18/28 (64.3%)	−8.7% −31.8, 14.3	0.461
Cr Cl ≥ 60	38/54 (70.4%)	34/70 (48.6%)	21.8% 4.8, 38.8	0.015
Serum creatinine, mg/dL				
Creatinine ≤ 1.2 [b]	36/52 (69.2%)	21/53 (39.6%)	29.6% 11.3, 47.9	0.002
Creatinine > 1.2 [b]	27/47 (57.4%)	31/45 (68.9%)	−11.4% −31.1, 8.2	0.256
Alveolar hemorrhage				
With alv hem	16/27 (59.3%)	11/23 (47.8%)	11.4% −16.3, 39.1	0.419
Without alv hem	47/72 (65.3%)	41/75 (54.7%)	10.6% −5.2, 26.4	0.190
ANCA Type				
MPO+	20/33 (60.6%)	21/33 (63.6%)	−3.0% −26.5, 20.5	0.800
PR3+	43/66 (65.2%)	31/65 (47.7%)	17.5% 0.7, 34.3	0.044
AAV Type				
MPA	16/24 (66.7%)	15/23 (62.5%)	4.2% −23.0, 31.3	0.763
WG	46/73 (63.0%)	37/74 (50%)	13.0% −2.9, 29.0	0.112
Systemic disease				
Yes	36/55 (65.5%)	35/65 (53.8%)	11.6 % −5.9, 29.1	0.197
No	27/44 (61.4%)	17/33 (51.5%)	9.8% −12.6, 32.3	0.387

BVAS/WG = Birmingham Vasculitis Activity Score for Wegener's granulomatosis; CI = confidence interval; MPA = microscopic polyangiitis; WG = Wegener's granulomatosis.

Note: A major renal item includes new or worsening events of the following two symptoms: RBC casts or rise in creatinine > 30% or fall in creatinine clearance > 25%.

Note: Results shown used worst case imputation for the primary endpoint.

[a] Two-sided χ^2 test of superiority.

[b] Median creatinine value at baseline.

Source: RAVE CSR Tables 9.3.5.1–9.3.5.4 and 9.3.5.7–9.3.5.11.

Change in ANCA Status Over 6 Months

Achievement of ANCA negativity after induction therapy has been associated with a lower rate of subsequent disease relapse. In addition to the hospital determination of baseline ANCA status, blood samples were collected at screening and at various time points after remission induction and were

analyzed for seroconversion. A total of 166 patients had a sample collected for the lab assay at Screening and a subsequent time point during the remission induction period (89% of patients in the RTX group and 80% of patients in the CYC group). Of these, the proportion of patients who became negative for ANCA was higher in the RTX group compared with the CYC group ($p = 0.050$). The greatest effect on becoming seronegative by 6 months was observed for patients who were PR3 + and were treated with rituximab ($p = 0.012$). The ability to induce seronegative results in MPO + patients was similar between the treatment arms.

Change from Baseline in Markers of Inflammation

In both groups, the ESR and CRP levels decreased between baseline and Month 6, with a larger improvement in the RTX group with respect to ESR levels: median reduction of 14 mm/hr vs. 3.0 mm/hr in the CYC group, and a difference in mean changes between the two arms of 7.6 mm/hr (95% CI: 2.2, 13.1), $p = 0.0064$.

The changes in CRP levels were comparable between the two arms, with a difference in means of 0.61 mg/dL (95% CI: – 0.50, 1.73), $p = 0.28$.

In exploratory analyses, age group (< 65, ≥ 65 years) was an important covariate, improving the estimation of the treatment effect. Adding the age group as an additional covariate in the ANCOVA model, the difference in mean reduction from baseline was 9.0 mm/hr (95% CI: 3.6, 14.5), $p = 0.0013$, for ESR and 0.88 mg/dL (95% CI: – 0.25, 2.00), $p = 0.13$, for CRP.

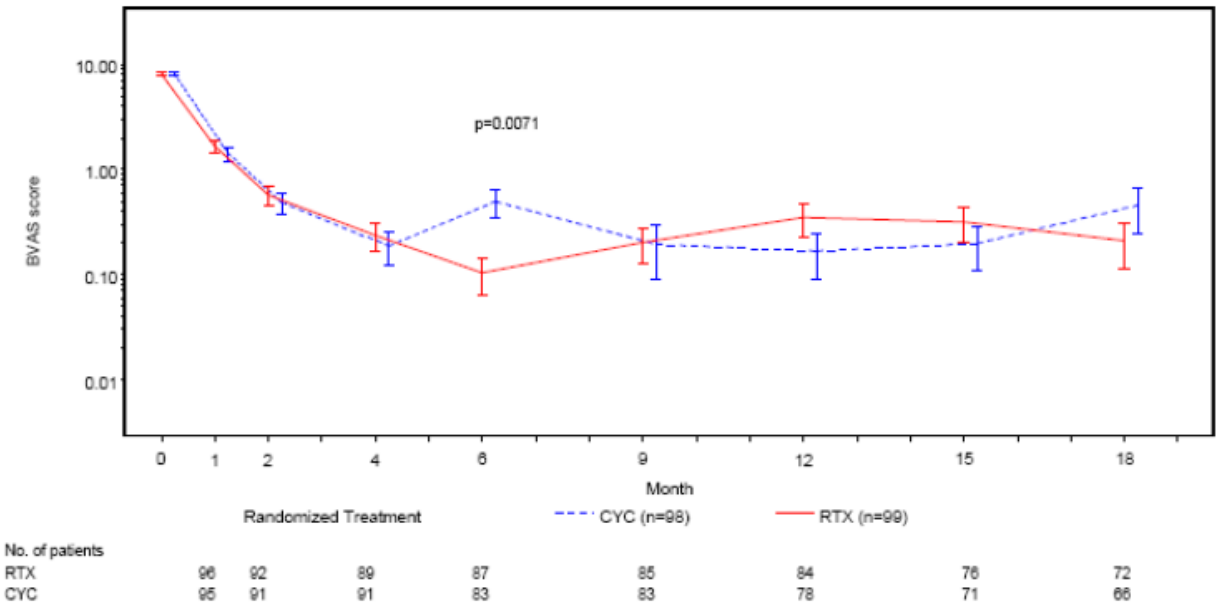
Additional exploratory analyses were performed to evaluate changes in other laboratory values relevant to AAV disease activity. The age group was included as a covariate in all these analyses.

Larger improvements were noted in the RTX group compared with the CYC group with respect to changes in hemoglobin ($p = 0.0025$), or hematocrit ($p = 0.0001$). Platelets were lower in both groups at Month 6, with smaller changes in the RTX group ($p = 0.0411$)

Patients in the CYC arm had a complete remission rate at 6 months of 54.7 % and a rate of remission on < 10 mg/day prednisone of 62.2%, while the remission rate regardless of the prednisone dose (BVAS/WG = 0) was 66.3%. These remission rates are consistent with the remission rate observed in the WGET study in patients with severe AAV treated with the same CYC regimen.

Onset of effect

Figure 4 Mean (SE) BVAS-WG scores in the study course



Persistence of Efficacy

Complete Remission and Remission on Background Corticosteroids.

Table 13 Remission rates according to different definitions of prednisone use (Worst-Case Imputation ITT analyses)

Timepoint	Rituximab (n=99)	Cyclophosphamide (n=98)	Difference (Two-sided 95% CI)
Complete Remission			
6 mos	63.6%	53.1%	10.6% (-3.2%, 24.3%)
12 mos	47.5%	38.8%	8.7% (-5.1%,22.5%)
18 mos	39.4%	32.7%	6.7% (-6.6%, 20.1%)
BVAS of 0 on prednisone dose of <10mg/kg/day			
6 mos	70.7%	61.2%	9.5% (-3.7%, 22.65%)
12 mos	59.6%	61.2%	-1.6% (-15.3%, 12.0%)
18 mos	54.5%	53.1%	1.5% (-12.4%, 15.4%)
BVAS of 0 irrespective of prednisone dose			
6 mos	78.8%	63.3%	15.5% (3.0%, 28.0%)*
12 mos	66.7%	63.3%	3.4% (-9.9%, 16.7%)
18 mos	56.6%	55.1%	1.5% (-12.4%, 15.33%)

Complete remission is defined as BVAS-WG=0 and no GC use, * p<0.05

Severe flares (rate per patient-month [cumulative nc		
6 mos	0.009 (5)	0.019 (10)
12 mos	0.014 (14)	0.020 (19)
18 mos	0.016 (22)	0.017 (23)
Limited flares (rate per patient-month [cumulative n		
6 mos	0.026 (14)	0.026 (14)
12 mos	0.029 (29)	0.024 (23)
18 mos	0.028 (38)	0.023 (30)

At 12 months, the proportion of patients who maintained complete remission was 47.5% in the RTX group and 38.8% in the CYC group. The treatment difference was 8.7% (numerically higher in the RTX

group), with 95% CI, −5.1% to 22.5%. At 18 months, the proportions of patients who maintained complete remission were 39.4% in the RTX group vs. 32.7% in the CYC group.

For the patients who met remission criteria at any glucocorticoid dose at 6, 12, or 18 months, the mean (median) cumulative prednisone dose in the RTX group was lower at all time-points when compared with the CYC group.

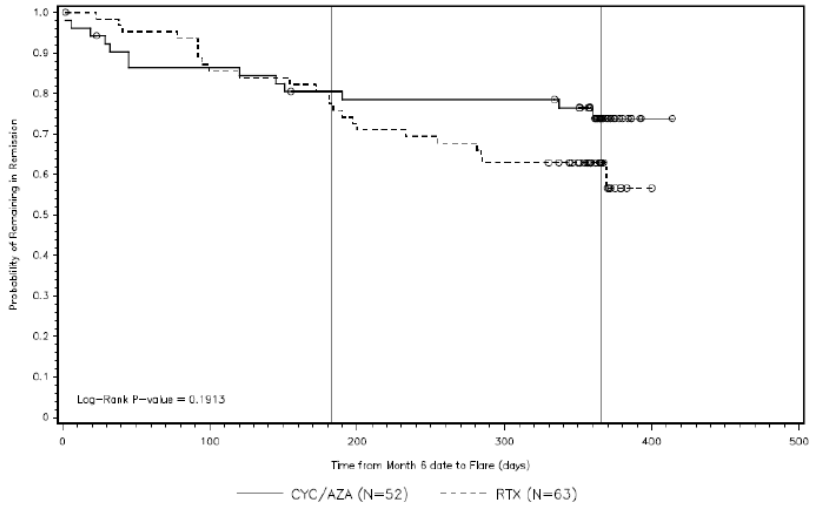
Exploratory analyses on the durability of complete clinical remission have been performed by demographic and disease characteristic subgroups (AAV type, ANCA type, renal involvement, history of alveolar hemorrhage, age, gender, presence of systemic disease). The results for both 12- and 18-month time points were consistent with those observed for the 6-month primary time point. In the RTX group, the highest remission rates were maintained by the patients with MPA, female patients, patients with systemic disease, and younger patients.

Time to flare analyses

For the Kaplan-Meier analyses of time to flare for patients who achieved complete remission, patients were censored at the time of withdrawal, switch of therapy, open-label rituximab, or BMJ, or at 18 months.

Figure 5.

Figure 10 Time to Flare from Complete Remission by Treatment Group



BWAS WG over time

The mean BVAS/WG for each treatment group was similar at all time-points during the maintenance period. The mean score was lower in the RTX group at Month 6 ($p < 0.01$), mirroring the results for remission (regardless of GC use).

Clinical Tolerance

Since the pre-specified definition of clinical tolerance requires that patients be off immunosuppression, and the CYC group received azathioprine during the maintenance phase of the study, tolerance can only be assessed for the rituximab group.

At 12 months, 41% of the rituximab patients achieved the Step 1 criterion of tolerance, with a similar breakdown for MPO + and PR3 + patients. Of these, in the MPO + group, approximately half were also ANCA negative, thus meeting the Step 2 definition of tolerance. Thus 21% of all MPO + patients met the Step 2 definition of tolerance at Month 12. A lower proportion of PR3 + patients (12% at Month 12) were in complete remission and also ANCA negative.

Applying the CD19 return criterion resulted in a total of 5 rituximab patients at Month 12 who met the Step 3 definition of tolerance. Findings at 18 months were consistent with the 12-month time-point.

B-cell Repletion and Maintenance of Efficacy in RAVE

The proportion of patients with ANCA-antibodies who became sero-negative for ANCA after induction treatment was higher in the rituximab arm compared with the CYC arm (44.3% vs. 28.0%, p = 0.050).

In the pivotal study RAVE, the number of peripheral-blood CD19+ B cells decreased to < 10 cells/µL after two infusions of rituximab and remained at that level in most patients through 6 months. In the RTX group, 87 of 92 patients (95%) had this degree of CD19+ depletion at 1 month. Among the 5 patients who did not have this degree of CD19+ depletion, 4 patients achieved the primary endpoint and 1 patient did not. At 6 months, 71 of 85 patients (84%) in the RTX group had this degree of CD19+ depletion. Among the 14 patients who did not have this degree of CD19+ depletion, 11 achieved the primary endpoint (79%). By Month 12, the majority of patients showed signs of B cell return with 66 of 82 (80.5%) patients with counts > 10 cells/µL. By Month 18, 61 of 70 patients (87.1%) had counts > 10 cells/µL.

Table 14: RAVE Study: % of patients with CD19+ B-cell counts < 10 /ul (median cell count levels).

	baseline	Month 1	Month 6	Month 12	Month 18
RTX	2.1% (median 211.9)	94.6% (1.0)	83.3% (1.8)	17.6% (60.8)	12.9% (107.8)
CYC/AZA	3.2% (153.5)	9.8% (48.6)	59.5% (8.1)	37.7% (13.1)	28.1% (15)

Supportive study

Study RITUXVAS

RITUXVAS was a Phase II, open-label, two-group, randomized study of 44 patients from eight centres in Europe and Australia. It was sponsored and conducted by the Cambridge University Hospitals NHS Foundation Trust (United Kingdom) and the European Vasculitis Study Group (EUVAS). Genentech was not involved in this study, and the summary provided in this submission is based on the published RITUXVAS data.

Methods

Inclusion criteria required a new diagnosis of AAV; ANCA positivity; and renal involvement, identified by either necrotizing glomerulonephritis on biopsy, red cell casts on urine microscopy, or haematuria (≥ ++) on urinalysis.

Prior to entry, patients were allowed plasma exchange or IV methylprednisolone (maximum 2 g) according to local practice for severe disease. After randomization, both groups received 1 g IV methylprednisolone and the same oral glucocorticoid regimen (initially 1 mg/kg/day, reduced to 5 mg/day at 6 months). Patients were randomized 3:1 to receive rituximab 375 mg/m^2 weekly for 4 weeks, plus IV CYC 15 mg/kg with the first and third rituximab infusions, or IV CYC pulse (15 mg/kg every 2 to 3 weeks, for 3 to 6 months) followed by AZA (2 mg/kg/day). (In this SCE, RITUXVAS patients in the experimental arm will be referred to as the RTX + low-dose CYC group or the RTX group.) Further rituximab or CYC was permitted for disease relapse. Relapses occurring before a minimum of 6 months of sustained remission were categorized as failures with respect to the primary

efficacy endpoint. Assessments were performed at 0, 1.5, 3, 6, 9, and 12 months and at relapse, which was defined as the appearance of any BVAS item attributable to active vasculitis.

Primary Outcome

The primary efficacy endpoint for RITUXVAS was sustained remission, defined as a BVAS score of 0 that was maintained for at least 6 months.

Secondary Outcomes

Secondary efficacy endpoints were time to remission, BVAS, change in GFR, prednisolone dose, and quality of life and disease damage (assessed through the Short Form 36 [SF-36] questionnaire and VDI between 0 and 12 months).

Results

Patients characteristics

Patients in RITUXVAS were all new-onset disease patients; median age of 68 yrs, disease severity of BVAS 19, all had renal insufficiency with a low GFR and a substantial proportion required dialysis.

Efficacy Results

Primary outcome

Sustained remission occurred in 25 of 33 patients (76%) in the RTX + low-dose CYC group and in 9 out of 11 patients (82%) in the CYC group. The absolute difference in sustained remission with rituximab compared with CYC was – 6% (95% CI: – 33, 21).

Among patients who reached 12 months, 93% of patients in the RTX + low-dose CYC group and 90% of patients in the CYC group achieved sustained remission. Reasons for not achieving sustained remission at 12 months included death (18% in the RTX + low-dose CYC group and 9% in the CYC group), re-treatment for incomplete remission (1 patient in the RTX + low-dose CYC group; subsequently led to full remission), and relapse within 6 months after achieving remission (1 patient from each treatment group). Nine patients were dialysis dependent at entry, 8 in the RTX + low-dose CYC group and 1 in the CYC group. Of these, 6 out of 8 patients from the RTX + low-dose CYC group had a sustained remission, with 5 patients becoming dialysis independent. The one patient from the CYC group who was dialysis dependent at the start of the study, died shortly after study entry.

Despite more severe AAV in the RITUXVAS population the proportion of patients who obtained remission at month 12 was higher than in the RAVE study; 76% to 82% (RITUXVAS) and 66% to 63% (RAVE). At month 12, 7 patients had died in the RITUXVAS compared to 3 patients in RAVE which can be explained by older age and more severe disease in RITUXVAS.

Secondary Outcomes

Time to Remission

Remission (defined in this study as a BVAS 2003 score of 0 for 2 months) occurred in 30 out of 33 patients (91%) in the RTX + low-dose CYC group and 10 of the 11 patients (91%) in the CYC group. The median time to remission was 90 days (IQR, 79–112 days) in the RTX + low-dose CYC group and 94 days (IQR, 91–100 days) in the CYC group.

BVAS 2003

In RITUXVAS, median BVAS fell from 19 (IQR, 14–24) at entry to 0 (IQR, 0–1.5) at 3 months in the RTX + low-dose CYC group and 18 (IQR, 12–25) at entry to 0 (IQR, 0–0) at 3 months in the CYC group.

Change in Glomerular Filtration Rate

The median estimated GFR (eGFR; mL/min/1.73 m^2) levels in the RTX + low-dose CYC group increased from 20 (IQR, 5–44) at entry to 39 (IQR, 20–45) at 12 months. In the CYC group, the median eGFR increased from 12 (IQR, 9–33) at entry to 27 (IQR, 12–47) at 12 months.

Prednisolone Dose

Prednisolone doses were reduced in both groups in accordance with the protocol, with 96% from the RTX + low-dose CYC group and 89% from the CYC group receiving 5 mg/day by 9 months. At 12 months, median weight-adjusted prednisolone doses (mg/kg/day) were 0.071 (IQR, 0.062–0.082) for the RTX + low-dose CYC group and 0.082 (IQR, 0.071–0.093) for the control group.

Quality of Life and Disease Damage

The median change in the VDI in the RTX + low-dose CYC group was 2 (IQR, 0–3) and was not significantly different from the CYC group's change of 1 (IQR, 0–2) ($p = 0.38$). Similarly, the treatment groups did not differ with respect to the change in the physical composite score of the SF-36 ($p = 0.36$).

The CYC group had an improved mental composite SF-36 score in comparison with the RTX + low-dose CYC group ($p = 0.04$); this difference was largely accounted for by 2 patients' scores in the RTX + low-dose CYC group. Exclusion of these 2 patients' data led to a $p = 0.32$.

2.5.3. Discussion on clinical efficacy

The development of rituximab in severely active Granulomatosis with polyangiitis and Microscopic polyangiitis, in combination with glucocorticoids is based on the anticipation of a long-term reduction of auto-antibody forming B-cells and on the hypothesis that depletion of B-cells could induce tolerance to self-antigens.

The MAHhas submitted 2 studies investigating the efficacy of rituximab in AAV; the pivotal RAVE trial and the supportive study RITUXVAS. Both were randomized and active-controlled – the RAVE study was also double-blinded. The inclusion and exclusion criteria are acceptable.

The choice of BVAS-WG as the instrument of the primary outcome is supported. This instrument is considered well validated to measure disease activity, without interference of pre-existing organ damage, and recommended to be used in trials on AAV by the EULAR. The definition of the primary outcome, BVAS-WG of 0, without any use of corticosteroids, is considered conservative, and supported.

No dose finding was performed. The dose rationale in the RAVE study was based on historical data, which show that the rituximab dose of 4 doses of 375 mg/m2 each given 1 week apart, was able to induce remission in patients with AAV, this is the same dose and posology as used in the approved indications.

In the pre-specified statistical analysis plan a non-inferiority margin of -20% was chosen and the lower boundary of the 95% CI for RTX remission should exceed 50% based on data from a historical control case series. Although the margin seems inadequate from a clinical point of view, the response rate was numerically higher in the experimental group versus standard therapy, and the lower limit of the CI was actually smaller than 5 %, no further concerns are raised on this issue. The fact that the lower limit of the 95% CI of the complete remission rate at 6 months in the RTX group was required to be $> 50\%$ is acceptable as a remission rate of approximately 70% after CYC treatment can be expected. A worst-case analysis has been included where missing data were recorded as treatment failures. This strengthens the robustness of the analyses.

Oral CYC became the standard regimen for severely active AAV and is considered acceptable as a comparator in this trial.

Patient disposition is adequately described and is compatible with characteristics of patients enrolled in recent studies of severe AAV. The WG and MPA patients were evenly distributed between treatment groups. Baseline characteristics were similar in the two arms except for gender (more females in the RTX group and more males in the CYC group) and age (the RTX population was older). It seems that the RTX patients had a worse baseline renal function compared to the CYC patients. The observed imbalances do not affect the overall conclusion.

Compared to RAVE the patients in RITUXVAS were all new-onset disease patients; they were markedly older (68 yrs vs. 52 yrs), and had much more severe disease (BVAS 19 vs. 8), all had renal insufficiency with a low GFR and a substantial proportion required dialysis.

A high rate of study adherence up to month 6 was observed in both treatment arms.

The RAVE study reached its primary goal by showing convincingly that RTX was non-inferior to oral CYC + AZA as at month 6 there were 64% of patients in the RTX arm in remission vs. 55% in the CYC arm. There were, however, major differences according to study centre. Patients treated at the Mayo Clinic had a remission rate of over 92% in the RTX arm compared to all other centres where the remission rate combined was 53.4%. Subgroup analyses showed that relapsing disease responded markedly better with RTX compared to CYC probably because these patients had undergone previous treatment cycles with CYC and therefore could be regarded as at least partial CYC failures. The response rate in newly diagnosed disease was slightly in favour of CYC (65% CYC vs. 60% RTX). The study failed to show superiority of RTX compared to CYC (secondary endpoint). In contrast to the CYC arm, there was no maintenance treatment with immune-suppressive drugs in the RTX arm. It was hypothesized a-priori, that the reduction of B-cells by rituximab could induce tolerance to MPO or PR-3. However, this was not confirmed by the data.

Patients in relapse at randomisation responded better to RTX induction therapy than re-treatment with CYC, as may be expected (difference 24.7%, 95% CI 5.8-43.6). In the newly-diagnosed patients, response to RTX was numerically less than for CYC (difference -4.2%, 95% CI -23.6-15.27). This is considered as relevant information for the prescribers at choosing between the two treatment options, and therefore subgroup-analyses are included in the SPC section 5.1.

The proportion of patients in the RTX group who achieved complete remission was numerically higher than in the CYC group; however, the 9.5% difference was not statistically significant (95.1% CI for the difference: -4.3%, 23.4%; $p = 0.177$, χ^2 test;). The outcome was similar using the worst case imputation (95.1% CI for the difference: -3.2%, 24.3%; $p = 0.132$). While the rituximab remission rate at 6 months was not statistically significantly superior to CYC at 6 months, the lower limit of the 95% CI of the complete remission rate at 6 months in the RTX group exceeded 50%, which was based on the upper bound of the 95% CI of the survival rate of the Walton cohort at 6 months. The mortality rate by 6 months is 1% (1/99) in rituximab-treated patients versus historical of 63% (35/56) mortality rate at 6 months in the patients described by Walton (), which is still significant even when considering advances in supportive medical care over the previous five decades.

Patients in the CYC arm had a complete remission rate at 6 months of 54.7 % and a rate of remission on < 10 mg/day prednisone of 62.2%, while the remission rate regardless of the prednisone dose (BVAS/WG = 0) was 66.3%. These remission rates are consistent with the remission rate observed in the WGET study in patients with severe AAV treated with the same CYC regimen. Based on this, the ability of CYC treatment to induce remission at 6 months remains greater than 20 percentage points, the protocol-specified non-inferiority margin M_2, with a likely treatment effect of approximately 50%.

Considering the mean BVAS scores in the first months of treatment, it seems that onset of the clinical effect is similar between both treatments. A sudden increase in BVAS scores was noted at 6 months in the CYC arm. This is concurrent with end of CYC induction therapy, and conversion to maintenance therapy with AZA, a milder acting immune-suppressive drug.

Rates of remission defined as BVAS/WG of 0 on a prednisone dose of < 10 mg/day and rates of remission irrespective of prednisone dose were similar across treatment groups at 6, 12, and 18 months. The results were generally consistent in the observed-case analysis and the worst-case analysis.

The time to flare analyses indicated that, the proportions of patients who remained in complete remission were comparable up to 12 months after randomization. After 12 months, the proportion of patients remaining in complete remission was numerically lower in the RTX group than in the CYC group. More severe flares occurred between 12 and 18 months in the RTX than CYC group (8 vs. 4). Between 6 and 18 months, more limited flares also occurred in the RTX than CYC group (24 vs. 16). The slightly higher number of limited flares after 6 months in the RTX group may partly be due to the lack of AZA maintenance and less GC use in this treatment group, as well as B-cell repletion.

There was a tendency of lower rate of serious flares under rituximab than under CYC in the induction phase. Flare rates, however, increased again at longer-term follow-up in the rituximab arm, when CD19+ B cells re-emerged. This raises the question whether follow-up maintenance therapy with rituximab, or other immune-suppressive drugs, is indicated. This issue cannot be solved by the available data, and future studies are required to establish the optimal maintenance therapy to prevent relapses, after rituximab induction treatment. A general recommendation was included in section 5.1. of the SmPC stating that maintenance therapy with immune-suppressant drugs may be considered after induction therapy with RTX, to prevent relapses, especially for patients considered at high risk.

In the pivotal study RAVE, the proportion of patients who became sero-negative for ANCA after induction treatment was higher in the rituximab arm compared with the CYC arm (44.3% vs. 28.0%, p = 0.050).

The use of the level of CD19+ B cells as a biomarker is justified as it is recognized that CD19 has been suggested as a therapeutic target in autoimmune diseases. The number of peripheral-blood CD19+ B cells decreased to < 10 cells/µL after two infusions of rituximab and remained at that level in most patients through 6 months. In the RTX group, 87 of 92 patients (95%) had this degree of CD19+ depletion at 1 month and 71 of 85 patients (84%) still had it at 6 months. However, the patients who didn't achieve depletion of B cells, still achieved the primary endpoint. By Month 12, the majority of patients showed signs of B cell return with 66 of 82 (80.5%) patients with counts > 10 cells/µL. By Month 18, 61 of 70 patients (87.1%) had counts > 10 cells/µL. In the CYC group, peripheral-blood CD19+ B-cell counts also decreased, but the rate and magnitude of the decrease were less than in the RTX group, and B-cell recovery appeared to occur more slowly. Of note, the majority of the CYC group received AZA maintenance therapy between 6 and 18 months, which may have contributed to slower B-cell recovery, whereas the RTX group did not.

The RAVE data evaluating efficacy up to 18 months suggest that the benefit generated with a cycle of rituximab persists past 6 months despite the lack of AZA maintenance therapy in the RTX arm. Pharmacodynamic data suggest a significant return of CD19-positive B cells between 6 and 12 months. Peripheral B-cell repletion seems to not impact complete remission rates over time but may have an impact on the occurrence of severe or limited flares between 12 and 18 months, which were 17 severe flares and 24 limited flares in the RTX arm compared with 13 severe flares and 16 limited flares in the CYC arm. It follows that B-cell depletion and ANCA-negative status might be associated with lower relapse rate and that PR3-ANCA positive patients, patients with GPA and relapsing disease at baseline might be associated with a higher risk of relapse, however these associations are only suggestive and

are not reliable as biomarkers of disease activity. Circulating CD19+ B-cells declined more rapidly and intensively after RTX as compared to after CYC treatment and recuperated 12 month after RTX treatment. As patients in the CYC arm received AZA maintenance therapy after CYC induction, the B-cell count remained reduced.

Not all patients may be candidates for maintenance therapy with immune-suppressive drugs, as about 40% of the subject did not relapse after long-term follow-up. Of interest are the experiences from the Mayo Clinic (US), of 10 years monitoring of 108 AAV patients treated with rituximab induction and maintenance. In this population, all observed relapse-cases (53) occurred after reconstitution of B cells and were accompanied or preceded by an increase in ANCA levels, in all but one patient (Cartin-Ceba et al., Arthritis Rheum 2010;62 Suppl 10 :680)**.** A treatment modality based on monitoring ANCA and B-cells is planned to be developed further after approval, when more data become available from ongoing studies.

2.5.4. Conclusions on the clinical efficacy

The non-inferiority of rituximab to standard treatment in terms of inducing remission in patients with severe MPA / GPA was convincingly demonstrated. Since the trial was not designed to allow conclusions of follow-up treatment with rituximab the wording of the indication has been adequately amended to reflect that rituximab is indicated for induction-therapy only.
Although the dose recommendation of 4 x 375mg/ m2 is considered sufficiently justified, the lack of dose-finding studies conducted with rituximab in AAV needs to be addressed and it is recommended to the MAH to explore a flat, less frequent and in total lower dose of 2 x 1000 mg as dosing regimen. As a lower dose may have an impact on improving the safety profile, this is included in the RMP (see discussion on Clinical Safety).

Patients in relapse at randomisation, appeared to respond better to rituximab induction therapy than re-treatment with CYC, as may be expected, however, a definite conclusion cannot be made due to the exploratory nature of the analysis. These data may be considered as relevant information for the prescribers and therefore subgroup-analyses are included in the SPC section 5.1.

The data showed that after 12 months the RTX patients experienced an increasing number of flares indicating that supplementary immunosuppressant drugs or retreatment with RTX are needed beyond month 12. Thus it recommended to add information in section 5.1 that maintenance treatment with immune-suppressants should be considered for relapse prevention, especially for patients at risk (i.e. with a history of earlier relapses and GPA, or in patients with a reconstitution of B-lymphocytes and PR3- ANCA at monitoring). Future studies are required to establish the optimal maintenance therapy to prevent relapses, after rituximab induction treatment. In this respect, study MAINRITSAN I is planned for completion in December 2013, and as agreed in the context of the RMP, data will be submitted to the CHMP for review. Furthermore, study RITAZAREM comparing rituximab to azathioprine as maintenance therapy in relapsing AAV is planned to be completed in 2016.

2.6. Clinical safety

Introduction

Rituximab has been in use since the late 90s initially for haematological indications and has subsequently received MA for rheumatoid arthritis. It is estimated that around 2 million patients have

been treated with this compound, thus a considerable amount of information regarding its safety profile has been made available. Adverse drug reactions (ADRs) of main importance are primarily infusion reactions within 24 hours after the infusion (either allergic or caused by the cytokine release syndrome), cardiac disorders, haematological abnormalities such as leukopenia, increase in the rate of infections among which reactivation of hepatitis B can be fatal and Progressive Multifocal Leukoencephalopathy (PML), which is often associated with immunosuppression due to cytotoxic treatment as in the NHL population, although a few cases have been reported in RA patients without concomitant immunosuppressive treatment.
In the pivotal study RAVE the primary safety analysis was based on the safety population, which included all patients who were randomized and who received at least one dose of the following study drugs: rituximab/rituximab placebo or CYC/CYC placebo.

Safety data were also obtained from RITUXVAS and published studies with rituximab in AAV.

Patient exposure

Primary Safety Analysis: RAVE

Disposition and Duration of Follow-Up Up to 6 months from randomization:

A total of 197 randomized and treated patients, all of whom received at least one dose of any study drug, were included in the safety analysis: n = 99 in the RTX group and n = 98 in the CYC group. At the 6-month analysis, a similar proportion of patients in each treatment group had remained on randomized treatment without switching or a change to a different treatment under BMJ (86 patients in the RTX group comprising the RTX only group and 85 patients in the CYC group comprising the CYC only group). The majority of patients in both groups completed the first 6 month study period (93 of 99 [94%] and 91 of 98 [93%] in the RTX and CYC groups, respectively). Safety information was summarized from randomization until the Month 6 visit or the point of study discontinuation, whichever occurred earlier, to yield a total duration of follow-up of 47.6 patient-years in the RTX group and 47.0 patient years in the CYC group. The follow-up time in the RTX only and CYC only groups was 41.9 and 40.5 patient years, respectively. Since only a small proportion of patients switched to the opposite treatment or received different treatment according to BMJ or as a result of a deviation from study drug administration during the first 6-month study period, the duration of follow-up for these patients was very limited (5.7 patient-years in the RTX other group and 6.5 patient-years in the CYC other group).

Up to 18 months from randomization, mean follow-up times were 1.4 years (16.8 months) in both treatment groups. From randomization to the CCO date, mean follow-up times were 3.0 and 2.8 years in the RTX and CYC groups, respectively.

In total, 123 patients completed 18 months on their randomized treatment (61 of 99 [62%] on rituximab and 62 of 98 [63%] on CYC) Twenty-nine patients remained on original treatment at the date of the CCO.

For the 18-month analysis, a total of 139.6 and 134.7 patient-years of follow-up were accrued in the RTX and CYC groups, respectively. For the analysis through the CCO date, patient-years of follow-up were 299.2 in the RTX group and 274.7 in the CYC group. For sensitivity analyses in which data were summarized until the point of treatment switch, patient-years of follow-up were 168.4 for the RTX group and 136.1 for the CYC group.

Extent of Exposure to Rituximab

All patients received at least one infusion of rituximab or rituximab placebo. The median cumulative dose of rituximab in the RTX group was 1500 mg/m^2 (range of 742 to 1687 mg/m^2) at month 6. The

total amount (volume) of infusions received was similar in both treatment arms, with the vast majority of patients (97% in both group) receiving ≥ 75% of the planned total amount.

Since the 6-month time point, 15 patients in the RTX group have received an additional course of open-label RTX between Months 6 and 18 and 11 patients have received at least one course of open-label rituximab in the CYC group. After 18 months, 1 additional patient in RTX group and 2 additional patients in CYC group received their first open-label rituximab treatment. In addition, 7 patients in the CYC arm received RTX due to switch to BMJ prior to 6 months.

Additional Data: RITUXVAS

Forty-four patients were randomized (33 to rituximab - low-dose CYC and 11 to CYC followed by AZA). Of these, 27 in the RTX - low-dose CYC group and 10 in the CYC group completed the full 12 month follow up. The total patient-years of follow-up were not reported.

All patients received methylprednisolone 1 g IV followed by oral steroids. Patients randomized to rituximab also received two doses of IV CYC; 2 patients in the RTX + low-dose CYC group received a third CYC dose (one treatment failure and one protocol violation).

Additional information regarding total dosages of study drug was not reported.

Additional Data: Other Published Investigator Initiated Studies

In total, a further 162 patients with AAV were exposed to rituximab in 12 published investigator-initiated studies. Patients generally received GC therapy and a number of different immunosuppressive therapies concomitantly with rituximab, most commonly CYC. Duration of follow-up varied between 3 and 55 months across patients in these studies.

Adverse events

Primary Safety Analysis: RAVE

Overall Adverse Event Profile

Up to 6 months:

The proportion of patients with adverse events leading to a permanent discontinuation of study drug was slightly higher in the CYC group (13.3%) compared with the RTX group (8.1%).

The proportion of patients who reported any selected adverse event was numerically lower in the RTX group (22.2%) than in the CYC group (34.7%). However, the rates of selected adverse events were similar between the two treatment groups (0.78 events/patient year in the RTX group vs. 0.96 events/patient-year in the CYC group; p-value = 0.250). 10 [10.1%] in the RTX group vs 4 [4.1%] in the CYC group required hospitalization, which was considered by the investigator to be related to disease activity or study therapy. Of the 10 patients who were hospitalized in the RTX group, 5 received rituximab only (RTX only group), while the remaining 5 received other therapies after receiving rituximab (RTX other group). All 4 patients in the CYC group received CYC only, without a different treatment by switching treatment or BMJ (CYC only group). However, these hospitalizations were due to serious adverse events, which were balanced across the two groups.

The incidence of events of special interest for rituximab, such as serious infections, serious cardiac adverse events, and malignancies, was similar across the two treatment groups over the 6-month treatment period. A similar proportion of patients experienced infusion reactions in each group.

Table 15. Selected AEs of interest in Induction period (first 6 months).

	Rituximab N=99	Cyclophosphamide N=98
Selected AE	**22 (22.2%)**	**34 (34.7%)**
Death (all causes)	1 (1.0%)	2 (2.0%)
Grade ≥2 leukopenia	5 (5.1%)	17 (17.3%)
Grade ≥2 thrombocytopenia	3 (3.0%)	1 (1.0%)
Grade ≥3 infections [a]	10 (10.1%)	10 (10.2%)
Hemorrhagic cystitis [b]	1 (1.0%)	1 (1.0%)
Malignancy	1 (1.0%)	2 (2.0%) [c]
Venous thromboembolic event [d]	5 (5.1%)	9 (9.2%) [e]
Hospitalization related to disease activity or study therapy per the investigator's assessment [f]	10 (10.1%)	4 (4.1%)
Cerebrovascular accident	0	0
Infusion reaction leading to study drug discontinuation [g]	1 (1.0%)	0
Other AEs of special interest		
Infusion-related reaction [h]	12 (12.1%)	11 (11.2%)
Any infection [i]	61 (61.6%)	46 (46.9%)
Serious infection [i]	11 (11.1%)	10 (10.2%)
Serious cardiac AE	1 (1.0%)	2 (2.0%)

[a] Includes 1 patient in the cyclophosphamide group who reported an event of Grade 3 infection on the Selected AE Case Report Form page but not on the AE Case Report Form page.
[b] Grade 2 hemorrhagic cystitis had to be confirmed by cystoscopy.
[c] Includes one malignancy and one pre-malignant event (high-grade prostate intraepithelial neoplasia in Patient 001015), which was reported as a malignancy by the investigator on the Selected AE Case Report Form page.
[d] Includes deep venous thrombosis or pulmonary embolism.
[e] Includes 1 patient (004016) who reported an event of deep vein thrombosis on the AE Case Report Form but not on the Selected AE Case Report Form.
[f] Resulted either from the disease or from a complication in study treatment per investigator assessment.
[g] Infusion reaction (per Principal Investigator assessment) within 24 h of an infusion that results in cessation of further infusions.
[h] Infusion-related reaction in RAVE is defined as adverse events occurring within 24 hours of an infusion and considered infusion-related by the investigator.
[i] Infection is any AE coding to the MedDRA system organ class of infections or infestations; serious infection refers to such events reported as serious adverse events.

Sub f: The primary reason for hospitalization for patients in the RTX arm included leukopenia (n=3), pneumonia, pulmonary hemorrhage, renal failure, pulmonary embolism, osteomyelitis, bronchitis, and hypersensitivity. Reasons for hospitalization for patients in the CYC arm included pneumonia (n=2), acute respiratory distress syndrome, and upper respiratory tract infection

Up to 18 months:

The overall 18-month adverse event profile in the RAVE safety population was generally consistent with the profile at 6 months and comparable between the treatment groups. Incidences and rates per patient-year of any adverse event, selected adverse events, Grade ≥ 3 adverse events, serious adverse events, and serious infections were similar across treatment groups. While a higher proportion of patients in the RTX group experienced infections, the rates of infection per patient-year were similar between the groups at 18 months. The proportions of patients who experienced Grade ≥ 3 adverse events were similar across the treatment groups. However, a higher proportion of patients reported Grade 4 events in the RTX group; with the difference largely due to disease-related respiratory and renal system events.

Results of the sensitivity analysis excluding events that occurred after switch of therapy were generally consistent with those from the primary 18-month analysis.

The overall numbers and rates of adverse events were similar across the RTX and CYC groups. Of these common events, those with an absolute increase of ≥5% in incidence in the RTX group over the CYC group were diarrhoea (24.2% vs. 17.3%), peripheral oedema (20.2% vs. 12.2%), urinary tract infection (UTI) (16.2% vs. 6.1%), and cough (28.3% vs. 18.4%). These differences are consistent with those reported at the 6-month time point except for the imbalance in UTI, the incidence of which had been similar in both treatment groups at 6 months (5% vs. 3% in the RTX vs. CYC group, respectively).

The higher proportion of patients with hypertension in the RTX group compared with the CYC group that was observed at 6 months remained at 18 months but was less marked. Of note, these events were self-limiting and did not lead to permanent discontinuation of study medication.

Common adverse events with an increased incidence (≥ 5%) in the CYC group compared with the RTX group were leucopenia (and decreased WBC), nausea, increased ALT and AST, rash, alopecia, RBC sedimentation rate increased, haematuria, haematocrit decreased, vomiting, pyrexia, and fatigue. Compared with the 6-month data, more adverse event terms were reported at an increased incidence (≥ 5%) in the CYC group compared to the RTX group by 18 months.

Table 16. Selected AEs of interest (total study duration 18 months).

	Rituximab N=99	Cyclophosphamide N=98
Selected AE	**33 (33.3%)**	**42 (42.9%)**
Death (all causes)	2 (2%)	2 (2%)
Grade ≥ 2 leukopenia	7 (7.1%)	23 (23.5%)[b]
Grade ≥ 2 thrombocytopenia	4 (4.0%)	1 (1.0%)
Grade ≥ 3 infections[c]	14 (14.1%)	14 (14.3%)
Hemorrhagic cystitis[d]	2 (2.0%)	1 (1.0%)
Malignancy	2 (2.0%)	1 (1.0%)
Venous thromboembolic event[e]	5 (5.1%)	8 (8.2%)[f]
Hospitalization related to disease activity or study therapy per the investigator's assessment[g]	13 (13.1%)	5 (5.1%)
Cerebrovascular accident	0	0
Infusion reaction leading to study drug discontinuation[h]	1 (1.0%)	0
Other AEs of special interest		
Infusion-related reaction[i]	14 (14.1%) j	12 (12.2%) j
Any infection[k]	79 (79.8%)	69 (70.4%)
Serious infection[k]	15 (15.2%)	15 (15.3%)
Serious cardiac AE	2 (2.0%)	2 (2.0%)

Up to Common Closeout Date:

The overall adverse event profile up to the CCO date was, in general, consistent with that observed at 18 months with one exception: a higher proportion of patients reported serious adverse events in the RTX group than in the CYC group (60% vs. 48%). However, the rate of serious adverse events was comparable between the treatment groups (0.41 vs. 0.36 per patient-year). The difference in the proportion of patients who experienced Grade 4 events between the two treatment arms (all but one of which was also reported as serious) was greater through the CCO date than what was observed at 18 months. In addition, several malignancies were diagnosed between 18 months and the CCO date.

Adverse Events by Severity

Up to 6 months

The majority of patients in both groups experienced adverse events of, at worst, mild-to-moderate intensity: Grade 1 - RTX group 20.2%, CYC group 22.4%; Grade 2 - RTX group 45.5%, CYC group 40.8%. Overall, similar proportions of patients experienced Grade ≥ 3 events in the RTX and CYC groups.

There were three Grade 5 (fatal) events: 1) multi-organ failure in a rituximab treated patient who received rituximab followed by CYC treatment according to BMJ 16 days after the first dose of RTX; 2) pneumonia in a CYC only–treated patient; and 3) septic shock also in a CYC only–treated patient.

Ten Grade 4 events occurred in 8 patients in the RTX group: pulmonary embolism (2 patients), leucopenia (2 patients), neutropenia (1 patient), accidental overdose of CYC placebo (1 patient), and pneumonia (1 patient) in the RTX only group and renal failure (1 patient), hyperkalemia (1 patient), and acute renal failure (1 patient) in the RTX other group

Four Grade 4 events occurred in 3 patients in the CYC group: febrile neutropenia, pneumocystis pneumonia, pulmonary embolism, and acute respiratory distress syndrome. All these events were reported in the CYC only group.

The most common type of Grade ≥ 3 events was infection, which occurred in 10 patients in each group. The most frequent Grade ≥ 3 infection included respiratory infections in both groups, most commonly pneumonia.

Up to 18 months:

The majority of patients in both treatment groups experienced adverse events of, at worst, mild-to-moderate intensity (Grade 1 or 2). Overall, the proportions of patients who experienced at least one Grade ≥ 3 event up to 18 months were similar between the two treatment groups (44.4% in the RTX group and 45.9% in the CYC group) Grade ≥ 3 events at 18 months had a similar profile to that observed at 6 months, including, most commonly, infections in both groups (13.1% in the RTX group and 13.3% in the CYC group).

In the RTX group, 39 patients experienced 81 Grade 3 adverse events, including 55 events up to the 6-month time point and 26 additional events between 6 and 18 months. In the CYC group, 79 Grade 3 events were reported in 43 patients by 18 months, with 56 events up to the 6-month time point and 23 events after 6 months. In both groups, the most common Grade 3 events were infections and disease-related respiratory disorders.

Overall, by 18 months, 10 patients in the RTX group experienced 13 Grade 4 adverse events and 4 patients in the CYC group reported 4 Grade 4 adverse events. This imbalance was attributable to disease-related respiratory and renal system events (4 vs. 2 events in the RTX and CYC arms, respectively) and haematological abnormalities (3 vs. 1 event, respectively), as well as to a number of individual events without a clear pattern.

The majority of Grade 4 events occurred prior to 6 months, with two events occurring between 6 and 18 months in the RTX group: an autoimmune thrombocytopenia (Patient 001007 patient narratives) and a suicide attempt (Patient 002025 patient narratives) in the RTX arm. The case of autoimmune thrombocytopenia occurred 8 months after the patient switched and received CYC. No additional Grade 4 adverse events were reported between 6 and 18 months in the CYC group.

In addition to the 2 deaths in the CYC group, both due to infections, and 1 death in the RTX group due to multi-organ failure attributed to underlying disease, reported up to 6 months, 1 additional death occurred in the RTX group after 6 months that resulted from PAH.

The majority of the Grade ≥ 3 adverse events (107 of 181, 59.1%) were also classified as serious. All but one Grade 4 adverse event (a case of neutropeniain the RTX group) were classified as serious.

Up to Common Closeout Date:

The analysis of adverse events collected through the CCO date shows a pattern consistent with that of the 18-month analysis. Overall, a slightly higher proportion of patients in the RTX group reported Grade ≥ 3 events compared with the CYC group (58.6% vs. 53.1%) as a result of a greater proportion of patients experiencing Grade 4 events in the RTX group. From randomization to the CCO date, 17 patients in the RTX group experienced 21 Grade 4 adverse events and 5 patients in the CYC group experienced 6 Grade 4 adverse events. Again, this imbalance was mainly attributable to disease-related respiratory and renal system events (9 vs. 4 events in the RTX and CYC arms, respectively) and hematological abnormalities (6 vs. 1 event, respectively).

Between 18 months and the CCO date, 1 CYC patient (001027 patient narratives) reported two Grade 4 events of renal failure, both occurring after the patient received therapy under BMJ. In the RTX group, 7 patients reported eight additional Grade 4 adverse events including anemia, cerebrovascular accident (CVA), WG, PAH, acute respiratory distress syndrome, PE, chronic renal failure, and aortic dissection. Four of these eight events (renal failure, CVA, WG, and aortic dissection) occurred after patients switched to therapy under BMJ. Given that most of the patients switched therapy to BMJ after 18 months, data collected after 18 months should be interpreted with caution.

Adverse Events by Relationship to Study Drug

Table 17. Adverse Drug Reactions occurring at 6-months in ≥ 5% of patients receiving MabThera, and at a higher frequency than the comparator group, in the pivotal clinical study.

Body System - Adverse event	Rituximab (n=99)
Blood and lymphatic system disorders	
Thrombocytopenia	7%
Gastrointestinal disorders	
Diarrhoea	18%
Dyspepsia	6%
Constipation	5%
General disorders and administration site conditions	
Peripheral oedema	16%
Immune system disorders	
Cytokine release syndrome	5%
Infections and infestations	
Urinary tract infection	7%
Bronchitis	5%

Herpes zoster	5%
Nasopharyngitis	5%
Investigations	
Decreased haemoglobin	6%
Metabolism and nutrition disorders	
Hyperkalaemia	5%
Musculoskeletal and connective tissue disorders	
Muscle spasms	18%
Arthralgia	15%
Back pain	10%
Muscle weakness	5%
Musculoskeletal pain	5%
Pain in extremities	5%
Nervous system disorders	
Dizziness	10%
Tremor	10%
Psychiatric disorders	
Insomnia	14%
Respiratory, thoracic and mediastinal disorders	
Cough	12%
Dyspnoea	11%
Epistaxis	11%
Nasal congestion	6%
Skin and subcutaneous tissue disorders	
Acne	7%
Vascular disorders	
Hypertension	12%
Flushing	5%

Up to 6 months:

A higher proportion of patients in the CYC group (58.1%) than in the RTX group (36.4%) had at least one adverse event probably or definitely related to study drug, per the investigator's evaluation.

The most frequent adverse events considered probably or definitely related to study drug, on the basis of the investigator's evaluation, in the CYC group were leukopenia (22.4%), decreased WBC count (11.2%), alopecia (8.1%), hyperglycemia (6.1%), and anemia (4.1%). The most frequent adverse events probably or definitely related to study drug, on the basis of the investigator's evaluation, in the RTX group included leukopenia (7.1%), cytokine-release syndrome (4.0%), and thrombocytopenia (4.0%).

Up to 18 months

Consistent with the 6-month analyses, by 18 months, a higher proportion of patients in the CYC group (70.4%) than in the RTX group (42.4%) had at least one adverse event probably or definitely related to study drug, per the investigator's evaluation.

The most frequent adverse events considered probably or definitely related to study drug, on the basis of the investigator's evaluation, in the CYC group were leukopenia (31.6%), decreased WBC count (15.3%), alopecia (8.2%), hyperglycaemia (6.1%), thrombocytopenia (5.1%), anemia (4.1%), and ALT increased (4.1%). The most frequent adverse events probably or definitely related to study drug, on the basis of the investigator's evaluation, in the RTX group included leukopenia (8.1%), cytokine-release syndrome (4.0%), thrombocytopenia (4.0%), WBC decreased (4.0%), and flushing (4.0%).

Up to Common Closeout Date:

The results of the analysis on data collected through the CCO date were consistent with the 18-month data.

Additional Data: RITUXVAS

Table 18: Safety summary of the supportive study RITUXVAS.

	Rituximab + Low-Dose Cyclophosphamide n=33	Cyclophosphamide n=11
No. (%) of patients experiencing		
Any AE	25 (76)	7 (64)
Grade ≥3 AE	14 (42)	4 (36)
Serious AE	16 (48)	4 (36)
Selected events of special interest		
Death	6 (18)	2 (18)
Hospitalization	12 (36)	4 (36)
Infection	12 (36)	3 (27)
Serious infection	6 (18)	2 (18)
Malignancy	2 (6)*	0
Infusion reaction	2 (6)	0
Neutropenia	2 (6)	1 (9)
Anemia	2 (6)	2 (18)
Thrombocytopenia	1 (3)	0
Hypogammaglobulinemia	1 (3)	0
AE rates/patient-year (95% CI)		
Grade ≥3 AEs	1.00 (0.69–1.44)	1.10 (0.61–1.99)
Infections	0.66	0.60

AE = adverse event.
* One occurred after 12 months

Serious adverse event / deaths / other significant events

Deaths

Primary Safety Analysis: RAVE

Up to 6 months:

In RAVE, 3 deaths occurred during the first 6-month period: 2 in the CYC group and 1 in the RTX group. The 2 deaths in the CYC group occurred in patients with newly diagnosed AAV. One patient who received CYC therapy followed by AZA, died on Study Day 123 of pneumonia that was considered possibly related to study treatment. This patient had a medical history notable for chronic obstructive pulmonary disease. One patient, who received CYC, died on Study Day 55 of septic shock, which was considered possibly related to study treatment. This event was preceded by a serious adverse event of *Pneumocystis* pneumonia despite prophylaxis (on Study Day 21) for which CYC treatment had been suspended. This patient also had a history of coronary artery disease and experienced a serious myocardial infarction during the study.

The 1 death in the RTX group was a patient randomized to rituximab who subsequently received CYC. This patient had a history of AAV for 18 months and relapsing WG with renal involvement at study entry. He received rituximab (three infusions) but was switched to BMJ after the onset of renal failure on Study Day 16, receiving open-label CYC until Study Day 36. The patient subsequently developed pancytopenia and sepsis and died of multi-organ failure approximately 1 month later. The event was attributed to the progression of AAV and considered unrelated to study treatment.

Up to 18 months:

Two patients in each arm died during the 18 months of study. One death was attributed to pulmonary alveolar haemorrhage 9 months into the maintenance phase in the RTX arm. This patient was treated with RTX induction, but for the subsequent 5 + 9 months was without any immunosuppressive therapy.

Up to Common Closeout Date:

There were no additional deaths reported between 18 months and the CCO date.

Additional Data: RITUXVAS

Eight deaths occurred in RITUXVAS, 6 (18%) in the RTX + low-dose CYC group prior to 12 months and 3 (27%) in the CYC group of which 2 occurred after 12 months. Only summary data on these deaths have been reported in the literature and data on one of the deaths in the CYC group is unpublished. The majority of the deaths occurred within 3 months of randomization, and the median time to death was 91 days (range of 22-330 days in the RTX + low-dose CYC group and range of 2-610 days in the CYC group). Compared with the overall study population, the patients who died were older (median age, 76 years; range, 63-84 years) and had low glomerular filtration rates (GFR; median GFR at baseline of 9 mLs/min/1.73 m^2), two known risk factors for death in this population. The causes of death were infections (RTX low-dose CYC group, n = 3; CYC group, n = 1), cardiovascular disease (RTX low-dose CYC group, n = 1; CYC group, n = 2), and complications of end stage renal failure (RTX + low-dose CYC group, n = 2).

Other Serious Adverse Events

Primary Safety Analysis: RAVE

In the safety population, 33 (33.3%) rituximab patients had a total of 46 serious adverse events and 33 (33.7%) CYC patients had a total of 54 serious adverse events during the first 6 months of treatment. The rate of serious adverse events per patient-year was 0.97 (95% CI, 0.72-1.29) in the RTX group and 1.15 (95% CI, 0.88-1.50) in the CYC group.

The rate of serious adverse events per patient-year was numerically lower in the RTX only group (0.69) compared with the CYC only group (0.94). Patients who switched treatment or who received a different treatment according to BMJ or as a result of errors in study drug administration had a numerically higher rate of serious adverse events per patient-year (RTX other: 2.98; CYC other: 2.47), although the data should be interpreted with caution because of the very limited sample size and duration of follow up in these groups. Patients in these groups had higher rates of disease exacerbation reported as serious adverse events, including renal failure, creatinine increase, and WG.

The most frequent serious adverse events in the overall safety population were DVT (10 patients, 5.1%), pneumonia (8 patients, 4.1%), anemia (5 patients, 2.5%), renal failure (including acute renal failure, 5 patients, 2.5%), and pulmonary embolism (4 patients, 2.0%). The only notable imbalance in these events between the RTX and CYC arms was in the incidence of serious DVT (2 patients in the RTX group vs. 8 patients in the CYC group). The reason for this imbalance is unknown.

There were three episodes of serious leukopenia reported in the RTX group. As noted previously, Grade ≥ 2 leukopenia, which includes nonserious events, occurred in a greater proportion of patients in the CYC group than the RTX group (17.3% vs. 5.1%).

Serious adverse events affecting the gastrointestinal system were observed in 4 patients in the RTX group compared with no patients in the CYC group. The serious gastrointestinal adverse events included diarrhea (2 patients, 2.0%) and ischemic colitis and upper gastrointestinal hemorrhage (1 patient each). The incidence of serious adverse events in each system organ class (SOC) was otherwise similar between treatment groups or lower in the RTX group than in the CYC group.

The SOC with the highest incidence of serious adverse events was infections and infestations (21 patients, 10.7% overall), with a similar proportion of patients reporting serious infections in the RTX (11, 11.1%) and CYC (10, 10.2%) arms.

The serious adverse event profiles between the RTX only and CYC only groups were similar to that observed between the RTX and CYC groups.

Up to 18 months:

The overall serious adverse event profile was similar in the RTX and CYC groups in RAVE through 18 months. In the safety population, 46(46.5%) rituximab patients had a total of 69 serious adverse events and 41 (41.8%) CYC patients had a total of 77 serious adverse events. The rates of serious adverse events per patient-year were comparable between the RTX (0.49 [95% CI, 0.39-0.63]) and CYC (0.57 [95% CI, 0.46-0.71]) groups. These rates were lower than those reported for the first 6 months of the study (0.97 [95% CI, 0.72-1.29] in the RTX group and 1.15 [95% CI, 0.88-1.50] in the CYC group). The decrease in rates may be due, at least in part, to lower disease activity and GC use later in the study.

The overall profile of events was consistent with that observed at 6 months with the most frequent type of serious adverse event, by SOC, being infection in both groups (15.2% for RTX group and 15.3% for CYC group). The most common serious infections were pneumonia (4.0% for the RTX group and 5.1% for the CYC group) and UTI (2.0% and 1.0% in the RTX and CYC groups, respectively).

Other common types of serious adverse events included respiratory disorders (9.1% vs. 11.2% in the RTX vs. CYC groups, mainly WG, PE, PAH, and laryngeal stenosis) and blood and lymphatic system disorders (overall 6.1% in each arm), which encompassed mainly anemia (2.0% in the RTX group vs. 4.1% in the CYC group) and leukopenia (3.0% in the RTX group vs. no patients in the CYC group, all occurring prior to 6 months).

Also consistent with the data at 6 months was the higher incidence of serious DVT in the CYC group (8.2% vs. 1.0% in the RTX group)—events that all required anticoagulant therapy that was administered in hospital—and a higher number of events affecting the gastrointestinal system in the RTX group (five vs. two in the CYC group). Gastrointestinal events occurring in the RTX group (ischemic colitis, diarrhea, gastritis, and upper gastrointestinal hemorrhage) had no clear pattern or unifying etiology. The two gastrointestinal events in the CYC group were both cases of acute pancreatitis.

No other clear imbalances were observed in events grouped by SOC. By 18 months, there were two serious cardiac events in the RTX group, both of which were atrial fibrillation. There were also two serious cardiac events in the CYC group: myocardial infarction and supraventricular tachycardia. Sensitivity analyses, which excluded events occurring after treatment switch, were overall consistent with the primary analysis at 18 months.

Up to Common Closeout Date:

Overall, 60 (60.6%) rituximab patients had a total of 122 serious adverse events and 47 (48.0%) CYC patients had a total of 100 serious adverse events through the CCO date. Importantly, the rates of serious adverse events per patient-year were comparable between the RTX (0.41 [95% CI, 0.34–0.49]) and CYC (0.36 [95% CI, 0.30–0.44]) groups. These rates were lower than those reported at 6 months (0.97 [95% CI, 0.72-1.29] in the RTX group vs. 1.15 [95% CI, 0.88-1.50] in the CYC group and at 18 months (0.49 [95% CI, 0.39-0.63] in the RTX group vs. 0.57 [95% CI, 0.46-0.71] in the CYC group), perhaps in part due to lower disease activity and GC use later in the study.

The overall profile of events was consistent with that observed at 6 and at 18 months, with the most common serious adverse event being infection in both treatment arms. As noted at the 18-month time point, the most common serious infections were pneumonia (8.1% in the RTX group and 10.2% in the CYC group) and UTI (2.0% in the RTX group and 1.0% in the CYC group)

Additional Data: RITUXVAS

At 12 months, 16 of 33 (48%) patients experienced 35 serious adverse events in the RTX — low-dose CYC arm of RITUXVAS (including 6 patients with fatal events). Six of these patients had serious infections. Four of 11 (36%) patients experienced 11 serious adverse events in the CYC arm, including 3 serious infections in 2 patients. Identical proportions of patients experienced outcomes of hospitalizations or life threatening events, serious infections, or deaths in each treatment group. The rate of serious adverse events per patient-year was not reported.

Preliminary unpublished data up to 2 years revealed that 20 of 33 (61%) patients experienced 50 serious adverse events in the RTX + low-dose CYC arm of RITUXVAS (including 6 patients with fatal events). Twelve of these patients had serious infections and 3 developed malignancies (melanoma, breast cancer and basal cell carcinoma [unpublished case]. Four of 11 (36%) patients experienced 15 serious adverse events in the CYC arm, including 5 serious infections in 2 patients. Three patients in the CYC arm had fatal events, one of which was an infection.

Adverse Events Leading to Discontinuation of Study Drug

Primary Safety Analysis: RAVE

Up to 6 months:

In total, 21 patients reported 27 events that led to discontinuation of study drug (rituximab/rituximab placebo, CYC/CYC placebo, or AZA/AZA placebo). All these adverse events occurred prior to a patient switching treatment or receiving other treatment under BMJ.

A higher proportion of patients experienced adverse events leading to a permanent discontinuation of study drug in the CYC group than in the RTX group. In the RTX group, 8 (8.1%) patients had 12 events that led to study drug discontinuation. In the CYC group, 13 patients (13.3%) experienced 15 adverse events that led to study drug discontinuation.

The most frequently reported adverse events that led to discontinuation of study drug were (acute) renal failure, leukopenia, and (drug) hypersensitivity. There was no clear imbalance between the RTX and CYC groups in the type of adverse events leading to study drug discontinuation except for leukopenia, which was only reported in 3 patients in the CYC group.

Among the adverse events that led to study drug discontinuation, none were considered infusion related by the investigator. However, one serious adverse event of hypersensitivity (Patient 006001) was recorded on the Selected Adverse Event CRF as an IRR despite it not occurring within 24 hours of an infusion as specified in the reporting instructions. This event occurred 2 days following the third infusion of rituximab. CYC placebo was interrupted and restarted at a reduced dose (50 mg), and the fourth infusion of rituximab was not administered for this reason.

Up to 18 months:

Between 6 and 18 months, 8 patients in the RTX group and 12 patients in the CYC group discontinued study drug as a result of adverse events, thereby yielding a total of 16 (16.2%) rituximab and 24 (24.5%) CYC patients who reported adverse events that led to a permanent discontinuation of study drug (rituximab/rituximab placebo, CYC/CYC placebo, or AZA/AZA placebo) from baseline to 18 months. The main reason for the difference in the number of patients discontinuing study drug treatment was the greater number of patients who discontinued because of leukopenia in the CYC group. The most common reasons for permanent drug discontinuation, by 18 months, were leukopenia (7 patients [5 leukopenia and 2 WBC decreased] in the CYC group and no patients in the RTX group), infections (2 patients in each treatment group), WG (2 patients in the CYC group and 4 in the RTX group), renal failure (2 patients in each group), and (drug) hypersensitivity (2 patients in the CYC group and 1 in the RTX group).

Up to Common Closeout Date:

After 18 months, two adverse events that led to permanent study drug discontinuation were reported: 1 event of bronchostenosis in the CYC group and 1 case of WG in the RTX group. Overall, the profile of adverse events leading to permanent study drug discontinuation was consistent with that reported at 6 months, with the addition of more withdrawals due to infection and to WG-related respiratory symptoms

Additional Data: RITUXVAS

No patient in the RTX + low-dose CYC group was reported to have stopped rituximab treatment early (course of four infusions).

Adverse Events Leading to Withdrawal from Study

Primary Safety Analysis: RAVE

Up to 18 months:

By 6 months, 2 patients in the RTX group and no patients in the CYC group withdrew prematurely from the study as a result of adverse events. Since the 6 month time point, and prior to 18 months, 1 additional patient in the RTX group and 1 patient in the CYC group withdrew as a result of adverse events. The serious adverse events reported in the 2 patients who withdrew prior to 6 months were pneumonia and osteomyelitis. The 2 patients who withdrew after 6 months reported serious adverse events of renal failure and colon cancer.

Up to Common Closeout Date:

No further withdrawals occurred after 18 months. Hence, overall, 3 patients in the RTX group and 1 patient in the CYC group withdrew from the study because of adverse events.

Additional Data: RITUXVAS

No patients were reported to have withdrawn from this study.

Selected Adverse Events Pre-Defined in RAVE

Selected adverse events included pre specified categories of events including death, bone marrow suppression, infection, hemorrhagic cystitis, malignancy, venous thromboembolic events, hospitalizations associated with AAV or study drug per the investigators opinion, CVAs and IRRs leading to discontinuation of further infusions. These events are key safety outcomes associated with underlying disease or treatment that can result in substantial morbidity in this patient population, and a significant reduction in their rates was deemed clinically important in the protocol. Therefore, the pre specified analysis of the safety of rituximab versus that of CYC focused on these events.

Key findings were as follows:

Up to 6 months:

- The proportion of patients experiencing the pre-specified selected adverse events in RAVE was 22.2% in the RTX group and 34.7% in the CYC group. However, as patients may have experienced multiple types of selected events, the rate of these events per patient-year was similar in each group (0.78 vs. 0.96, respectively; p = 0.250).
- There were more cases of leukopenia and venous thromboembolic events in the CYC group than in the RTX group in RAVE, although the higher incidence of leukopenia in the CYC group did not translate into a higher number of infections during the first 6 months.
- In RAVE, 10 patients experienced hospitalizations considered related to disease activity or study therapy in the RTX group (5 RTX only patients and 5 RTX other patients) and 4 patients in the CYC group (4 CYC only patients).

Up to 18 months and Common Closeout Date:

- By 18 months, the proportion of patients experiencing any of the pre-specified selected adverse events in RAVE was 33.3% in the RTX group and 42.9% in the CYC group. The rate of these events per patient-year was 0.47 per patient-year in the RTX group vs. 0.48 per patient-year in the CYC group.
- Leukopenia remained more frequent in the CYC group compared with the RTX group at 18 months.
- The subset of hospitalizations associated with AAV or study drug per the investigator's opinion remained more frequent in the RTX group at 18 months. The majority of hospitalizations associated with AAV or study drug per the investigator's opinion were due to infections in both groups. Importantly, hospitalizations are a subset of serious adverse events, and the percent incidences and rates of serious adverse events and serious infections were balanced across treatment groups.

- At the 18-month time point, the incidences and rates of severe (Grade ≥ 3) infections remained balanced across treatment arms.
- These findings at the 18-month time point were consistent with the analysis up to the CCO date.

Progressive Multifocal Leukoencephalopathy

No cases have been observed in the AAV studies included in this filing.

Malignancies

The total number of cancers reported from randomization up to the CCO Date was six malignancies in 5 patients randomized to rituximab and two malignancies in 2 patients randomized to CYC. Table 19 summarizes the malignancy events in RAVE up to CC date..

Table 19. Malignacy events in RAVE up to CCO date

Patient ID	Malignancy Type	Age (Yr)/ Sex	Study Day of Diagnosis	History of Tobacco Use	Other Relevant Medical History	Treatment Exposure prior to Cancer Diagnosis (Days) Prior to Study Start [a]	During Study
RTX group							
002115	Prostate cancer	75/M	93	No		NA	RTX (71)
001020	Uterine cancer	66/F	909	Yes		MTX (3102)	RTX (909)
004001	Colon cancer metastatic	74/F	454	No	History of basal cell carcinoma	MTX (1590) CYC (240)	RTX (454)
006108	Bladder cancer	69/F	811	Yes	History of cervical cancer	MTX (1600)	RTX (811)
	Adenocarcinoma of the colon		1180			MTX (1600)	RTX (1180)
006110	Malignant lung neoplasm	78/M	532	Yes		CYC (10)	RTX (532)
CYC group							
006020	Prostate	53/M	53	Yes		NA	CYC (53)
001010	Papillary thyroid cancer	62/F	798	Yes	History of multinodular goiter	CYC (365) MTX (30)	CYC (798) AZA (698) RTX (306)

AZA=azathioprine; CCO=common closeout date, CYC=cyclophosphamide; MTX=methotrexate; NA=not applicable; RTX=rituximab.

[a] For medications received prior to study start, number of days represents duration of therapy.

Laboratory findings

HEMATOLOGY AND BIOCHEMISTRY

Primary Safety Analysis: RAVE

In the 18-month study period of RAVE, the median values and median changes from baseline of standard hematologic and biochemistry parameters were similar across treatment groups for most laboratory parameters. These changes were consistent with those observed over the first 6 months of RAVE.

The most common newly occurring Grade 3 or 4 abnormalities during the 18-months of follow-up in RAVE were lymphopenia and hyperuricemia, consistent with the analysis at 6 months. In patients with lymphocytes in the normal range at baseline, there was a higher incidence of Grade 3 or 4

lymphopenia in the CYC group (88.5%) compared with the RTX group (48.1%), consistent with the known effects of these treatments. Hyperuricemia occurred more frequently in the RTX group than in the CYC group (30.3% vs. 15.9%), also consistent with previous experience with rituximab in other indications (MabThera SmPC). The hyperuricemia was transient and without obvious consequence and was likely related to DNA catabolism resulting from B-cell lysis. The cumulative incidence of Grade ≥ 3 neutropenia over 18 months was marginally increased in the CYC group (20.7%) compared with the RTX group (17.9%), with more Grade 4 neutropenia in the CYC group (18.4% vs. 10.7%). This difference is consistent with the more frequent reporting of leucopenia adverse events in the CYC group.

LABORATORY EVALUATIONS OF SPECIAL INTEREST

Human Anti-Chimeric Antibody

Primary Safety Analysis: RAVE

Thirty-one patients tested positive for HACA (defined as >5 RU/mL and immunodepletable with rituximab) at any time: 25 from the RTX group and 6 from the CYC group (3 out of these tested positive after exposure to rituximab as a result from switching, receiving open-label rituximab, or receiving rituximab under BMJ). Hence, in total, 28 (of a total of 124 ever exposed to rituximab) patients tested HACA positive after exposure to rituximab. The maximum HACA titer values for each of these 28 patients ranged from 9.78 to 12,100 RU/ml, with a median of 38.5 RU/mL (the 3 CYC patients who were HACA positive without or prior to exposure to rituximab had values ranging from 24.9 to 374.0 RU/mL). Of note, 22 of the 25 HACA-positive patients in the RTX group tested positive after 6 months (time points at which serum levels of rituximab would be expected to be low and less likely to interfere with the detection of HACA).

Of the 25 patients in the RTX group, 7 received a second course of rituximab as open-label treatment and 4 were tested HACA positive prior to receiving repeated rituximab. None of these 4 patients experienced an IRR with their second course of treatment.

HACA-positive patients are defined as those who tested HACA positive after their first exposure to rituximab, which includes 25 patients in the RTX group and 3 patients randomized to CYC who received rituximab as switch or open-label rituximab or under BMJ. For patients randomized to CYC, only events that occurred after their first infusion of active rituximab were included in the analysis. The overall safety profile was similar in HACA-positive and HACA-negative patients. There was no clear difference in the proportions of patients who experienced any adverse events, serious adverse events, and selected adverse events or in the respective rates of these events.

The proportion of patients who reported IRRs was similar in the HACA-positive group (4 of 28 or 14.3%) compared with the HACA-negative patients (11 of 96 or 11.5%) but should be interpreted cautiously because of the small numbers of events and HACA-positive patients. IRRs are defined as those adverse events that occurred within 24 hours of an infusion and are considered infusion related by the investigators. Ten IRRs were reported in 4 patients who tested HACA positive, including 1 CYC patient (001024) who received rituximab as switching treatment. All these IRR events were mild to moderate in severity, all occurred prior to the detection of HACA, and none of them were reported as serious adverse events or resulted in discontinuation of therapy. The events reported as IRRs in the HACA-positive patients comprised cytokine release syndrome (four events), flushing (one event), hypotension (one event), oropharyngeal discomfort (one event), diarrhea (one event), and hyperhidrosis (two events).

Pharmacodynamics (CD19 B Cell Counts)

The number of peripheral-blood CD19-positive B cells decreased to <10 cells/µL after two infusions of rituximab and remained at that level in most patients through 6 months. At 6 months, 70 of 84 patients (83%) in the RTX group had this degree of CD19-positive depletion. By Month 12, the majority of patients showed signs of B cell return with 66 of 82 (80.5%) patients with counts >10 cells/µL. By Month 18, 61 of 70 patients (87.1%) had counts <10 cells/µL (excluding data collected after switch to RTX or open-label RTX).

Immunoglobulins

A substantial proportion of patients receiving either RTX or CYC/AZA had low Ig concentrations at baseline, perhaps resulting from immunosuppression prior to trial entry. The proportions of patients with low Ig increased at 6 months and 18 months in both groups. On the basis of these data, and consistent with hypogammaglobulinaemia (low IgG or IgM) observed following RTX treatment in the RA clinical trial population, hypogammaglobulinemia is considered an Adverse Drug Reaction following RTX treatment in GPA and MPA patients. Low Ig was not associated with increased rates of infections.

Neutropenia

Primary Safety Analysis: RAVE

In RAVE, similar proportions of patients developed newly occurring CTC Grade ≥ 3 neutropenia, based on laboratory data, in the RTX group and CYC groups at each time point (10.8% vs 13.7% at 6 months, 16.8% vs 20.7% at 18 months and 24.1% vs 23.0% at CCO). About 30% of patients who developed Grade ≥ 3 neutropenia by the CCO date (7/20 in the RTX group and 4/20 in the CYC group), did so after switching therapy (cross-over, open-label RTX, or BMJ). Due to frequency of treatment switches, attribution of neutropenia to specific therapies is unclear.

Importantly, most episodes of Grade ≥ 3 neutropenia were resolved by the next visit and there was no clear association between occurrence of Grade ≥ 3 neutropenia and increased risk of serious infection in either treatment group. One of the twenty patients in the RTX group and one of the twenty in the CYC group with grade ≥ 3 neutropenia up to the CCO date developed a serious infection within 30 days of the reported neutropenia: one serious grade 2 infection of viral URTI was reported in RTX patient within 30 days of a grade 4 neutropenia and 1 serious, grade 2 viral infection was reported within 30 days of a grade 4 neutropenia in a patient in the CYC group.

On the basis of these data, and consistent with neutropenia observed following an initial course of RTX in the RA clinical trial population, neutropenia is considered an Adverse Drug Reaction following a single course of RTX in GPA and MPA patients.

Safety in special populations

Subgroup analyses of the safety profile in RAVE were primarily based on the data collected up to 6 and up to 18 months regardless of switch of therapy and presented in the following sections. The subgroup safety profiles were, in general, consistent between the 18-month and CCO analyses.

Age

Among the 197 patients randomized and treated in RAVE, 55 (28%) were aged ≥ 65 years of which 12 (6%) were aged ≥ 75 years. There were more patients aged ≥ 65 years old in the RTX group compared with the CYC group (36/99 vs. 19/98). Of the 12 patients aged ≥ 75 years, 8 were in the RTX group. Within each age group, the safety profile of the RTX group compared with that of the CYC group was broadly similar to that observed in the overall safety population. Patterns observed in the data through 18 months were consistent with those seen at 6 months, with the following key observations:

- Higher incidence and rates of severe (Grade ≥ 3) and serious adverse events in older patients (difference primarily attributable to anemia and leukopenia, gastrointestinal disorders, and general disorders and administrational site reactions [chest pain and chills])
- Deaths only occurred in older patients, with a similar incidence in the two treatment groups.
- The subset of hospitalizations related to AAV or study drug per investigator's opinion occurred more frequently in older patients in the RTX group, with no hospitalizations occurring in older patients in the CYC group. The difference in the proportion of patients hospitalized between the two treatment groups was less in the group of younger patients. Hospitalizations reported in older patients (all in RTX group) stemmed from acute renal failure, pulmonary hemorrhage, steroid-induced diabetes, and three cases of pneumonia (two of which were associated with leukopenia).
- In the group of younger patients (<65 years), Grade ≥ 2 leukopenia was mostly reported in the CYC group, whereas in older patients, the proportions of patients reporting these events were similar across treatment groups.
- Cardiac events occurred more frequently in older patients in the RTX group, mainly attributable to Grade 1 or 2 atrial fibrillation and tachycardic events. In the CYC group, the proportion of patients reporting cardiac events was similar in older and younger patients. Serious cardiac events were infrequent in both age groups for both treatment groups.
- There was no clear or consistent trend in the rates of infections and serious infections in younger versus older patients in either treatment group.

Safety Profile by Onset of Disease in RAVE: New versus Relapsing Disease

Of the 197 patients randomized and treated in RAVE, 96 (48.7%) were newly diagnosed at the time of screening with a similar proportion in each treatment group. The vast majority of patients who had relapsing disease (79 of 101) had been treated with CYC prior to trial entry, while only 6 patients in the newly diagnosed group had received prior CYC. The overall safety profiles of the treatment arms for the subgroups of new and relapsing diseases were similar to those observed in the overall safety population.

Patterns observed in the data through 18 months were consistent with those seen at 6 months, with the following key observations:

- The safety profiles of patients with newly diagnosed disease versus those with relapsing disease were, in general, comparable.
- The overall incidences of infections and serious infections were similar in newly diagnosed patients and those with relapsing disease.
- The incidences of Grade ≥ 2 leukopenia and thrombocytopenia were higher in newly diagnosed patients compared with those with relapsing disease.
- In the patients with newly diagnosed disease, hospitalizations were only reported in the RTX group. In the relapsing group, the proportions of patients reporting hospitalization were similar in the two treatment groups.

Safety Profile by Baseline Renal Function in RAVE

In RAVE, the mean baseline creatinine clearance rate was 84.0 mL/min and the median 74.71 mL/min in the 197 randomized and treated patients. Baseline renal function was better in patients in the CYC group compared with those in RTX group. The proportion of patients with a baseline creatinine clearance rate below the median (74.71 mL/min) was higher in the RTX group (54.5%) compared with the CYC group (44.9%).

As with the previous subgroup analyses, these data should be interpreted with caution because of the limited sample size in each subgroup. Also of note, baseline renal function can be related to age and other baseline demographic or disease characteristics, potentially confounding the subgroup analysis. Key findings from the 18-month analysis were as follows:

- A higher proportion of CYC group patients with a lower baseline creatinine clearance (<74.71 mL/min) experienced severe or serious adverse events, infections, and serious infections than those with a higher baseline creatinine clearance rate in the CYC group.
- All deaths occurred in patients with worse baseline renal function.
- The numerical imbalance between treatment groups in patients hospitalized as a result of disease activity or study drug per the investigator's opinion was larger in patients with worse baseline renal function. Patients with worse baseline renal function in the RTX group who reported hospitalizations were also older patients (≥ 65 years).
- More serious adverse events of anemia, pneumonia, and renal failure occurred in the subgroup with worse renal function. In contrast, however, serious PE (four cases) occurred only in the group of patients with a higher creatinine clearance rate at baseline in either treatment group. The incidences of DVTs, however, were balanced across the subgroups.
- There were no clear differences in the incidences and rates of infections and serious infections between patients with higher or lower baseline creatinine clearance rates.
- The proportion of patients experiencing UTIs was slightly higher in patients with the lower baseline creatinine clearance rate than in those with better renal function at baseline. In both these groups, more patients in the RTX group experienced UTI than patients in the CYC group.

EXTRINSIC FACTORS

Patients with a history of CYC use in RAVE largely corresponded to the subgroup of patients with relapsing disease. Seventy nine out of the 101 patients with relapsing disease (78.2%) had a history of CYC use. Only 6 of 96 (6.3%) patients with new onset disease had previously used CYC. Therefore, a separate subgroup analysis was not performed on history of CYC use.

Safety related to drug-drug interactions and other interactions

No formal drug interaction studies have been performed with rituximab in the target population. However, a population pharmacokinetic analysis of RA patients suggests that co administration with CYC, methotrexate, or GC has no effect on the pharmacokinetics of rituximab. Furthermore, as the elimination of rituximab is mediated by both the specific CD20 receptor-mediated pathway and the nonspecific immunoglobulin G clearance pathway, rituximab is not expected to interact with other drugs through protein binding, effects on cytochrome P450 activity, renal excretion, and/or competition for common drug transporter proteins.

Safety in special populations

Pregnancy

One pregnancy of a patient's partner was reported by a patient who was randomized to the RTX arm of RAVE. This patient did not switch to CYC during the first 6 months on study. The pregnancy ended in miscarriage, with no additional details reported.

Post marketing experience

Rituximab is approved for Wegener's granulomatosis and microscopic polyangiitis in the USA since April 2011. Spontaneous serious adverse events of rituximab in AAV reported to the Global Safety Database have been summarized in this safety summary where relevant. The reported events were consistent with underlying disease and previous experience, for rituximab. Many of these patients were reported to be taking concurrent immunosuppressive therapies.

A search in the Global Safety Database for spontaneous serious adverse events received through 31 August 2011 in Antineutrophil cytoplasmic antibody positive vasculitis, Wegener's granulomatosis, and microscopic polyangiitis resulted in 99 case reports: 94 in WG, 4 in MPA, and 1 in ANCA-positive vasculitis.

In the 99 case reports, a total of 81 serious adverse events were reported. These events were most commonly in the infections and infestations SOC, followed by respiratory, thoracic, and mediastinal disorders SOC.

Four events of Pneumocystis jiroveci pneumonia (PJP) have been spontaneously reported to the safety database in AAV patients receiving rituximab; alternative risk factors, typically use of corticosteroids and other immunosuppressants, may have contributed in the majority of case reports. In addition, it is unknown if any of these patients received PJP prophylaxis, which is the standard of care in patients with AAV given their known risk of development of PJP (Green et al, 2007). Of note, the reporting rate of PJP from the safety database was lower than the rate reported in the literature in AAV patients (Ognibene et al, 1995**,** Ward and Donald, 1999**;** Falagas et al 2007). Given the known risk of PJP in patients with AAV, the data presented here does not suggest that rituximab increases the risk of PJP in AAV patients. Four additional opportunistic infections (unconfirmed PML), cytomegalovirus infection, Kaposi's varicelliform eruption, bronchopulmonary aspergillosis) with fatal outcome were reported. As interpretation of spontaneous reporting is limited by incomplete reporting of events as well as an unknown denominator, reporting rates cannot be directly compared to incidences.

The events described in these cases were consistent with the types of events typically reported for patients with these disease states (WGET Research Group 2005; de Groot et al. 2009).

No confirmed cases of PML in rituximab-treated AAV patients in the Global Safety Database were reported as of the cutoff date of 17 May 2011 or in the literature. There has been one suspected but unconfirmed case of PML in a patient with WG that occurred approximately 2 months after the last dose of rituximab reported in the Global Safety Database. The patient also had diabetes mellitus, and renal insufficiency and was treated with multiple concomitant immunosuppressive medications, including prednisone, CYC, and adalimumab. Cerebrospinal fluid analysis was negative for JC virus. The patient subsequently experienced pneumonia and died. No additional case details were reported despite multiple contact attempts with the clinician. One recent case of confirmed PML was reported with a GPA patient treated with rituximab during the assessment of this application. JC virus was detected following observation of neurological symptoms and the patient started antiviral therapy.

Following the submission of a Drug Safety Report as part of a parallel ongoing safety variation to include Stevens Johnson's syndrome (SJS) / toxic epidermal necrolysis (TEN) occurred in autoimmune indications in the SmPC, one case of SJS was reported in a patient treated with Mabthera for GPA.

2.6.1. Discussion on clinical safety

The main reason to develop alternative treatment options for AAV, was the toxicity concerns of CYC.

Rituximab has been in use since 1997 initially for NHL indications and later approved for rheumatoid arthritis. Estimated around 2 million patients have been treated with this compound, thus a

considerable amount of information regarding adverse effects has been made available. Of main interest are primarily infusion reactions within 24 hours after the infusion either allergic or caused by the cytokine release syndrome, increase in rate of infections among which reactivation of hepatitis B can be fatal, cardiac disorders, haematological abnormalities such as leukopenia. The most feared complication is PML where activation of JC-virus can cause a rapid deteriorating neurological condition often resulting in death or severe neurological deficiencies. This complication is found most often in the lymphoma population where patients apart from RTX also receive a combination of cytotoxic drugs. A few cases have been described in patients with rheumatic conditions without concomitant immunosuppressive treatment.

In the RAVE study the pattern of AEs did not deviate from what could be anticipated. The incidence of leukopenia was significantly lower for RTX treatment than for CYC however, the overall safety profile was comparable for the two treatments. The incidence of serious infections, malignancies or urotoxic events like (haemorrhagic) cystitis, was similar between RTX and CYC arm. There were similar rates per patient-year of any adverse event, however, specific AEs varied across treatment groups. The investigators had a priori selected AEs of special interest; these were: death, bone marrow suppression, infections, hemorrhagic cystitis, malignancies, venous thromboembolic event, hospitalizations, CVAs, and IRRs.

As expected, more grade 2-4 lymphopenia/leukopenia was observed in the CYC group compared with RTX leading to a number of drug discontinuation. More hospitalizations occurred in the RTX group mainly due to infections or disease flares. Infections were upper respiratory or UTI. This could probably in part be explained by the slightly higher age of patients in the RTX group and a higher incidence of impaired renal function in that group. DVTs occurred more often in the CYC group (1% in the RTX group vs. 8.2% in the CYC group at 18 months). IRRs were similar across the treatment arms and all were moderate or mild in severity. Cardiac events were higher in the RTX group by month 18; 18.2% vs. 12.2%. This was largely due to low-grade tachycardias and atrial fibrillation occurring in the RTX arm. Mild hypertension was also more pronounced in the RTX group.

No case of PML has been reported in the trial or from spontaneous reports received up to the cut-off of 31 August 2011, but one case was received from spontaneous reports while this procedure was ongoing. The overall rate of PML in vasculitis has been estimated to be 10.8 (0.27-60.39)/100,000 person-years on the basis of a review of medical records of cases in the Normative Health Informatics claims database [Amend et al, 2010]. In a global literature review covering the years 1989 to 2010, there were five published reports of confirmed PML in WG patients treated with CYC and prednisone, two of them had received additional immunosuppressive therapies (AZA, methotrexate, and cyclosporine in 1 patient and AZA and mycophenolate mofetil in the other).

PML is known to occur in AAV patients treated with other therapies, is a known adverse drug reaction associated with rituximab and its risk increases when RTX is combined with other immunosuppressive (in particular cytotoxic) drugs. As AAV patients often have received one or more cycles of CYC before commencing RTX these patients should probably be placed in the same risk category as NHL patients in the enhanced PhV plan and instead of the category of autoimmune conditions such as RA.

There were 6 malignancies in 5 patients initially treated with rituximab and 2 malignancies in 2 patients initially treated with CYC over a total of 573.90 patient-years of follow up. Four of 5 patients in the RTX group who were diagnosed with malignancies had previous exposure to CYC, and the fifth patient, who did not have a history of prior immunosuppressive use, was diagnosed only 93 days into the study, thereby suggesting a prevalent rather than incident cancer. Similarly, the rates of malignancy across both treatment groups in RAVE at the end of longer-term study follow-up (mean of 3.0 years in the RTX group, range 0.08 to 5.02 years) are consistent with the published malignancy rates (based on SIRs) in AAV with or without treatment with CYC as concluded from a literature

comparison (). Long term data are needed to study malignancies and for this purpose the follow-up of the RAVE study population and collection of data from participation in an EU registry are agreed in the context of the RMP.

The infusion-related-reactions with RTX were in general of low incidence and of mild character. This might be due to high concurrent doss of corticosteroids.

One of the advantages of RTX therapy seems to be that the incidence of venous thrombotic events was considerably lower than for CYC.

There are no adequate and well-controlled studies of rituximab in pregnant women. Postmarketing data indicate that B-cell lymphocytopenia generally lasting fewer than 6 months can occur in infants exposed to rituximab in utero. Rituximab was detected postnatally in the serum of infants exposed in utero.

As follow up data on safety are considered important several options were being considered as follows:

The MAH is conducting a multicenter (U.S.-based), prospective, observational study designed to follow 100 rituximab-treated patients with GPA or MPA for a maximum of 4 years (Study WA27893 [RAVeR]). An interim analysis will be performed when all patients are enrolled and approximately 50% of the estimated total patient-year exposure data (327 patient years) have been collected.

The MAH is in contact with principal investigators (PIs) from national patient registries. In addition to the German Register in Autoimmune Diseases-II (GRAID-II) the MAH is investigating additional European registries to generate additional standardised data, including BIOGEAS and BIOBADASER (Spain) and has committed to undertake additional follow-up with EUVAS in order to identify and evaluate additional data sources. registries in the E.U. to investigate the possibility of obtaining standardized biannual (or annual) adverse event (AE) reports from cohorts of rituximab-treated and rituximab-naive ANCA-associated vasculatis (AAV) patients: the National Czech Registry of AAV Patients (Hruskova Z et al. 2012), and two Spanish patient registries that recruit biologic-treated, non-rheumatoid arthritis (RA) patients (BIOGEAS and BIOBADASER studies; Ramos-Casals M et al. 2010; BIOBADASER 2012). The MAH will continue to monitor European Vasculitis Study Group (EUVAS) activities in case any relevant data sources may be identified in the future. The MAH will also monitor the development of the planned Norwegian National Registry of Biologics (NOKBIL). This national registry will recruit patients with an autoimmune or chronic inflammatory disease indication treated with a biologic agent. The details of the methodology and data collection are not yet finalized. The registry is planned to commence in 2013 and progress on the methodology will be monitored in collaboration with the affiliate.

The medical importance of limiting the exposure to the lowest possible corticosteroid dose is recognized. For this purpose, reports and publications from the PEXIVAS trial, or other trials evaluating lower steroid doses in conjunction with rituximab, will be provided to the CHMP once they have been published and become available to the MAH. Following publication of the updated EULAR recommendations for the Management of Primary Small and Medium Vessel Vasculitis in 2013 the requirement for providing guidance on this issue will be reassessed.

2.6.2. Conclusions on clinical safety

In conclusion, the pattern of adverse events demonstrated in the RAVE study does not raise any new safety signals for rituximab. Long term safety data will be provided from ongoing studies (see RMP).

The investigation of a lower fixed dose, which could lead to a better safety profile (e.g. in terms of infections), is recommended to the MAH. This is included in the RMP under section “infections’, so that the CHMP will be kept informed about further developments regarding dose finding.

It is expected that use of registry data will add to the long term safety profile of rituximab in GPA, MPA. Data access from 3 E.U. registries (National Czech Registry of AAV Patients, two Spanish patient registries BIOGEAS and BIOBADASER) is planned in the context of the RMP, detailed protocols and possible addition of a 4th registry will be included in the next revision of RMP to be submitted to the CHMP for assessment by June 2013.

2.6.3. PSUR cycle

The PSUR cycle remains unchanged.

2.7. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the MAH fulfils the legislative requirements.

Risk management plan

The MAH proposed that the identified risks, Acute Infusion-Related Reactions, Infections, Impaired Immunisation Response, PML, HBV Reactivation, and Hypogammaglobulinaemia (newly identified) and the potential risks De Novo HBV, Opportunistic Infections, Malignant Events, Impact on Cardiovascular Disease, GI Perforation and neutropenia (newly identified) should also apply to the GPA/MPA indication. In addition, "Off-label use in paediatrics – all indications" was added as an Important Potential Risk throughout the EU RMP, version 9.2.

"Long term safety in GPA/ MPA patients" is missing with regard to RTX re-treatment and relapse. Therefore, "Long term safety in GPA/ MPA patients" is included in the RMP as missing information and data access from the identified E.U. registries (National Czech Registry of AAV Patients, two Spanish patient registries BIOGEAS and BIOBADASER, one in UK) should be included in the next revision of RMP as an additional Pharmacovigilance activity. Draft study protocols should be submitted for assessment, in the upcoming planned RMP update.

It is noted that the MAH will actively review all academia- and investigator-sponsored studies with different doses of rituximab to identify significant differences in the risk of severe infections related to the dose regimen. A next revision of the RMP will be included in an ongoing procedure and is expected to be submitted in June 2013. Added under RMP measures regarding the potential risk of 'Infections': to provide reports and publications from the PEXVIAS trial, or other trials evaluating lower steroid doses add-on to rituximab, as soon as available.

The medical importance of limiting the exposure to the lowest possible corticosteroid dose is recognized. For this purpose, reports and publications from the PEXIVAS trial, or other trials evaluating lower steroid doses in conjunction with rituximab, will be provided to the CHMP once they have been published and become available to the MAH. The EULAR Recommendations for the Management of Primary Small and Medium Vessel Vasculitis last updated in 2009 will be updated in 2013. Following publication of the updated EULAR recommendations in 2013 the requirement for providing separate guidance on this issue will be reassessed as an RMP measure.

Table 21 Summary of the EU Risk Management Plan

Safety issues	Agreed Pharmacovigilance Activities (Routine and Additional)	Agreed Risk Minimisation Activities (Routine and Additional)
Important Identified Risks		
Acute Infusion Related Reactions[a]	**RA** Routine Pharmacovigilance Activities Additional: In ongoing and planned clinical trials, prospective data collection and evaluation of serious/severe infusion reactions will continue to be carried out in long term follow-up for patients in open-label extensions. As part of the proposed rituximab-specific protocols, the British Society of Rheumatology Biologics Register (BSRBR), the Swedish registry (ARTIS) and the German registry (RABBIT) will report serious infusion reactions. Additional: Spontaneous reports of possible infusion reactions will be assessed and evaluated using good pharmacovigilance practices **GPA/MPA** Routine pharmacovigilance activities WA27893 and the GRAID registry will collect data for their study populations. The possibility of obtaining additional (S)AE-focused reports from other GPA/MPA registries is being investigated (section 1.2.1.7). **NHL/CLL** Routine pharmacovigilance activities	**RA** Routine: The sponsor considers the use of IV corticosteroid as pre-medication to be advisable prior to all rituximab infusions. This advice is reflected in the SPC. Educational material is provided to physicians, nurses and pharmacists on adminstering infusions of rituximab (see annex 8 page 1). AAV Routine: for WG and MPA patients, glucocorticoids are given in combination with rituximab as part of the specified indication. **NHL/CLL** Routine: Infusion-related reactions cannot be reliably predicted or prevented. However, the incidence and severity may be reduced by premedication and appropriate monitoring and treatment. See Annex 1 page 1 for search terms. Section 4.4 of the SPC states "MabThera solution for subcutaneous injection should be administered in an environment where full resuscitation facilities are immediately available and under the close supervision of an experienced healthcare professional".
Infections[a]	**RA** Routine Pharmacovigilance Activities (including guided questionnaire for hepatitis B reports). Additional: In ongoing and planned clinical trials, prospective data collection and focused evaluation of all infections/symptoms of infection is conducted. All reports of tuberculosis or reactivation of tuberculosis will be carefully analysed and reported to the agency. As part of its rituximab-specific protocol, the BSRBR, ARTIS and RABBIT will collect data regarding the incidence of serious infections and the administration of IV immunoglobulins. **GPA/MPA** Routine Pharmacovigilance Activities WA27893 and the GRAID registry	**RA** Routine: The labelling for the RA indication cautions prescribers regarding the use of rituximab in patients with an active infection or other predispositions to serious infection, and regarding the prompt evaluation and treatment of infections that occur following rituximab therapy. Company representatives will be informed as part of their training to draw prescribers' attention to this information. **GPA/MPA** Routine: The MAH considers the information provided in the CDS sufficient to inform prescribers of this risk. **NHL/CLL** Routine: The MAH considers the wording in the SPC sufficient to inform prescribers of this risk.

Safety issues	Agreed Pharmacovigilance Activities (Routine and Additional)	Agreed Risk Minimisation Activities (Routine and Additional)
	will collect data for their study populations. The possibility of obtaining additional (S)AE-focused reports from other GPA/MPA registries is being investigated (section 1.2.1.7). **NHL/CLL** Routine Pharmacovigilance Activities	
Impaired Immune Response[a]	**RA** Routine Pharmacovigilance Activities **GPA/MPA** Routine Pharmacovigilance Activities. Additional: WA27893 and the GRAID registry will collect data for their study populations. **NHL/CLL** Routine Pharmacovigilance Activities	**RA and GPA/MPA** Routine: The current SPC advises that Physicians should review the vaccination status of patients being considered for treatment with MabThera and follow local/national guidance for adult vaccination against infectious disease. Vaccination should be completed at least four weeks prior to first administration of MabThera. Live vaccines are not recommended in patients while B-cell depleted". **NHL/CLL** Routine: This information is contained in the SPC [based on results of a study in patients with NHL].
PML[a]	**RA and GPA/MPA** Routine Pharmacovigilance Activities (including guided questionnaire) The occurrence of PML is being monitored through the sponsor's enhanced pharmacovigilance system. For events reported to the sponsor's pharmacovigilance system as spontaneous reports, additional data will be collected by means of a Guided Questionnaire. Continued collection of reports from spontaneous reporting and clinical trial sources. The MAH aggressively pursues additional information from reporters for a number of pre defined terms that could potentially be representative of PML, in the form of a guided questionnaire **NHL/CLL** Routine + continued expedited reporting of new cases/questionnaire used to better characterise all such reports (all indications).	RA and GPA/MPA Additional: Patient alert card was implemented and educational material is provided above. NHL/CLL Routine only. The MAH considers the wording in the SPC sufficient to inform prescribers of this risk with extended information in the label.

Safety issues	Agreed Pharmacovigilance Activities (Routine and Additional)	Agreed Risk Minimisation Activities (Routine and Additional)
Neutropenia[a]	Routine All cases/reports will be evaluated and reported in the PSUR/PBRER per routine PV procedure	Routine: The MAH considers the wording in the SPC sufficient to inform prescribers of this risk.
HBV Reactivation[a]	Routine Pharmacovigilance (including guided questionanaire). As part of its rituximab-specific protocol, the BSRBR, ARTIS and RABBIT will collect data regarding the incidence of serious infections.	Routine: The wording in the SPC for all indications has been updated to provide enhanced guidance on screeing for hepatitis B infection in high risk patients.
Tumour Lysis Syndrome[b]	Routine Pharmacovigilance	Routine: The MAH considers the wording in the SPC sufficient to inform prescribers of this risk.
Serious Viral Infections[b]	Routine Pharmacovigilance	Routine: See Infections
GI Perforation[b]	Routine Pharmacovigilance	Routine: There are no known ways of preventing GI perforation in patients receiving rituximab for haematological malignancies.
PRES[b]	Routine Pharmacovigilance (including guided questionnaire).	Routine: an update to the SPC has been performed. The MAH has implemented a guided questionnaire for PRES in all indications.
Hypogamma-globulinaemia[c]	Routine Pharmacovigilance	Routine: the wording in the SPC sufficient to inform prescribers of this risk.
Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis[a]	Routine Pharmacovigilance	Routine: The MAH considers the wording in the SPC sufficient to inform prescribers of this risk.
Important Potential Risks		
De Novo HBV[c]	RA Routine Pharmacovigilance Activities Additional: In ongoing and planned clinical trials, prospective data collection and evaluation of the occurrence of any infection is undertaken. Comparison of incidence and rates between rituximab and placebo are made using pooled analyses from long term follow up of patients who continue with rituximab in open label studies is conducted. As part of the core protocol, the BSRBR, ARTIS and RABBIT collect data regarding infections and outcomes. GPA/MPA Routine WA27893 and the GRAID registry will collect data for their study populations.	Routine: See recommendations for infections (including serious infections) above.

Safety issues	Agreed Pharmacovigilance Activities (Routine and Additional)	Agreed Risk Minimisation Activities (Routine and Additional)
Opportunistic Infections[a]	Routine pharmacovigilance activities As part of its rituximab-specific protocol, the BSRBR, ARTIS and RABBIT will collect data regarding the incidence of serious infections. WA27893 and the GRAID registry will collect data for their study populations.	Routine: See Infections
Malignant Events[c]	RA Routine Pharmacovigilance Activities (including guided questionanaire). Additional: In ongoing and planned clinical trials, prospective data collection and evaluation of the occurrence of any neoplasm is carried out. Comparisons of incidence and rates between rituximab and placebo are made using pooled analyses from long-term follow-up of patients who continue with rituximab in open-label studies is conducted Standardised Incidence Ratios (SIRs) compared to the US general population are made using the SEER database, together with comparison of SIRs to those from other RA cohorts. As part of the core protocol, the BSRBR, ARTIS and RABBIT collect data regarding malignant events and outcomes. GPA/MPA Routine Pharmacovigilance Activities WA27893 and the GRAID registry will collect data for their study populations. The possibility of obtaining additional (S)AE-focused reports from other GPA/MPA registries is being investigated (section 1.2.1.7).	Routine: There are no options above and beyond standard cancer screening methods for malignant neoplasms.
Impact on Cardiovascular Disease[c]	RA Routine Pharmacovigilance Activities Additional: Data regarding serious cardiac events will be monitored in the PSURs/PBRERs. As part of the respective core protocols, the BSRBR, ARTIS and RABBIT collect data regarding the incidence of any serious co-morbidity leading to hospitalisation, including serious cardiac events. GPA/MPA Routine WA27893 and the GRAID registry will collect data for their study populations. The possibility of obtaining additional (S)AE-focused reports from other GPA/MPA registries is being investigated (section 1.2.1.7).	Routine: Guidance pertaining to cardiovascular risk is provided in the SPC

Safety issues	Agreed Pharmacovigilance Activities (Routine and Additional)	Agreed Risk Minimisation Activities (Routine and Additional)
GI Perforation[c]	RA Routine Pharmacovigilance Activities, plus the additional data collection from three registries BSRBR, ARTIS and RABBIT GPA/MPA Routine WA27893 and the GRAID registry will collect data for their study populations. The possibility of obtaining additional (S)AE-focused reports from other GPA/MPA registries is being investigated (section 1.2.1.7).	Routine: GI perforation events in patients treated in autoimmune indications will continue to be monitored by the MAH
Prolonged B-cell depletion[a]	Routine	Routine: B-Cell depletion is the expected therapeutic outcome with rituximab, detailed information on B-cell and immunoglobulin changes is provided in the SPC. Labelling documents updated to state: in PRIMA approximately half of the patients with available data on B-cell recovery after end of MabThera/Rituxan induction treatment, it took 12 months or more for their B-cell levels to return to normal values
Grade 3/4 and serious blood and lymphatic system Aes in >70year patients[b]	Routine	Routine. The SPC already includes information on blood and bone marrow system disorders (without reference to age categories). The new text is also proposed for the SPC.
AML/MDS[b]	Routine	Routine:
Second malignancies[b]	Routine pharmacovigilance including guided questionnaire	Routine: The MAH has implemented a guided questionnaire for all malignancies. All cases/reports will be evaluated and reported in the PSUR/PBRER per routine PV procedure
Off label use in autoimmune diseas[c]	Routine: good pharmacovigilance practices (including monitoring of medical literature, dedicated sections in PSUR/PBRER) Additional: Assessment of exposure figures ARTIS (Sweden) registry, . Rituximab Drug Utilization Study (DUS – 5EU). The Planned submission date for the feasibility assessment report and main study protocol to EMA is end-July 2012.	The MAH believes that the best place to advise prescribers of the risks associated with the use of rituximab is in the label. Therefore it is proposed to ensure that label wording is maintained to reflect appropriate information related to off-label use.
Off label use in paediatric patients[a]	Routine: good pharmacovigilance practices (including monitoring of medical literature, dedicated sections in PSUR/PBRER). GPA/MPA study (WA25615). NHl PIP study	The MAH does not consider that additional risk minimisation measures are required for off label use in paediatric patients as the MAH notes that the wording in the label was recently strengthened for this topic.

Safety issues	Agreed Pharmacovigilance Activities (Routine and Additional)	Agreed Risk Minimisation Activities (Routine and Additional)
Embryofoetal toxicity resulting from systemic exposure to rHuPH20 (rituximab SC)[e]	**Routine**: Monitor published literature dealing with acute toxicity and/or embryofoetal toxicity in association with rHuPH20, and AE case reports involving spontaneous abortion, stillbirth and intrauterine growth restriction, and any other relevant pregnancy-related events Monitor AE case reports involving administration route error (IV administration of the SC formulation). Provision of an internal checklist to assist Safety Operations to accurately code and follow-up cases involving medication error, to capture all possible information concerning the potential cause of the error and adverse events.	**Routine**: Labels for ritiximab IV and SC advise contraception for all patients receiving rituximab, and all those receiving treatment with chemotherapy agents or methotrexate. Label for rituximab SC recommend that patients who conceive whilst treated with rituximab SC should discontinue treatment with the SC formulation. Change to the IV formulation should only be considered if the possible benefit of continued treatment with rituximab outweighs the potential risk to the developing foetus. Differentiation of IV and SC package material. **Additional**: Education of healthcare professionals will emphasize package differentiation, injection technique and indications for SC and IV formulations
Relapsed[d]	**GPA/MPA** Routine Pharmacovigilance Activities Additional: Continue with a collection of reports from ongoing and planned studies on maintenance therapy after induction with rituximab (MAINRITSAN I, MAINRITSAN II and RITAZAREM studies).	**GPA/MPA** The MAH does not consider that additional risk minimisation measures are required for relapse until such a time when new information is identified.
Important Missing Information		
Use in Pregnancy and Lactation[a]	**RA** Routine Pharmacovigilance Activities Additional: In ongoing and planned clinical trials, prospective data collection and evaluation of pregnancies that occur and their outcomes is carried out. The BSRBR, ARTIS and RABBIT register the occurrence of pregnancies in enrolled patients and follows outcome of the pregnancy by asking the patients. **GPA/MPA** Routine **NHL/CLL** Routine	**RA and GPA/MPA** Routine: The SPC currently advises that due to the long retention time of rituximab in B-cell depleted patients, women of childbearing potential should use effective contraceptive methods during treatment and for 12 months following MabThera therapy. **NHL/CLL** Routine: The MAH considers the wording in the SPC sufficient to inform prescribers of this risk.

Safety issues	Agreed Pharmacovigilance Activities (Routine and Additional)	Agreed Risk Minimisation Activities (Routine and Additional)
Immunogenicity and Autoimmune Disease[c]	Routine: In ongoing and planned clinical trials, evaluation of serology data for HACA is carried out prospectively under open-label conditions. Focused evaluation of symptoms of immune complex disorder (e.g., serum sickness) is also carried out. Additional: As part of their rituximab-specific protocols, the BSRBR, ARTIS and RABBIT will document the occurrence of serious immunological reactions. Data accrued from all clinical trials, spontaneous reports, and planned observational studies will be evaluated regularly for overall trends, new signals, and consistencies and/or inconsistencies across the various data sources. Spontaneous reports will continue to be analysed using event report frequencies. Data from ongoing and planned trials will be reported in Development Safety Update Reports and from spontaneous reports and literature sources within Periodic Safety Update Reports.	Routine
Immunogenicity associated with the subcutaneous formulation[e]	**Routine**: Regular assessment of anti-rituximab and anti-rHuPH20 antibodies will continue in ongoing and planned studies involving the SC formulation.	**Routine**: The product label describes the incidence of HACA and anti-rHuPH20 antibody formation in patients receiving rituximab SC in clinical trials.

[a] All indications
[b] NHL/CLL
[c] RA and GPA/MPA
[d] GPA/MPA
[e] NHL

Pharmacoepidemiology studies refer to the Registry studies (British Society of Rheumatology Biologics Register (BSRBR) and the AntiRheumatic Therapy in Sweden Group (ARTIS) discussed in Section 3.3.1 in the respective pharmacovigilance plans). The BSRBR prospectively evaluates the safety profile of biologic agents, in particular the risks of neoplasms, serious co-morbidity and death in cohorts of patients taking particular biologics, compared with a cohort of patients who are being treated with non-biologic DMARDs only. The Swedish Registry is performing a post-marketing surveillance study including the presently available biologics used in treating patients with rheumatic diseases. This is performed in collaboration with the Swedish Society of Rheumatology and the Swedish Medical Products Agency, and aims to provide long term safety data on major comorbidities with the use of biologics.

The below Pharmacovigilance activities are needed to investigate some of the safety concerns.

Table 22: Ongoing and planned studies in the PhV development plan

Activity/Study title	Safety concerns addressed	Status	Date for submission of interim or final reports
British Society of Rheumatology Biologics Register	*Immunogenicity and Autoimmune Disease; Pregnancy and*	*Ongoing*	*Planned Submission of Interim data – Q2 2013 (due to slow*

Activity/Study title	Safety concerns addressed	Status	Date for submission of interim or final reports
	Lactation; Gastrointestinal Perforations; Impact on Cardiovascular Disease; Malignant Events; De Novo HBV, HBV Reactivation; Infections; Infusion Related Reaction		*recruitment during initial phase of rituximab cohort).*
ARTIS – Sweden	*Immunogenicity and Autoimmune Disease; Pregnancy and Lactation; Off label use in autoimmune disease; Gastrointestinal Perforations; Impact on Cardiovascular Disease; Malignant Events; De Novo HBV, HBV Reactivation; Infections; Infusion Related Reaction*	*Ongoing*	*Planned Submission of Final Data for BSRBR – Q2 2014*
RABBIT – Germany	*Immunogenicity and Autoimmune Disease; Pregnancy and Lactation; Gastrointestinal Perforations; Impact on Cardiovascular Disease; Malignant Events; De Novo HBV, HBV Reactivation; Infections; Infusion Related Reaction*	*Ongoing*	*Planned Submission of Final Data for RABBIT – Q4 2012*
WA27893	*Infections; Opportunistic Infections; De Novo HBV, HBV Reactivation; Malignant Events; Impact on Cardiovascular Disease; Infusion Related Reaction*	*Recruiting*	*Planned Submission of Final Data , April 2018*
GRAID II - Germany	*De Novo HBV, HBV Reactivation;*	*Ongoing*	*Within 12 months of end of study,*

Activity/Study title	Safety concerns addressed	Status	Date for submission of interim or final reports
	Infections; Malignant Events; Impact on Cardiovascular Disease; Infusion Related Reaction		*anticipated to be 2015*
WA25615	*Pregnancy and Lactation*	*Ongoing*	*The common closeout date will occur 18 months after the enrollment of the last patient.*
BA28478 (Drug Utilization Study) PASS	*Off label use in autoimmune disease*	*Planned*	*Depending on study start after having received the EMA approval of the protocol, it is expected that a final study report will be submitted in 2014.*
RAVELOS	*Long-Term Follow-Up safety of ANCA-associated vasculitis*	*Ongoing*	*Planned Submission of Final Data , Q2, 2015*
Plasma Exchange and Glucocorticoids for Treatment of Anti-Neutrophil Cytoplasm Antibody (ANCA)-Associated Vasculitis (PEXIVAS)	*Infections*	*Ongoing*	*Started in 2010 with a plan to complete in 2016*
Multicenter, randomized, controlled trial comparing rituximab with azathioprine as maintenance therapy in relapsing ANCA-associated vasculitis (MAINRITSAN I)	*Pregnancy and Lactation*	*Ongoing*	*Started in 2008, estimated study completion date December 2013, final data collection date for primary outcome measure in June 2013*
Maintenance of Remission Using Rituximab in Systemic ANCA-associated Vasculitis II (MAINRITSAN II)	*Pregnancy and Lactation*	*Ongoing*	*Started in November 2012, estimated study completion date February 2018, final data collection date for primary outcome measure in August 2017*
An International, Open	*Pregnancy and*	*Ongoing*	*Start date December*

Activity/Study title	Safety concerns addressed	Status	Date for submission of interim or final reports
Label, Randomised Controlled Trial Comparing Rituximab With Azathioprine as Maintenance Therapy in Relapsing ANCA associated Vasculitis (RITAZAREM)	*Lactation*		*2012, estimated study completion date December 2016, final data collection date for primary outcome measure in December 2016*

PRAC advice

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

2.8. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the SmPC have been updated (see Annex to this report). The Package Leaflet has been updated accordingly.

Furthermore, since post authorisation measures have been agreed in the RMP and the CHMP has requested a revision (version 9.3) to be submitted by June 2013, this was reflected in the Annex in line with the latest QRD template rev. 9.

Section “Additional risk minimisation measures” has been added to reflect the additional risk minimisation measures (educational material and patient alert card) agreed following the assessment of a previous RMP version (v7.0) and a related follow-up measure FUM070.1.

Annex IIIA has been updated to reflect that the patient alert card is addressed to all patients with non-oncology indications (not only addressed to Rheumatoid Arthritis patients).

3. Benefit-Risk Balance

Benefits

Beneficial effects

The RAVE study showed convincingly that RTX was non-inferior to oral CYC + AZA. At month 6, 64% in the RTX arm was in remission vs. 55% in the CYC arm (95.1% CI of the difference: -4.3% – 23.4%). thus, the primary objective of the study was achieved.

The conclusion of non-inferiority in terms of percentage of patients who achieved complete remission at month 6, is considered valid; The pivotal study design is acceptable and appropriate assay sensitivity is established. One single RCT is considered acceptable, given the rareness of the disease, the high response rate in an otherwise fatal disease, and the predictable control-response. Subgroup

analyses showed that non-inferiority was shown for both disorders (GPA and MPA). The rate of flares and the proportion of patients remaining in complete remission was comparable in the two arms at 12 months.

Rituximab is demonstrated to be non-inferior as compared to standard CYC treatment for induction of remission in MPA and GPA and seems to be particularly effective in the relapsing forms of these conditions.

Uncertainty in the knowledge about the beneficial effects

Although the dose recommendation is considered sufficiently justified, the lack of dose-finding studies conducted with rituximab in AAV is can be suggested that a flat, less frequent, and in total lower dose as applied in RA (booster of 2 x 1000 mg followed by maintenance of 1000mg every 6 months as maintenance) may be as efficacious as the recommended dosing regimen of 4 x 375mg/ m2. Relevant measures to investigate this are agreed within the RMP.

The RAVE study was designed to evaluate induction therapy at 6 months, and to observe the duration of the PD and clinical effect of rituximab in the long-term follow-up. As the study was designed to evaluate induction therapy, and maintenance of efficacy was not established, the original general indication has been restricted to induction of remission in adult patients with severe~~ly~~ active Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA).

The need of active maintenance therapy to *prevent relapses* was not investigated. However, relapse-prevention is considered relevant as relapses may be severe and life-threatening. A relevant statement that maintenance treatment with immunosuppressants should be considered for relapse prevention, especially for patients at risk (e.g. with a history of earlier relapses and GPA, or patients with a reconstitution of B-lymphocytes and PR3-ANCA at monitoring) is added in section 5.1 of the SmPC. Further studies on maintenance therapy are agreed in the context of the RMP.

With the restriction of the indication to induction therapy earlier issues on a general treatment of GPA/MPA due to limitations of the design of the pivotal RAVE trial, are now obsolete.

Risks

Unfavourable effects

The safety profile of rituximab is well known from its use in lymphoma and rheumatoid arthritis patients. ADRs of special importance are primarily infusion reactions within 24 hours after the infusion either allergic or caused by the cytokine release syndrome, cardiac disorders, haematological abnormalities such as leukopenia increase in rate of infections among which reactivation of hepatitis B and PML can be fatal.

In the RAVE study the pattern of AEs did not deviate from what could be anticipated. The overall safety was comparable between the 2 groups, with similar rates per patient-year of any adverse event, however, specific AEs varied across treatment groups. The investigators had *a priori* selected AEs of special interest; these were: death, bone marrow suppression, infections, hemorrhagic cystitis, malignancies, venous thrombo-embolic event, hospitalizations, CVAs, and IRRs. As expected, more grade 2-4 lymphopenia/leukopenia was observed in the CYC group compared with RTX leading to a number of drug discontinuation. More hospitalizations occurred in the RTX group mainly due to infections or disease flares. Infections were upper respiratory or UTI. This could probably in part be explained by the slightly higher age of patients in the RTX group and a higher incidence of impaired

renal function in that group. DVTs occurred more often in the CYC group (1% in the RTX group vs. 8.2% in the CYC group at 18 month). IRRs were similar across the treatment arms and all were moderate or mild in severity. Cardiac events were higher in the RTX group by month 18; 18.2% vs. 12.2%. This was largely due to low-grade tachycardias and atrial fibrillation occurring in the RTX arm. Mild hypertension was also more pronounced in the RTX group. There were six malignancies in 5 patients initially treated with rituximab and two malignancies in 2 patients initially treated with CYC over a total of 573.90 patient-years of follow up in RAVE. The rates of malignancy across both treatment groups are consistent with the published malignancy rates (based on SIRs) in AAV with or without treatment with CYC.

The use of rituximab is also associated with JC-virus (PML) and other opportunistic infections, although these are also reported for cyclophosphamide in the literature.

The incidence of venous thrombotic events was considerably lower for RTX than for CYC (5.1% versus 9.2%), which may be of interest in patients at risk. Furthermore, rituximab is not known to be teratogenic or reducing fertility.

In conclusion, the pattern of adverse events demonstrated in the RAVE study does not raise any new concerns.

Uncertainty in the knowledge about the unfavourable effects

The high rate of infections may be due to the co-medication of high doses of steroids, or the relatively high rituximab dose. The proposed corticosteroid dose is established for standard therapy with cyclophosphamide. In the SPC of rituximab, also high doses of glucocorticosteroids (GC) are recommended as co-medication for the ANCA-vasculitis indication. Although rituximab caused less leukopenia, earlier B-cell reconstitution, and less T-cell cytopenia compared to CYC, the rate of serious infections was the same. This might be partly related to the high GC doses that were used add-on to rituximab. Therefore, an additional RMP measure is requested for an update with data from an ongoing randomized trial in AAV patients, investigating whether a reduced cumulative dosing regimen of GCs is as effective as a standard regimen, add-on to rituximab.

Regarding malignancies, the follow-up may be too short and the number of subjects may be too low to evaluate the risk. So far, rituximab is not clearly associated with a higher incidence of solid tumors in other indications. Although there may be confounding factors such as earlier use of CYC, smoking and high age, the risk could however is not to be fully excluded. A longer follow-up of the RAVE study population, data from ongoing studies and participation in registries are expected to provide more information on long term safety and are agreed within the RMP.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The data derived from study RAVE are considered to demonstrate a clinically relevant benefit to patients as induction therapy considering the limited treatment options available for this serious disorder, since non-inferiority to CYC was demonstrated in terms of efficacy and a comparable safety profile is established.

From a safety point of view the profile of rituximab there may be potential advantages as compared to CYC, such as lower risk of neurotoxicity, and infertility. These potential advantages cannot be detected yet based on short-term studies, but are considered relevant.

In general, treatment with rituximab was tolerable for the majority of subjects and overall the adverse event profile was consistent with previous experience. There are no options available for patients resistant and intolerant to standard care with cyclophosphamide, and this is considered an unmet medical need.

Benefit-risk balance

The Benefit/Risk balance is considered positive for rituximab as induction treatment of severe GPA/MPA flares as rituximab may serve as an alternative treatment option for standard care with CYC, as non-inferiority has been shown regarding efficacy and safety.

Cyclophosphamide has specific toxicity which is not evident for rituximab, such as urotoxicity, teratogenicity, and impaired fertility. These potential advantages cannot be detected yet based on short-term studies, but are considered relevant.

Discussion on the Benefit-Risk Balance

The indication has been limited to the treatment of adults patients as the PDCO has issued a deferral for an observational paediatric study in 25 subjects aged 2-18 years of age. A waiver has been given for the population younger than 2 years of age.

The benefit-risk of Mabthera in the indication:

> MabThera, in combination with glucocorticoids, is indicated for the induction of remission in adult patients with severely active Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA).

is therefore considered positive.

4. Recommendations

The application for the following indication

> MabThera, in combination with glucocorticoids, is indicated for the induction of remission in adult patients with severely active Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA).

is approvable since major objections and other concerns have all been resolved.

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**
C.1.6 a)	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Update of section 4.1 of the SmPC in order to extend the indication of Mabthera to include the use of Mabthera in combination with glucocorticoids for the induction of remission in adult patients with

severely active Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA). SmPC sections 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 are also updated to reflect the efficacy and safety data for this indication. The Package Leaflet is updated in accordance.

Furthermore, the Annex II is being brought in line with the latest QRD template version 9 to state the deadline for the next RMP update (v9.3) and has also been updated to reflect the additional risk minimisation measures following the assessment of a previous RMP version (v7.0) and a related follow-up measure FUM070.1. Annex IIIA has been updated to reflect that the patient alert card is addressed to all patients with non-oncology indications (not restricted to Rheumatoid Arthritis patients).
The requested variation proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet.

Conditions and requirements of the marketing authorisation

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management system

The MAH shall perform the pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the Marketing Authorisation and any agreed and subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency.
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

An updated RMP shall be submitted by June 2013

- **Additional risk minimisation measures**

The MAH must ensure that all physicians who are expected to prescribe MabThera are provided with the following:

Product information
Physician information
Patient information
Patient Alert card

The physician information about MabThera should contain the following key elements:

- The need for close supervision during administration in an environment where full resuscitation facilities are immediately available

- The need to check, prior to MabThera treatment, for infections, for immunosuppression, for prior/current medication affecting the immune system and recent history of, or planned, vaccination
- The need to monitor patients for infections, especially PML, during and after MabThera treatment
- Detailed information on the risk of PML, the need for timely diagnosis of PML and appropriate measures to diagnose PML
- The need to advise patients on the risk of infections and PML, including the symptoms to be aware of and the need to contact their doctor immediately if they experience any.
- The need to provide patients with the Patient Alert Card with each infusion

The Patient information about MabThera should contain the following key elements:

- Detailed information on the risk of infections and PML
- Information on the signs and symptoms of infections, especially PML, and the need to contact their doctor immediately if they experience any
- The importance of sharing this information with their partner or caregiver
- Information on the Patient Alert Card

The Patient Alert Card for MabThera should contain the following key elements:

- The need to carry the card at all times and to show the card to all treating health care professionals
- Warning on the risk of infections and PML, including the symptoms
- The need for patients to contact their health care professional if symptoms occur