Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Rituximab

Proprietary Product Name: Mabthera

Sponsor: Roche Products Pty Limited

Date of first round CER: 17 August 2012

Date of second round CER: 5 December 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
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About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
AE	Adverse event
ANCA	Anti-Neutrophil Cytoplasmic Antibodies
AUC	Area under the curve
AZA	Azathioprine
BMI	Body mass index
BMJ	Best Medical Judgement
BSA	Body Surface Area
BVAS/WG	Birmingham Vasculitis Activity Score for Wegener Granulomatosis
CCO	Common Close Out Date
CI	Confidence interval
CL	Clearance
CrCl	Creatinine clearance
CRP	C-Reactive Protein
CS	Corticosteroids
CYC	Cyclophosphamide
EUVAS	European Vasculitis Study Group
ICH GCP	International Conference on Harmonisation and Good Clinical Practice
FDA	Food and Drug Administration (USA)
GPA	Granulomatosis with Polyangiitis
HACA	Human Anti-Chimeric Antibodies
IV	Intravenous
Ig	Immunoglobulin
IQR	Inter Quartile Ratio

Abbreviation	Meaning
IRR	Infusion Related Reaction
LOCF	Last Observation Carried Forward
MPA	Microscopic Polyangiitis
MPO	Myeloperoxidase
PD	Pharmacodynamic
PK	Pharmacokinetic
PML	Progressive Multifocal Leukoencephalopathy
PR-3	Proteinase 3
RTX	Rituximab
SAE	Serious adverse event
SD	Standard Deviation
SEER	Surveillance Epidemiology and End Results
SIR	Standardized Incidence Ratio
SOC	System Organ Class
TNF	Tissue Necrosis Factor
URTI	Upper Respiratory Tract Infection
USA	United States of America
Vd	Volume of distribution
WG	Wegener Granulomatosis
WOCF	Worst Observation Carried Forward

1. Introduction

This application is a hybrid submission requesting an extension of indication for rituximab (RTX) to include the induction of remission in patients with severely active Granulomatosis with polyangiitis (GPA, previously known as Wegener Granulomatosis) and Microscopic Polyangiitis (MPA) in combination with corticosteroids (CS). The sponsor application letter is dated 12 April 2012.

Orphan drug designation has been granted for RTX use in this patient population. The hybrid submission contains a single pivotal controlled trial (RAVE Study) with supporting efficacy and safety data provided by published investigator-sponsored studies, which have evaluated the utility of RTX for the treatment of severe GPA or MPA. The supporting trials are limited by small sample sizes, lack of blinding (open label design) and/or no appropriate comparator group. The methodology of the literature search part of this submission was approved by the TGA.

The proposed additional indication is

> *Mabthera in combination with glucocorticoids is indicated for the induction of remission in patients with severely active Granulomatosis with polyangiitis (GPA, also known as Wegener's granulomatosis) and Microscopic polyangiitis (MPA).*

Rituximab is administered by intravenous infusion. The sponsor has proposed a dosing regimen for the induction of remission in GPA and MPA of 375 mg/m^2 weekly for 4 weeks. This dose was used in the single pivotal trial (RAVE Study), and is consistent with the approved dose regimen for treating patients with Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukaemia.

1.1. Orphan drug designation

Rituximab has been granted orphan drug designation for "the induction of remission in patients with severely active Anti-Neutrophil Cytoplasmic Antibody (ANCA) – associated vasculitis." The 2 most common types of ANCA associated vasculitis are GPA and MPA, however, a third and most rare type of vasculitis, Churg-Strauss Syndrome, also fits under the collective term of ANCA associated vasculitis. The sponsor is only applying for an indication in treating GPA and MPA, which is narrower spectrum of disease indication than the designated orphan disease category of ANCA-associated vasculitis. I concur with the sponsor proposal that orphan designation remains valid in this situation, and the submitted clinical dataset is consistent with an indication restricted to use in patients with GPA and MPA. Patients with Churg-Strauss Syndrome were not involved in the pivotal RAVE trial, and the pathogenic link between this condition and the presence of ANCA is less established than with GPA and MPA.

ANCA-associated vasculitis is a rare, multisystem, autoimmune disease characterized by small to medium sized vessel vasculitis and the production of ANCA in the majority of cases. The 2 commonest types of ANCA-associated vasculitis, GPA and MPA, have similar clinical features (in particular, a predilection for pulmonary and renal involvement) and comparable treatment responses. Both conditions require long-term treatment and follow-up as the reported incidence of disease relapse can be as high as 50% at 7 years after diagnosis. The reported incidence of GPA varies from 2-12 per million of population, and the estimated prevalence varies from 24-157 per million of population. There is some geographical variation, for example GPA is more common in northern compared to southern European countries. Although not formally recognised in precise definitions, there are at least 2 different phenotypes of GPA – systemic/generalized/severe forms (about 2/3 of all cases); and localised/limited forms (approximately 1/3 of all cases). Systemic GPA is typically characterized by kidney involvement (72-80%; usually a necrotizing pauci-immune glomuleronephritis), lung disease (65%; nodules and/or pulmonary haemorrhage), systemic features (weight loss and fever) and often

involvement of at least 1 other organ (most commonly, the ENT, skin or nervous system). In systemic GPA, approximately 90% of patients have positive serum c-ANCA (diffuse cytoplasmic immunofluorescence pattern) with anti-PR3 (proteinase 3) specificity on further testing.

The incidence of MPA is estimated to be 3-24 cases per million of population, and prevalence estimates vary between 25-94 per million. MPA has been reported to occur worldwide and can affect all ethnic groups, but with predominance in Caucasian people. Males are affected slightly more frequently (male to female ratio varies from 1.2-1.8). The mean age of onset for MPA is 50 years, while GPA typically affects a slightly younger population (mean age of onset 41 years). The most common reported disease manifestations of MPA are renal involvement (nearly 100%; usually a necrotizing pauci-immune glomuleronephritis), generalized systemic features (70-75%; often myalgia and arthralgia), pulmonary disease (~50%; typically alveolar haemorrhage), gastrointestinal manifestations (~50%; mainly abdominal pain and occasionally bleeding), skin lesions (~50%) and peripheral nervous system involvement (~50%; usually mononeuritis multiplex). Positive ANCA serology is detected in 2/3 of cases, with the major observed pattern being p-ANCA (perinuclear staining) with anti-MPO (myeloperoxidase) specificity. It is noteworthy that neither the ACR criteria (1990) nor the Chapel Consensus Conference (CHCC, 1994) on the nomenclature of systemic vasculitis incorporate ANCA positivity as a diagnostic feature.

Of further importance, the medical literature with the support of professional associations (such as the American Colleges of Rheumatology, Chest Physicians and Nephrology) are proactively removing eponymous associations from disease nomenclature, so that Wegener Granulomatosis is being progressively replaced with the syndrome name, “Granulomatosis with polyangiitis (GPA)”.

2. Clinical rationale

ANCA-associated vasculitis is a rare, multisystem, autoimmune disease characterized by small to medium sized vessel vasculitis, the production of ANCA, and the frequent occurrence of significant respiratory tract and kidney disease in its severe form. There are 3 types of ANCA-associated vasculitis, but the 2 commonest sub-types are GPA and MPA. Cyclophosphamide (CYC) and corticosteroids (CS) have been the standard of care for inducing remission in these diseases for more than 40 years, however, both therapies are associated with significant potential toxicity (short and long-term), treatment failures and disease relapses (de Groot *et al*, 2009). There is a major unmet clinical need for alternative treatments in patients suffering from severe ANCA-associated systemic vasculitis.

B-Lymphocytes play an important role in the pathogenesis of autoimmune diseases, including ANCA-associated vasculitis, whereby the percentage of activated peripheral blood B-lymphocytes has been shown to correlate with disease activity, and certain effects of CYC on B-cells are associated with a positive treatment response. Rituximab, an anti-CD20 monoclonal antibody approved for use in RA, NHL and CLL, depletes B-lymphocytes through several potential mechanisms including complement mediated toxicity, antibody-dependent cell mediated cytotoxicity, as well as the inhibition of B-cell proliferation and the induction of apoptosis. Furthermore, short-lived plasma cells are considered to be the primary source of various pathogenic autoantibodies (including ANCA), and these cells are the progeny of antigen-specific B-cell precursors. Hence, the administration of RTX may result in the disruption of pivotal B-cell contributions to disease pathogenesis and suppress autoantibody production. Moreover, preliminary open-label, small patient number experiences suggested a potential role for RTX in controlling severe refractory GPA and MPA, which subsequently led to the

development of controlled trials such as the RAVE Study to more rigorously examine a potential treatment effect and safety profile for RTX use in this patient population (Jones *et al*, 2009[1]).

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

Module 5

- 1 clinical pharmacology sub-study of the pivotal RAVE Study, which provided pharmacokinetic and pharmacodynamic data collected from 97 subjects with ANCA associated vasculitis treated with RTX.
- 1 population pharmacokinetic analysis of that data.
- 1 pivotal efficacy/safety study called the RAVE Study (Stone *et al*, 2010).
- No dose-finding studies.
- 1 supporting efficacy/safety study called RITUXVAS (Jones *et al*, 2010).
- 12 published, investigator-initiated studies identified by a literature search.

Module 1

- Application letter, application form, draft Australian PI and CMI, Pre-submission documents, literature search submission documents, FDA-approved product label, European Summary of Product Characteristics, and Risk Management Plan

Module 2

- Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

3.2. Guidance

This submission is consistent with the pre-submission planning advice given to the sponsor by the TGA. There are no specific regulatory guidelines pertaining to the requested indication. However, the TGA delegate recommended review of related guidelines for consideration in compiling this evaluation report. Two EMA guidelines, both adopted by the TGA are noteworthy:

- CPMP/EWP/2330/99 "Points to consider on application with 1. Meta-analyses; 2. One Pivotal Study"
- CHMP/EWP/83561/2005 "Guideline on Clinical Trials in Small Populations".

The TGA have approved the literature search strategy, including the exclusion criteria for identifying all relevant publications, as part of the hybrid submission. The literature search process for rituximab use in ANCA-associated vasculitis was conducted in November 2011. All types of publications including review articles, case reports, letters and commentaries were retained. In total, 643 citations were retrieved by the literature search, but 627 articles were excluded after the exclusion criteria were applied leaving a total of 16 references requiring evaluation. These citations will be considered as supportive data for the indication, and will be discussed in detail later in this report. The reasons for citation exclusion (n=627) from

[1] Erratum: the correct reference is Stone *et al*., 2010.

consideration were: - no relevant reported safety of efficacy data (372; 59.3%), no relevant disease condition (111; 17.7%), case reports of efficacy only (57; 9.1%), editorial opinion (46; 7.3%), reviews of efficacy data (34; 5.4%) and retrospective efficacy reports (7; 1.1%).

An important omission from the literature-based submission is the retrospective study with standardised data collection published by Holle *et al* (2011), which examined the effectiveness of RTX in treating the granulomatous versus vasculitic manifestations of GPA. This publication may have post-dated the data cut-off time-point, as it does not appear to be excluded on the basis of the literature search process methodology. The results of this trial will be included in both the efficacy and safety sections of this report.

3.3. Paediatric data

The submission did not include paediatric data.

3.4. Good clinical practice

The 2 main studies (1 pivotal [RAVE], and the other trial [RITUXVAS] was supportive) evaluating the use of RTX in adult subjects with GPA or MPA were conducted in accordance with the principles of Good Clinical Practice (GCP) and compliance with ethical requirements was met. No major protocol deviations were recorded in either of the 2 main studies.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

The single pivotal RAVE Study was the only source of pharmacokinetic (PK) data for this submission.

4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional PK studies in humans.

4.2.1. Pharmacokinetics in the target population

In the pivotal RAVE Study, RTX levels were evaluated prior to the first and third doses of therapy, and thereafter on study days 29, 60, 120, 180, 270 and 545. Patients in this trial received a weekly dose of 375 mg/ m^2 of RTX for 4 consecutive weeks. Data for PK analysis was available for a total of 97 patients (out of a possible 99 subjects) who were administered RTX. One patient's results were excluded from the PK analysis because of implausibly low RTX concentrations following the end of infusion. The data was analysed with non-linear mixed effects modelling using NONMEM software.

RTX is known to be eliminated by 2 pathways: a target mediated pathway related to B-cell binding, and a target-independent process similar to that observed with endogenous IgG antibodies. The structural model that best describes the PK of RTX is a 2-compartment linear model. A summary of the key PK parameters of RTX in the ANCA associated vasculitis population is presented in Table 1.

Table 1. Key PK parameters of RTX in the ANCA associated vasculitis population

PK parameter	N	Mean	SD	Median	Range
Clearance (mL/day)	97	313	131	281	116 - 726
Volume of Distribution (L)	97	4.50	1.08	4.40	2.25 - 7.39
Half-life (Days)	97	24.3	8.05	23.4	9.38–48.7
AUC_{0-inf} (mg/mL*day)	97	10.6	3.93	10.1	3.14–24.5

AUC_{0-inf}=area under concentration time curve from time 0 to infinity; PK=pharmacokinetic; SD=standard deviation

The median of individual estimates of terminal elimination half-life for RTX among the 97 patients in the RAVE Study was 23.4 days (range: 9.38-48.7 days). Median RTX clearance (CL) was 281 mL/day (range: 116-726 mL/day), and the drug's volume of distribution (Vd) in the central compartment was 4.40 L (range: 2.25-7.39 L). The inter-patient variability (and % standard error of estimates) for CL and Vd were moderate at 42.1% (13.8%) and 26.8% (18.9%), respectively. The PK parameters observed for RTX in patients with ANCA vasculitis are similar to those observed in adult patients with active RA.

Gender and the presence of Human Anti-Chimeric Antibodies (HACA) were important covariates explaining the inter-individual variability in CL, but still only account for 30% of the observation. Males had 31.4% faster CL than females, and HACA-positive subjects had 37% faster CL than HACA-negative patients. However, based on modelling, half-life between males and females was similar (23.6 days for men versus 24.9 days for women). The presence of HACA shortened half-life estimates from 25.6 to 19.0 days, and was also correlated with a lower exposure to RTX (as determined by the AUC-time curve from 0-infinity [AUC_{0-Inf}]). In the population PK analysis using HACA status at any time as a covariate, HACA-positive patients had an AUC_{0-Inf} of 8.00 mg/mL*days compared with 11.2 mg/mL*days for HACA-negative subjects.

Gender and Body Surface Area (BSA) are the important covariates explaining the inter-individual variability on Vd, accounting for 56% of that variability. Males had a 21.6% larger Vd than females. Patients with a larger BSA had a larger Vd (e.g. if BSA >2.30 m^2, then Vd 18% higher).

The relationship between RTX exposure (AUC_{0-Inf}) and efficacy response was also explored in the RAVE Study. Patients were dichotomously divided into being either above or below the median AUC_{0-Inf} of 10.2 mg/mL*day with n=47 in each group. At 6 months, a similar proportion of patients in each of the groups (low versus high AUC) achieved complete remission (defined as BVAS/WG score of 0 and successful CS taper) and remission (defined as BVAS/WG score of 0). Using the per protocol population, the absolute response rate for complete remission is 61.7% (29/47) for low exposure and 70.2% (33/47) for high exposure. For remission, the response rate is 80.9% (38/47) for low AUC and 83.0% (39/47) for high AUC. In addition, Table 2 shows that AUC_{0-Inf} is similar between patients who obtained complete remission at 6 months and those who did not.

Table 2. AUC_{0-Inf} for Rituximab-treated patients with and without complete remission at 6 months (Per Protocol Population)

Complete Remission [a] At 6 months		AUC_{0-inf}				
	n	Mean	SD	Median	Minimum	Maximum
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.

4.2.2. Pharmacokinetic interactions

There is limited information available for RTX with respect to potential PK interactions (as per the current approved product information) and this submission did not provide any additional data to address this issue.

4.3. Evaluator's overall conclusions on pharmacokinetics

In this submission, the PK properties of RTX when used in patients with ANCA associated systemic vasculitis were assessed from data collected in a single pivotal clinical trial (RAVE Study) involving 97 patients who received a single induction course of RTX (375 mg/m^2 weekly, for up to 4 weeks of therapy). The majority of subjects were middle-aged and Caucasian. Overall, the population PK analysis of the collected data demonstrated that RTX has PK characteristics in patients with ANCA associated vasculitis that are similar to those observed in adult patients with RA. In particular, the presence of HACA significantly increases RTX clearance, with a consequent reduction in half-life and overall exposure to the drug. Gender also has a moderate effect on clearance and volume of distribution, and volume of distribution is additionally impacted upon by the subject's body surface area. RTX demonstrates moderate inter-individual variability, the majority of which cannot be readily explained. There are significant deficiencies to the current known PK characteristics of RTX use in patients with autoimmune disease. This is reflected in the limited rationale provided by the sponsor in the justification of the RTX dose selected for assessment in the pivotal clinical study. In particular, no dose ranging studies have been performed to accurately determine the minimum effective dose to obtain effect (PD or clinical). Dosing studies after repeat courses of RTX (including those with extended intervals between dosing) have not been performed. This may be a potential problem in the future as it is biologically plausible that increased rates of HACA development may occur with repeat courses and/or extended dose intervals, which would then have significant implications for the PK characteristics of RTX.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

The single pivotal RAVE Study was the only source of pharmacodynamic (PD) data for this submission.

5.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional PD studies in humans.

5.2.1. Mechanism of action

RTX binds specifically to the CD20 antigen located on the transmembrane of pre-B and mature B-cells. This action consequently results in B-cell lysis through several putative mechanisms including complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity.

5.2.2. Primary pharmacodynamic effects

Using flow cytometry of peripheral blood, it is possible to evaluate the primary pharmacodynamic (PD) effect of RTX by measuring the change in CD19+ B-cells following RTX. Although CD20+ B-cells are the primary target of RTX, it is unreliable to use this B-cell type for PD assessment as residual RTX may interfere with the cytometric analysis.

After 2 infusions of RTX in the RAVE Study, the number of peripheral blood CD19+ B-cells decreased to <10 cells/μL in the majority of patients (93.5%; 87/93) and remained at that

depleted level for most patients through to 6 months (83.3%; 70/84) – refer to Table 3. By 12 months, the majority of patients (80.5%; 66/82) showed signs of B-cell repletion (i.e. CD19+ count > 10 cells/μL). At 18 months of follow-up following a single induction course of RTX, 87.1% (61/70) of subjects had evidence of B-cell repletion. From this data, it is difficult to infer the optimal timing for repeat courses of RTX (if required for relapsed disease), and on what measure repeat dosing should be based (empiric therapy at pre-determined time intervals, upon B-cell repletion, or clinical relapse). The sponsor is requesting an indication listing for induction treatment only, but given the high rate of disease relapse over the long-term (several years) it is likely that the question of repeat courses of RTX be considered by clinicians.

Table 3. Proportion of patients with CD19 counts ≤ 1 and <10 cells/μL over time.

	Rituximab N=99	Cyclophosphamide N=98
Baseline (n= no. of evaluable patients)	94	93
<10 cells/μL 2	2 (2.1%)	3 (3.2%)
Week 2 (n)	93	95
≤ 1 cell/μL	39 (41.9%)	0
< 10 cells/μL	87 (93.5%)	6 (6.3%)
Month 1 (n)	92	92
≤ 1 cell/μL	46 (50.0%)	0
< 10 cells/μL	87 (94.6%)	9 (9.8%)
Month 2 (n)	91	89
≤ 1 cell/μL	46 (50.5%)	1 (1.1%)
< 10 cells/μL	84 (92.3%)	40 (44.9%)
Month 4 (n)	73	74
≤ 1 cell/μL	30 (41.1%)	6 (8.1%)
< 10 cells/μL	67 (91.8%)	49 (66.2%)
Month 6 (n)	84	74
≤ 1 cell/μL	33 (39.3%)	3 (4.1%)
< 10 cells/μL	70 (83.3%)	44 (59.5%)
Month 12 (n)	82	73
≤ 1 cell/μL	2 (2.4%)	2 (2.7%)
< 10 cells/μL	16 (19.5%)	26 (35.6%)
Month 15 (n)	74	69
≤ 1 cell/μL	2 (2.7%)	0
< 10 cells/μL	13 (17.6%)	26 (37.7%)
Month 18 (n)	70	64
≤ 1 cell/μL	2 (2.9%)	0
< 10 cells/μL	9 (12.9%)	18 (28.1%)

Data collected after cross-over or open-label RTX are excluded from the analysis

For patients in the CYC treatment group, peripheral blood CD19+ B-cell counts also decreased in up to 2/3 of subjects by 6 months, but at slower rate and of reduced magnitude compared with the RTX group. Nonetheless, significant numbers of patients treated with CYC induction did achieve this PD outcome and the effect has been linked to a possible mechanism of action for CYC in treating patients with vasculitis. Between 12- 18 months of follow-up, a higher proportion of patients maintained B-cell depletion in the CYC group, most of whom received AZA as their maintenance therapy. In contrast, patients given RTX induction therapy did not receive maintenance immunosuppression in the RAVE Study.

Another way that the sponsor could effectively demonstrate the PD effect of RTX in patients with vasculitis is to examine the change in CD19+ B-cell expression at the sites of organ involvement (e.g. kidney, ENT or orbital disease) with sequential tissue analysis following RTX. This submission did not contain such information but would be valuable if already performed, or is under consideration for further investigation.

5.2.3. Secondary pharmacodynamic effects

This was not presented in the current submission.

5.2.4. Time course of pharmacodynamic effects

Animal and human studies indicate that peripheral blood B-cell numbers are reduced by more than 95% in comparison with pre-treatment values within 24 hours of administration of the first RTX dose. However, changes in clinical status are typically not observed until at least 2 weeks after receipt of the first RTX infusion.

5.2.5. Relationship between pharmacodynamic effects and efficacy

The RAVE Study also investigated the relationship between PD effect (B-cell depletion) and efficacy. Most patients (94.6%; 87/92) in the RTX group achieved B-cell depletion at 1 month, but among the 5 subjects who did not obtain this degree of B-cell reduction, 4 achieved the primary efficacy endpoint at 6 months, and 1 did not. At 6 months, 14 patients (16.5% of 85) in the RTX group did not have evidence of B-cell depletion, yet 11 (79%) of those subjects achieved the primary efficacy endpoint. These results suggest a limited relationship between B-cell depletion and efficacy outcomes in the first 6 months following induction therapy with RTX. However, the data beyond 6 months suggests a different outcome. As Table 3 shows, many RTX treated patients had a significant return of CD19+ B-cell counts between 6 and 12 months. Peripheral B-cell repletion did not appear to impact upon the rate of complete remission over time (up to 18 months), but showed a signal towards recurrence of ANCA disease. The number of disease flares between 6 and 18 months were 17 severe and 24 limited flares for the RTX group compared with 13 severe and 16 limited for the CYC/AZA arm. This result suggests the loss of RTX treatment effect beyond 6-12 months, which may be associated with B-cell recovery.

5.2.6. Genetic-related differences in pharmacodynamic response

There is a significant amount of published evidence linking polymorphisms of Fc gamma receptors to improved clinical response, and also toxicity (e.g. long term risk of neutropenia in patients after autologous bone marrow transplantation) from RTX for a variety of autoimmune conditions (RA and SLE) and lymphoma (Ruyssen-Witrand *et al*, 2012). The sponsor has not examined this potential relationship in patients with ANCA associated vasculitis.

5.2.7. Pharmacodynamic interactions

This was not presented in the current submission.

5.3. Evaluator's overall conclusions on pharmacodynamics

For this submission, the PD properties of RTX when used in patients with ANCA associated systemic vasculitis were assessed from data collected in a single pivotal clinical trial (RAVE Study) involving 197 patients, 99 of whom received a single induction course of RTX (375 mg/m^2 weekly, for up to 4 weeks of therapy). The majority of subjects were middle-aged and Caucasian. The sponsor has appropriately nominated changes in peripheral blood CD19+ B-cell levels following RTX as the pivotal PD marker to support the biological plausibility of the drug in ANCA associated vasculitis. More than 90% of patients treated with RTX demonstrate B-cell depletion by 2-4 weeks following commencement of therapy, and most patients (83.3%; 70/84) maintained this effect until at least 6 months of follow-up. By 12 months, the majority of patients (80.5%; 66/82) showed signs of B-cell repletion. The relationship between achieving B-cell depletion and efficacy outcomes in the first 6 months following induction therapy with RTX is limited. However, with increasing rates of B-cell repletion 6 months after RTX induction, there appears to be a trend towards disease related flares (both severe and limited) suggesting a loss of effect with time for RTX beyond 6-12 months. The sponsor has not performed studies in patients with systemic vasculitis which may have examined the relationship between a reproduction of the desired PD effect with repeat RTX courses

6. Dosage selection for the pivotal studies

The dose and administration frequency of RTX used in the pivotal RAVE study (375 mg/m^2 weekly for 4 doses) is poorly justified by the sponsor and is a significant area of uncertainty requiring further examination. The sponsor states that previous studies (RITUXVAS) and case series/reports have utilised the same dose and regimen, but no dose-finding studies have been performed for this indication. The dose and regimen of RTX appears to have been extrapolated

from that which is approved for the indication of treating lymphoma. However, there are several case reports/series in a diverse range of autoimmune conditions such as idiopathic thrombocytopenia purpura, autoimmune haemolytic anaemia, pemphigus vulgaris, myasthenia gravis which indicate that substantially lower doses of RTX (e.g. 100 mg weekly for 4 weeks, or 500 mg x 2 given a fortnight apart) are clinically effective, and are able to achieve the desired pharmacodynamics effect of prolonged CD19+ B-cell depletion (Barcellini *et al*, 2012; Horvath *et al*, 2012; and Blum *et al*, 2011). Furthermore, the design of the RAVE Study (i.e. by using a single induction course of RTX) provides no information about repeat dosing (either scheduled maintenance, or on-demand for disease relapse) of RTX in patients with ANCA associated vasculitis. This is a major deficiency in the current knowledge regarding the utility of RTX treatment for patients with vasculitis, and requires further on-going studies or analysis by the sponsor.

The doses of CYC, AZA and corticosteroids used in the pivotal RAVE study were appropriate, consistent with contemporary clinical practice, and based on several previous historical studies in patients with systemic vasculitis.

7. Clinical efficacy

7.1. Studies provided for the proposed indication

The sponsor proposes the additional indication: *"Mabthera in combination with glucocorticoids is indicated for the induction of remission in patients with severely active Granulomatosis with polyangiitis (GPA, also known as Wegener's granulomatosis) and Microscopic polyangiitis (MPA)".*

Table 4 shows a tabular listing of the efficacy and safety studies contained within this submission.

Table 4. Submitted efficacy and safety studies

Study	Treatment arms	Total n; Gender; Median Age	Patient Population	Concomitant Therapies	Primary Endpoint	Results
Pivotal, NIAID-sponsored, randomized, controlled study						
ITN021AI/ RAVE: 5.3.5.1.1/Vol.1/p.1	1. Experimental arm: IV RTX wkly × 4 2. Control arm: oral CYC daily	197; M: 99 F: 98; 52 years	Severe AAV (147 WG, 48 MPA)	GC	Complete remission (BVAS/WG score = 0) and successful taper of GC treatment at 6 months after randomization	64% of patients in the rituximab arm achieved complete remission at 6 months compared with 55% of patients in the CYC arm.
Investigator-initiated, randomized, controlled study						
RITUXVAS [10065: 5.4/Vol.15/p.529]	1. Experimental arm (n = 33): IV RTX weekly × 4 and 2 × IV CYC pulses 2. Control arm (n = 11): IV CYC and AZA	44; M: 23 F: 21; 68 years	Newly diagnosed AAV with renal involvement	GC	Sustained remission (BVAS/WG score = 0) at 12 months after randomization	Sustained remission achieved in: 25/33 patients (experimental arm); 9/11 patients (control arm)
Uncontrolled Studies and case series						
Aries et al. 2006 [10153: 5.4/Vol.18/p.1364]	RTX 375 mg/m^2 every 4 weeks × 4	8; M: 5 F: 3; 41 years*	WG with granulomatous manifestations refractory to standard therapy	CYC, MMF, MTX, GC	Remission defined as BVAS indicating absence of signs of new or worse disease activity and persistent activity for <=1 item	Remission: 2/8 patients
Brihaye et al. 2007 [10025: 5.4/Vol.14/p.34]	RTX 375 mg/m^2 weekly × 4	8; M:5 F: 3 50 years*	Refractory WG	GC, IS	Remission defined as BVAS 2003 = 0	Complete remission :3/8; Partial remission : 3/8
Eriksson et al. 2005 [10036: 5.4/Vol.14/p.110]	RTX 500 mg weekly × 4 (n = 6) RTX 500 mg weekly × 2 (n = 3)	9; M:5 F:4; 59 years	Therapy-resistant or relapsing ANCA-positive vasculitis (7 WG, 2 MPA)	MMF, AZA, CYC, GC	Complete remission (BVAS 1994 = 0) at 6 months after start of RTX.	Complete remission: 8/9; Partial remission: 1/9

Table 4 continued. Submitted efficacy and safety studies

Study	Treatment arms	Total n; Gender; Median Age	Patient Population	Concomitant Therapies	Primary Endpoint	Results
Jones et al. 2009 **[10064:** 5.4/Vol.15/p.516]	RTX 1 g×2, 2 weeks apart RTX 375 mg/m^2 weekly×4	65; M: 34 F: 31 47 years	Refractory AAV (46 WG, 10 MPA, 5 CSS, 4 unclassified)	GC, Anti-TNF, IVIG, AZA, MTX, MMF, CYC	Complete remission defined as absence of disease signs and symptoms, using DEI, with reduction in GC.	Complete remission: 49/65; Partial remission: 15/65
Keogh et al. 2005 **[10066:** 5.4/Vol.15/p.539]	RTX 375 mg/m^2 weekly×4	11; M: 6 F: 5; 31 years	Severe, refractory, active AAV (10 WG, 1 MPA)	Plasma exchange for nephritis, GC	Complete remission defined as BVAS/WG=0	Complete remission: 10/11; Partial remission: 1/11
Keogh et al. 2006 **[10067:** 5.4/Vol.15/p.546]	RTX 375 mg/m^2 weekly×4	10; M: 7 F: 3; 57 years	Severe, active AAV refractory to CYC	GC	Complete remission defined as BVAS/WG=0. Stable remission defined as BVAS/WG=0 for >6 months [b]	Complete remission: 10/10 patients, who remained stable for several months
Lovric et al. 2009 **[10074:** 5.4/Vol.16/p.631]	RTX 375 mg/m^2 weekly × 4	15; M:8 F: 7 45 years	Refractory or relapsing AAV (13 WG, 1 MPA, 1 CSS)	AZA, MMF, CYC, CsA, MTX, IFX, GC	Partial remission (reduction in BVAS 1994 – 0 by > 50%); Complete remission (BVAS 1994 – 0) b	Complete remission: 6/15; Partial remission: 8/15
Omdal et al. 2005 **[10087:** 5.4/Vol.16/p.714]	RTX 375 mg/m^2 weekly × 4	3; M:3 38 years a	Refractory WG	GC, MTX	Remission assessed via chest radiography, lab parameters (proteinuria, ANCA, ESR) b	Complete remission: 3/3
Sanchez-Cano et al. 2008 **[10099:** 5.4/Vol.16/p.837]	RTX 375 mg/m^2 weekly × 4	4; M:3 F: 1 45 years a	Refractory WG	CYC, GC, MTX	Remission monitored using BVAS/WG b	Complete remission: 2/4; Partial remission: 2/4

AZA = azathioprine, BVAS = Birmingham Vasculitis Activity Score; CsA = cyclosporine; CSS = Churg-Strauss Syndrome; CYC = cyclophosphamide; DEI = Disease Extent Index; GC = glucocorticosteroids; MMF = myoophenolate mofetil; IFX = infliximab; IVIG = intravenous immunoglobulin; MTX = methotrexate; RTX = rituximab; TNF = tumor necrosis factor; WG = Wegener's granulomatosis.
[a] Mean age.
[b] In some investigator-initiated studies, the primary efficacy endpoint was not clearly defined.

7.1.1. Pivotal efficacy studies

7.1.1.1. Study ITN021A1 (also referred to as the RAVE Study)

7.1.1.1.1. Study design, objectives, locations and dates

The RAVE Study was a phase II/III, randomized, active-controlled, double-blind, double-dummy, parallel-group trial that enrolled adult subjects with severe ANCA-associated vasculitis. The objective of the trial was to demonstrate that RTX was non-inferior to conventional therapy for the induction of remission, and superior to historical control. The study period was 21 December 2004 to 9 January 2009. Nine centres enrolled patients, 8 of which were in the USA and 1 in the Netherlands. The Mayo Clinic was the highest recruitment centre with 53 patients (26.9% of all enrolled patients) followed by 2 other large patient recruitment centres (n=43 for Boston University and n=35 for John Hopkins University).

The original protocol (V1.0 - 1 July 2004) was amended 7 times. The last 2 amendments occurred after the 6-month data lock. None of the amendments resulted in major changes to the study design, which may have affected the outcome or statistical analysis.

7.1.1.1.2. Inclusion and exclusion criteria

To be eligible for inclusion, patients had to be at least 15 years of age, weigh at least 40 kg, and have a diagnosis of WG or MPA according to the definitions of the Chapel Hill Consensus Conference. The vasculitis had to be active (baseline BVAS/WG score of 3 or more) and severe (at least 1 major BVAS/WG item and/or requiring CYC), and the patient had to be positive for either anti-PR3 or anti-MPO-ANCA. In addition, the diagnosis of WG or MPA either had to be

new at screening, or the patient had to have a disease flare that fulfilled the criteria for disease activity, severity and ANCA status.

The exclusion criteria involved 5 domains and patients meeting any 1 of the criterion were excluded:

- Diagnosis – Churg Strauss Syndrome as per the Chapel Hill Consensus Conference, or anti-GBM disease;
- Severity – limited disease not usually treated with CYC, or severe disease requiring mechanical ventilation because of alveolar haemorrhage;
- Co-morbidities – active systemic infection, deep space infection in the last 6 months (e.g. septic arthritis, empyema, lung abscess), active or previous hepatitis B or C or HIV infection, malignancy within the last 5 years (except squamous or basal cell skin cancer or cervical carcinoma in situ);
- Baseline results – total WCC <4000/μL, Platelet count <120,000/μL, ALT or AST > 2.5 upper limit of normal, or serum creatinine > 4.0 mg/dL;
- Past treatments – use of CYC within the preceding 4 months or previous intolerance, plasma exchange within the last 3 months, prior treatment with monoclonal antibodies (including RTX), and live vaccine within 4 weeks of randomization, or CS for longer than 14 days before screening.

7.1.1.1.3. Study treatments

The RAVE Study had 2 treatment periods: a 6-month induction of remission phase followed by a 12-month maintenance of remission period (18 months in total). During the induction of remission phase, patients were randomized to either the experimental treatment group to receive IV RTX at a dose of 375 mg/m^2 of BSA once weekly for 4 weeks plus daily placebo tablets of CYC for 3-6 months. The control arm received placebo IV infusions plus daily oral CYC at a dose of 2 mg/kg (adjusted for renal insufficiency) for 3-6 months. The initial dose of CYC was rounded to the nearest multiple of 25, with the daily dose not to exceed 200 mg. Measurements of weight and height were performed in the 14 days leading up to study baseline.

Both treatment groups received the same CS regimen consisting of 1-3 IV pulses of 1000 mg of methylprednisolone followed by a protocol mandated oral prednisone taper starting at 1 mg/kg (but not exceeding 80 mg/day initially). Prednisone tapering was to be completed by the month 6 visit in order to meet the definition of complete remission. However, depending on the patient's clinical disease state, the investigator could repeat the IV pulse of CS for up to, but not exceeding, 3 further days of therapy (i.e. a total of 3000 mg of methylprednisolone or equivalent).

Patients who experienced severe disease flares or treatment failure between visit 5 (1 week after last IV infusion of either RTX or placebo) and visit 8 (6 month visit) were crossed over in a blinded manner to the opposite treatment arm. Patients in either group who achieved remission (defined as BVAS/WG score of 0) before 6 months were switched from CYC/CYC placebo to AZA/AZA placebo tablets. No patient in either group was allowed to switch from CYC or CYC placebo before completing 3 months of treatment unless they suffered from haemorrhagic cystitis.

The cross-over design allowed patients with treatment failure (severe or limited disease flares between visits 5 and 8) to receive the other treatment strategy. Maintaining the treatment blinding optimized the data collection without compromising patient care. Furthermore, patients had a third treatment option according to Best Medical Judgement (BMJ), which allowed continued data collection with follow-up in the trial.

During the maintenance of remission phase (months 6-18), patients in the control group discontinued CYC and had their treatment switched to oral AZA (2 mg/kg/day – as per the patient weight at switchover). The initial dose of AZA was rounded to the nearest multiple of 25, and up-titrated according to weekly safety laboratory tests and patient tolerability. Patients in the experimental (RTX) group discontinued their placebo CYC tablets and received daily oral AZA placebo medicine. The AZA or matching placebo tablets were to continue to 18 months in both treatment groups. All patients who completed 18 months of study follow-up were thereafter treated according to BMJ.

For prophylaxis against Pneumocystis jiroveci pneumonia (PJP), patients in both treatment groups received daily single or double-strength trimethoprim-sulfamethoxazole tablets. If allergic to this medicine, alternative treatments for PJP prophylaxis were dapsone 100 mg/day or atovaquone 750 mg twice daily. Measures to prevent and treat osteoporosis were encouraged including use of oral calcium and/or vitamin D supplement, and bisphosphonates if they were appropriate.

7.1.1.1.4. Efficacy variables and outcomes

The **main efficacy variables** (described further below) were:

- BVAS/WG score – the achievement of a score of 0=complete remission, and 2 or less=partial remission;
- Prednisone taper – ability to cease CS completely without a disease flare;
- Severe or limited disease flares - defined according to changes in the BVAS/WG score, and the new occurrence of major or minor items on this instrument.

The primary efficacy outcome of the RAVE Study was the percentage of patients in each treatment group who achieved complete remission at month 6, defined as a BVAS/WG score of 0 and successful completion of corticosteroid taper (i.e. receiving no CS at month 6).

The BVAS/WG score is the appropriate main efficacy instrument to use in studies evaluating ANCA associated vasculitis. It is a modification of the Birmingham Vasculitis Activity Score (BVAS), which has been refined for measuring disease activity in WG. It is an internationally accepted, validated instrument with good inter- and intra-observer reliability used for the assessment of disease activity and response to treatment (within the last 28 days) in patients with ANCA associated vasculitis (Mukhtyar *et al*, 2009). The score ranges from 0-68, although in the validation studies the score range was typically 0-13. Disease features are only scored if they are due to active vasculitis as opposed to damage. Nine organ systems are assessed (e.g. pulmonary, renal, nervous system) and items are weighted as either major (each worth 3 points) or minor (each valued as 1 point). Major items refer to those which pose an immediate threat to the patient's survival or the function of a vital organ e.g. urinary red blood cell casts, pulmonary haemorrhage, mononeuritis multiplex. Minor items are defined as those which don't immediately threaten the patient's survival or vital organ function (e.g. swollen salivary glands, purpura, nasal crusting) and typically could be managed with CS (commencement or increased dose). A severe flare is defined as an increase in the BVAS/WG score of at least 3, or the occurrence of at least 1 major item following a period in which the BVAS/WG had improved. A limited flare is defined as the new occurrence or worsening of 1 or more minor BVAS/WG items following a period of improvement.

The sponsor has nominated the ability to taper prednisone completely by 6 months without a disease flare as an essential part of assessing treatment efficacy. Although it is desirable to reduce the cumulative CS exposure because of long term toxicity potential (e.g. osteoporosis, cataract formation) there is a significant and growing body of evidence from large patient databases such as EUVAS, and published trial evidence to indicate that the likelihood of relapse over the medium-longer term (2-5 years) is much higher in patients who do not continue to receive continuous low dose CS (i.e. prednisone 5-7 mg/day) for at least 18 months after

commencement of treatment. As such, the achievement of no CS by 6 months may be a desirable outcome in shorter-term follow-up (<12 months) but does not equate to improved patient outcomes over longer-term follow-up (up to 5 years). For example, the results of the CYCAZAREM Study show a relatively low relapse rate of vasculitis at 18 months in patients who received continuous low dose CS plus either AZA (15.5%) or CYC (13.7%) – Jayne *et al*, 2003. This finding is replicated at 28 months of follow-up in the WEGENT Study, whereby remission rates were 72% with CS + AZA, and 75% with CS + MTX (Seror *et al*, 2010). However, as mentioned later in this report, the 18-month relapse rate was 64% with RTX and 69% with AZA therapy in the subset of patients in the RAVE Study who did not receive low dose maintenance CS beyond 6 months. The evidence supports the continued use of low dose CS until at least 18 months to optimize long-term response rates, hence, the nomination of no CS at 6 months is an inappropriate and undesirable efficacy endpoint in terms of long-term (multi-year) outcomes.

Other efficacy outcomes (secondary and tertiary) included:

- Superiority of RTX compared to CYC for the percentage of subjects in each treatment group who had a BVAS/WG score of 0 and successful completion of CS by month 6 (This was a secondary analysis of the primary efficacy endpoint),
- The cumulative BVAS/WG area under the curve (AUC) during the 6 months after randomization,
- The percentage of subjects who achieved and maintained partial remission defined as having a BVAS score of 2 or less, and receiving no CS at month 6,
- The percentage of patients who achieved a BVAS/WG score of 0 on prednisone <10 mg/day at 6 months,
- The median cumulative CS exposure at 6 months,
- The number of severe flares (defined as an increase in BVAS/WG of 3 or more, or experiencing 1 major BVAS/WG item requiring treatment with CYC) at 6 months,
- The number of limited flares (defined as new occurrence or worsening of 1 or more minor BVAS/WG items) at 6 months, and
- Changes in ANCA status and serum inflammatory markers (ESR and CRP) at 6 months.

The endpoints for the assessment of maintenance of efficacy (assessed to 18 months) included the duration of complete remission, and the time to limited and/or severe flare after complete remission in the 2 treatment groups. Clinical outcomes of the 2 study arms in the maintenance phase were compared every 6 months (i.e. at 12 and 18 months).

7.1.1.1.5. Randomisation and blinding methods

The RAVE Study aimed to recruit 200 patients who were to be randomized in a 1:1 ratio to the experimental (RTX) or control arm (conventional therapy). Because differences in organ involvement, prognosis, and relapse rate have been documented between anti-PR3 positive ANCA and anti-MPO positive ANCA subjects, randomization was stratified by type of ANCA (PR3 or MPO), as well as study centre. The randomization was not further stratified by the clinical type of ANCA-associated vasculitis (WG or MPA), as there is overlapping clinical features, and limited data showing a different treatment response based on clinical disease type. However, to ensure that the proportions of WG and MPA patients were similar to those in the general ANCA-associated vasculitis population (i.e. generalized applicability), the maximum percentage of MPA patients to be recruited into the study was 50% of all subjects (n=100). Treatment assignments were generated in permuted blocks controlled by a central independent centre.

All activities in the study were conducted in a blinded manner including the supply of generic oral medicine kits as well as RTX/TRX placebo vials without patient or treatment identifiers. To minimize potential bias due to infusion reactions from RTX, patients in both arms received

concurrent CS with infusions to minimize the risk of systemic reactions. To conceal possible hair thinning associated with CYC, subjects wore hats to their study visit assessments for the duration of CYC or placebo CYC therapy, and for 6 months following discontinuation of this treatment. At visits, subjects were assessed by 2 independent physicians - a safety officer and an investigator who performed the BVAS/WG assessment. Patients who experienced treatment failure before 6 months were not unblinded, but switched to the other treatment option in a blinded fashion.

7.1.1.1.6. Analysis populations

The efficacy analyses in the RAVE Study were conducted on the intention-to-treat (ITT) population, defined as all randomized patients who received any study medication. Sensitivity analyses of the efficacy endpoints were performed using the per-protocol (PP) population. This was a subset of the ITT cohort, which excluded patients without any BVAS/WG assessments after randomization, and those who received less than 75% of the total calculated dose of their RTX or placebo infusions. The ITT population included 197 treated patients, while the PP population included 188 (95.4%) subjects, with 4 and 5 patients from the RTX and CYC arms excluded, respectively.

7.1.1.1.7. Sample size

A sample size of 100 patients per treatment group was estimated to yield 83% power to conclude non-inferiority using a 1-sided 0.025 level test. This calculation was derived using several assumptions. Firstly, data from other treatment studies of ANCA associated vasculitis indicated that 70% of patients receiving CYC/AZA could be expected to attain complete remission during the first 6 months of treatment. Secondly, a non-inferiority limit for the difference in percentage complete remission between RTX and CYC was estimated to be 20%. This non-inferiority margin was considered to preserve at least 60% of the treatment effect size of the active comparator (CYC/AZA) compared to historical data with no CYC treatment. Thirdly, a dropout rate of 10%, equally distributed between the 2 treatment groups was assumed. The sample size was to be re-evaluated if the dropout rate assumptions changed markedly during the study.

7.1.1.1.8. Statistical methods

The primary efficacy endpoint at 6 months was the percentage of subjects in each treatment group who achieved complete remission. Statistical analyses were performed using 2-sided hypothesis tests at the 0.05 level of significance. However, because the primary endpoint had an interim efficacy analysis performed by the Data Safety Monitoring Board once half of all patients completed their 6-month assessment, a 0.049 significance level was employed. If the lower limit of the 2-sided 95.1% CI for the difference in the primary endpoint between RTX and CYC/AZA was above -20%, then it could be concluded that RTX was non-inferior to CYC/AZA. Data for patients missing their 6-month primary endpoint assessment was not imputed for the primary analysis. As a sensitivity analysis, the primary endpoint was also evaluated using the worst-case imputation for the ITT population who discontinued study treatment or withdrew consent before 6 months. Another sensitivity analysis used the PP population for the primary efficacy evaluation.

The main secondary efficacy objective was to determine if RTX was superior to CYC/AZA in achieving complete remission at 6 months. If the lower limit of the CI for the difference in remission rates between the 2 groups was greater than 0, and the lower limit of the 95.1% CI was at least 50% (in favour of RTX) than it could be concluded that RTX was superior to CYC/AZA. The other supporting efficacy endpoints were assessed by various appropriate statistical means. For example, the cumulative BVAS/WG AUC was calculated using the trapezoidal rule over the 6-month period with linear extrapolation applied for missing values. The cumulative CS dose at 6 months was compared between the treatment groups using the

Wilcoxon rank sum test. Number of flares (severe and limited) were both analysed by a Poisson regression model adjusting for the type of ANCA.

7.1.1.1.9. Participant flow

A total of 198 patients were randomised into the RAVE Study with 99 subjects assigned to each treatment group. One subject allocated to receive CYC withdrew consent prior to receiving any study medication, and was not included in the ITT analysis. A summary of patient disposition at 6 months is shown in Table 5.

Table 5. Patient disposition at 6 months

	Rituximab N=99 n (%)	Cyclophosphamide N=98 n (%)
Randomized and treated[a]	99 (100)	98 (100)
Completed 6 months	93 (93.9)	91 (92.9)
Without crossover or BMJ	82 (82.8)	79 (80.6)
Crossed over without BMJ by 6 months	5	7
BMJ by 6 months, no crossover	6	5
Discontinued by 6 months	6 (6.1)	7 (7.1)
Without crossover or BMJ	3	5
Crossed over without BMJ by 6 months	1	0
BMJ by 6 months, no crossover	2	2
Primary reason for discontinuation by 6 months		
Voluntary withdrawal	2	5
Death	1	2
Adverse event[b]	2	0
Other	1	0

a, b, [Information redacted]

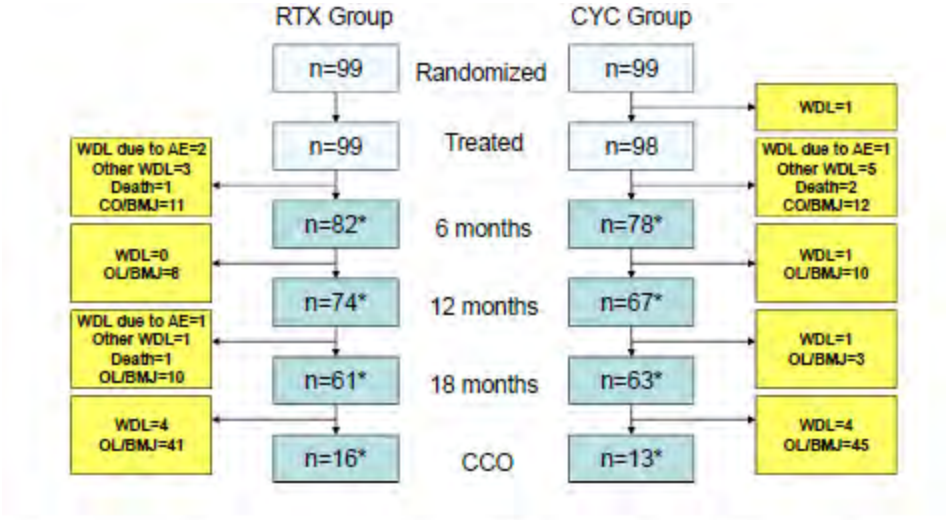
At 6 months of follow-up, 82.8% (82/99) of patients in the RTX group and 80.6% (79/98) subjects in the CYC group completed treatment without crossover or change to BMJ. At 6 months, the 2 treatment groups had similar proportions of patients who discontinued therapy, crossed over, or were on BMJ.

In the maintenance phase of the RAVE study, patients were followed to a common closeout date, corresponding to the last patient's 18-month visit. In total, 123 patients completed 18 months of treatment follow-up, including 61.6% (61/99) of subjects in the RTX group and 63.3% (62/98) of patients in the CYC arm. Figure 1 (below) displays patient disposition until study common close-out.

7.1.1.1.10. Major protocol violations/deviations

A total of 8 protocol deviations in 7 patients potentially affected the primary efficacy endpoint assessment, with an equal distribution between the 2 treatment groups (2.4% [4/99] for RTX and 2.9% [4/98] for CYC). These deviations included incorrect study drug administration, dose switching at inappropriate time points (i.e. before the BVAS/WG score reached 0), and not tapering CS dose according to protocol.

Figure 1: Patient Disposition until Common Close-out date in the RAVE 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.

7.1.1.1.11. Baseline data

Both treatment groups in the RAVE Study had similar demographic characteristics at screening in terms of age, gender and ethnicity. Subjects in the RTX group were slightly older with a mean age of 54.0 years compared with 51.5 years for the CYC arm (range 15-92 years). In both groups, about half of all subjects were male, and more than 93% had Caucasian ethnicity. The baseline characteristics (age, gender and ethnicity) of patients enrolled in RAVE trial were comparable to subjects enrolled in other recent studies of severe vasculitis and clinical practice in Australia.

Table 6 summarizes the important baseline disease characteristics of the ITT population. The majority of patients (74.6%, 147/197) had a diagnosis of GPA, 24.4% (48/197) had a diagnosis of MPA and 2 subjects had an indeterminate or unknown type of ANCA associated vasculitis. Nearly half of all patients (48.7%, 96/198) were newly diagnosed at the time of screening, including the majority of patients with MPA (81%, 39/48). However, patients recruited with GPA primarily had relapsing disease (61%, 90/147). The majority of patients in each treatment group had renal (66%), pulmonary (53%), systemic (61%), or ear/nose/throat (58%) involvement.

Table 6. Baseline Disease Characteristics of patients in RAVE Study (ITT Population)

	Rituximab N=99	Cyclophosphamide N=98	All Patients N=197
ANCA-associated vasculitis type (%)			
Wegener's granulomatosis	73.7	75.5	74.6
Microscopic polyangiitis	24.2	24.5	24.4
Indeterminate	1.0	0	0.5
Missing	1.0	0	0.5
Newly diagnosed at enrollment (%)	48.5	49.0	48.7
BVAS/WG score[a] (mean [SD])	8.1 (2.82)	8.0 (3.41)	8.0 (3.12)
Creatinine clearance (mean [SD]) mL/min	76.5 (46.27)	91.4 (49.24)	83.9 (48.23)
Organ involvement (%)[b]			
Renal	65.7	66.3	66.0
Hematuria	28.3	28.6	28.4
Red blood cell casts	37.4	35.7	36.5
Rise in creatinine >30% or fall in creatinine clearance >25%	34.3	36.7	35.5
Pulmonary	52.5	54.1	53.3
Alveolar hemorrhage	27.3	23.5	25.4
Endobronchial involvement	4.0	9.2	6.6
Nodules or cavities	18.2	27.6	22.8
Other lung infiltrate	25.3	21.4	23.4
Pleurisy	8.1	9.2	8.6
Respiratory failure	2.0	0	1.0
Systemic[c]	55.6	66.3	60.9
Ear/nose/throat	60.6	56.1	58.4
Mucous membranes/eyes	27.3	25.5	26.4
Nervous system	25.3	15.3	20.3
Cutaneous	20.2	16.3	18.3
Gastrointestinal	2.0	0	1.0
Mesenteric ischemia	2.0	0	1.0
Cardiovascular	0	1.0	0.5
Pericarditis	0	1.0	0.5

Baseline disease characteristics were generally balanced between the 2 treatment arms, however estimated creatinine clearance (by Cockcroft-Gault formula) was an exception to this. Mean (SD) creatinine clearance was 76.5 (46.3) mL/min for the RTX group and 91.4 (49.2) mL/min for the CYC/AZA group. The median values were also lower in the RTX group (67.61 mL/min) compared to the CYC/AZA arm (87.47 mL/min). Impaired renal function at baseline is associated with poorer prognosis (Hayne *et al*, 2005; Pagnoux *et al*, 2008).

In each arm, approximately two-thirds of patients were positive for c-ANCA by immunofluorescence, and the other one-third were positive for p-ANCA. Similarly, in each arm, approximately two-thirds of patients were positive for PR3-specific antibodies, and one-third were positive for MPO-specific antibodies – refer to Table 7.

Table 7. Anti-Neutrophil Cytoplasmic Antibody Status in RAVE Study ITT Population

	Rituximab N=99 n (%)	Cyclophosphamide N=98 n (%)	All Patients N=197 n (%)
Positive immunofluorescence assay ANCA results[a]	97 (100)	94 (100)	191 (100)
C-ANCA	65 (67.0)	61 (64.9)	126 (66.0)
P-ANCA	33 (34.0)	33 (35.1)	66 (34.6)
Positive ELISA results for ANCA[a,b]	97 (98.0)	98 (100)	195 (99.0)
PR3	66 (68.0)	65 (66.3)	131 (67.2)
MPO	32 (33.0)	33 (33.7)	65 (33.3)

ANCA=anti-neutrophil cytoplasmic antibody; C-ANCA=cytoplasmic ANCA; CRF=case report form; ELISA=enzyme-linked immunosorbent assay; ITT=Intent-to-Treat; MPO=myeloperoxidase; P-ANCA=perinuclear ANCA; PR3=proteinase 3

[a] Percentage is based on number of subjects with non-missing values.

[b] One patient in the rituximab group had a CRF page without a check mark for positive immunofluorescence or ELISA results; however, results were entered for the specific ANCA pattern/antigen on the CRF.

Concomitant medication use taken throughout the study and present at screening included Bactrim (175 patients, 88.8%), paracetamol (96 patients, 48.7%), multivitamins (71 patients, 36.0%), omeprazole (61 patients, 31.0%), calcium carbonate (55 patients, 27.9%), zolpidem (51 patients, 25.9%) and alendronate (50 patients, 25.4%).

Of the 98 patients randomized to receive CYC, 97 took at least one active dose. The initial dose of CYC was determined by the patient's weight and renal function at baseline. At subsequent visits, the dose of CYC dose could be adjusted according to renal function, white blood cell count, and other tolerability factors. On average, patients in the CYC arm received 76.8% of the initial calculated CYC dose, adjusted for renal function at baseline as per the study protocol (median 74.6% of dose). The mean chronic dose of CYC used during the 6-month induction phase was also lower than the protocol-defined initial dose, but may have been confounded by dose alterations due to tolerability and safety concerns. This is a common observation in clinical practice when managing patients receiving CYC for vasculitis.

Most patients (191/197, 97.0%) received at least 75% of the total amount of RTX or RTX placebo infusions. One patient in each group received between 50-75% of their total infusion amount. The remaining 4 subjects (2 in each group) received 25-50% of their total amount of infusion.

7.1.1.1.12. Results for the primary efficacy outcome

At 6 months, 64.3% (63/98; 95.1% CI 54.76, 73.81) of patients in the RTX group achieved complete remission compared to 54.7% (52/95; 95.1% CI 44.68, 64.79) of patients in the CYC group. The treatment difference in the rate of complete remission was 9.5, with a lower limit of the 2-sided 95.1% CI being -4.3 (upper limit 23.4), which was greater than -20. Therefore, the protocol-specified non-inferiority margin was achieved and RTX therapy demonstrated non-inferiority to CYC in the induction of complete remission for ANCA associated vasculitis.

Similar results were obtained with the "as-treated" analysis of both the ITT and PP populations (under which early treatment failures continuing on the initial treatment were not classified as primary endpoint failures but were assessed at Month 6). All of these sensitivity analyses showed a treatment difference of approximately 10% in favour of RTX, with a lower limit of the

95.1% CI never exceeding -5 (i.e. the non-inferiority margin of -20 percentage points not breached).

In addition, if the patients from the largest enrolling centre (Mayo clinic: 27% of all patients [53/197]) were excluded, the complete remission rates between the 2 treatment groups were similar. In this sensitivity analysis, the 6-month complete remission rates were 53.4% in the RTX group and 50.7% in the CYC group, leading to a difference in complete remission rates of 2.7 (95.1% CI -13.7, 19.1). Despite the lower sampler size, the lower bound of the 95% CI did not exceed -20, thus supporting the non-inferiority conclusion.

The primary endpoint results (complete remission at month 6) by patient subgroups based on the actual dose of CYC received were also analysed. The adequacy of CYC dosing was calculated as a percentage of the protocol-defined initial dose, adjusted for renal function and weight at baseline. There was no clear difference in the frequency of complete remission at 6 months in patients who received more than 80% of the protocol-defined dose of CYC (54.1%; 20/37) compared to those who received only 65-80% of the protocol defined dose (58.1%, 18/31). However, for those who received less than 65% of the protocol-defined dose of CYC, the proportion of patients achieving complete remission at 6 months was lower (48.3%, 14/29).

The RAVE Study performed certain patient subgroup analyses of the primary endpoint to explore the effects of various baseline characteristics including age (<52, >52, <65, >65 years), gender, disease status at baseline (new versus relapsing disease), organ involvement at baseline (alveolar haemorrhage, and systemic disease (yes/no) and baseline renal function (creatinine clearance [<60, >60 mL/min]). A higher proportion of patients in the RTX group were of older age (>65 years) compared with the control group (36.4% [36/99] versus 19.4% [19/98]), and the complete remission rate appeared somewhat lower in both treatment arms for patients aged >65 years (55.6% [20/36] for RTX and 42.1% [8/19] for CYC) compared to those <65 years (68.3% [43/63] for RTX and 55.7% [44/79] for CYC). However, the difference in the rate of complete remission between the 2 treatment groups was of similar size (12.6-13.5%) across the comparable age range.

The rates of complete remission rate and treatment difference were similar for males and females.

Table 8 displays the rates of complete remission at 6 months by baseline disease characteristics and the results are revealing for identifying potential patient subgroups that may benefit the most from receiving RTX in comparison to CYC induction. In relation to baseline disease status, a significantly higher proportion of patients with relapsing disease at baseline in the RTX group met the primary endpoint (66.7%, 34/51) compared with those in the CYC group (42%, 21/50; p=0.013). However, the rates of complete remission were similar between the 2 groups in patients with newly diagnosed disease at baseline (60.4% [29/48] for RTX versus 64.6% [31/48] for CYC).

Table 8. RAVE Study: Complete Remission at 6 months according to baseline disease subgroup characteristic (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

In the RTX treatment group, patients with better renal function at baseline (as defined by creatinine level <1.2mg/dL, or creatinine clearance >60 ml/min, or no major renal item on the baseline BVAS/WG score) had significantly higher response rates at 6 months compared to those with renal disease or impairment (RTX remission rates were 66.7% [32/48] for no major renal item and 60.8% [31/51] for renal disease), or who received CYC (62.7% [32/51] for renal disease and 42.6% [20/47] for no renal disease). Of note, nearly half (45.5%, 45/99) of all patients in the RTX group had a baseline creatinine clearance of <60ml/min compared with 28.6% (28/98) of patients in the CYC group. Regardless of treatment, patients with renal impairment tended to have lower rates of remission compared to those with relatively preserved renal function at baseline, which is a finding replicated in the literature.

Patients with PR3+ ANCA status or GPA (WG) by ANCA vasculitis type appeared to derive a beneficial treatment effect with RTX compared with CYC, whereas MPO+ ANCA or MPA vasculitis patients had a similar response rate independent of treatment administered (RTX or CYC).

Although most of the patient subgroup comparisons were underpowered because of small sample size to make definitive conclusions, they do generate further interest in subject subgroups most likely to derive benefit from a particular treatment strategy.

7.1.1.1.13. Results for other efficacy outcomes

The main secondary efficacy objective for RAVE Study was to assess the *superiority of RTX compared to CYC/AZA* in terms of the percentage of patients who achieved complete remission at 6 months. Although the proportion of patients in the RTX group who achieved complete remission was numerically higher than in the CYC group (64.3% versus 54.7%), the 9.5% treatment difference (95.1% CI -4.3, 23.4) was not statistically significant (p=0.177). However, because the lower limit of the 95.1% CI for the rate of complete remission in the RTX group exceeded 50%, this finding confirms that RTX is superior to historical placebo.

Using worst observation carried forward (WOCF) imputation, the *mean (SD) BVAS/WG score AUC/month over the first 6 months* was 1.29 (1.33) points for the RTX group and 1.25 (1.03) points for the CYC group. No significant difference was observed between the treatment arms.

In the RTX group 70.7% of patients (70/99) achieved a *BVAS/WG score of 0 at 6 months while on <10mg prednisone per day* (WOCF imputation method). In the CYC group, fewer patients (61 of 98, 62.2%) achieved this outcome. However, the resulting treatment difference (8.5%; 95% CI -4.67, 21.6) was not statistically significant (p=0.208).

Using WOCF imputation, 70 patients (70.7%) in the RTX group and 61 patients (62.2%) in the CYC group achieved a *BVAS/WG score of 2 or less while off CS at 6 months* (i.e. the definition of partial remission). These were the same rates as those for complete remission on < 10mg/day of prednisone (immediately above), however the responder groups were not exactly the same.

An exploratory analysis was performed to determine the *rate of remission (BVAS/WG score=0) regardless of prednisone use*. Using WOCF 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 2.33, 26.6), which was statistically significant (p=0.021).

In the first 6 months of the RAVE Study, no significant difference in *severe or limited flares* was observed between the 2 treatment arms – refer to Table 9. In this analysis, flares that occurred after crossover were excluded. Five (5.1%) patients in the RTX group experienced a total of 6 severe disease flares, and 10 (10.2%) patients in the CYC group experienced a total of 10 severe flares. This corresponds to a rate of 0.011 and 0.019 severe flares per patient-month in the RTX and CYC treatment groups, respectively, which is not statistically significant (p=0.293). Both groups recorded 14 limited disease flares, which occurred at an equal incident rate of 0.026 per patient-month.

Table 9. Severe and limited flares during the first 6 months (ITT population)

	Rituximab N=99	Cyclophosphamide N=98	p-value[a]
Severe flares			
Total number of severe flares	6	10	
Patients with ≥1 severe flare	5 (5.1%)	10 (10.2%)	
Sum of patient-months	533.4	531.8	
Rate of severe flares	0.011	0.019	0.293
Limited flares			
Total number of limited flares	14	14	
Patients with ≥1 limited flare	12 (12.1%)	14 (14.3%)	
Sum of patient-months	533.4	531.8	
Rate of limited flares	0.026	0.026	0.980

ITT = Intent-to-Treat
Note: Flare assessments for patients during crossover were excluded from this analysis.
[a] P-value for the treatment effect was derived from the Poisson regression model and adjusted for clinical study center and the type of anti-neutrophil cytoplasmic antibody. The natural logarithm of patient-months was used as an offset in this model.

For the 2 weeks prior to study randomization, the median cumulative dose of prednisone was 240 mg in the RTX group and 270 mg in the CYC group. From randomization through to 6 months, IV administration of methylprednisolone was identical in both treatment arms, with a median dose of 1000 mg. The *median cumulative dose of prednisone from baseline to 6 months* was slightly lower in the RTX group (3310 mg) compared with the CYC group (3450 mg), but this was not statistically significant (p=0.055). Nonetheless, these results indicate that the efficacy outcomes seen in the RTX group were not due to an increased prednisone exposure compared with the control group.

Attainment of negative *ANCA serology status* after induction treatment has been associated with a lower rate of disease relapse. Blood samples for ANCA status were collected at screening and at various time points during the first 6 months, and were analysed for seroconversion. In total, 166 patients had a sample collected at screening and a subsequent time point (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 (44.3%, 39/88) compared with the CYC group (29.5%, 23/78; p=0.050). Patients who were PR3+ and treated with RTX had the highest likelihood of becoming seronegative by 6 months (47.5%, 29/61 for RTX versus 25.0%, 14/56 for CYC; p=0.012). However, the ability for treatment to induce seronegative results in MPO+ patients was similar between the 2 treatment groups (39.3%, 11/28 for RTX versus 40.9%, 9/22 for CYC; p=0.907).

Regarding the *change from baseline in markers of inflammation*, ESR and CRP levels decreased in both groups between baseline and 6 months with a larger improvement in ESR seen in those administered RTX. The RTX arm had a median ESR reduction of 14 mm/hr (baseline median 30) compared with a median ESR reduction of 3 mm/hr in the CYC group (baseline median 35). The difference in mean ESR change from baseline between the 2 treatment groups was 7.6 mm/hr (95% CI: 2.2, 13.1), which was statistically significant (p=0.0064). However, median changes in CRP were similar between the 2 arms. Over 6 months, the RTX group had a mean CRP reduction of 2.69 mg/dL (baseline mean 4.18) compared with a mean CRP reduction of 2.84 mg/dL in the CYC group (baseline mean 4.93). The difference in mean CRP change from baseline between the 2 treatment groups was 0.61mg/dL (95% CI: -0.50, 1.73), which was not statistically significant (p=0.2782).

Table 10 provides a summary of the key efficacy endpoints at 6, 12 and 18 months as a representation of the *maintenance of remission beyond 6 months*. Comparable proportions of patients maintained complete remission at 12 and 18 months of follow-up in both groups (induction RTX versus induction CYC followed by maintenance AZA). Similarly the overall rates of severe and limited disease flares up to 18 months were comparable between the 2 groups. However, more severe flares occurred between 12 and 18 months in the RTX (n=8) versus CYC/AZA group (n=4) suggesting a loss of treatment effect over time with RTX. Similarly, the number of limited disease flares after 6 months was higher in the RTX group (15 between months 6-12, and 9 between months 12-18) compared with the CYC/AZA arm (9 between months 6-12, and 7 between months 12-18). A further significant finding which highlights the role of low dose maintenance CS in managing ANCA associated vasculitis is the rate of relapse at 18 months of follow-up in the subset of patients who did not receive CS beyond 6 months: 64% with RTX, and 69% with AZA therapy. This rate of relapse in the medium term (18 months) is markedly higher than expectations from other published studies and patient databases. Overall, the efficacy results from the RAVE Study indicate that RTX is non-inferior to CYC in achieving remission when used as an induction therapy, but the increased rates of disease flare (severe and limited) beyond 6-12 months of follow-up reinforce the requirement for maintenance therapy (AZA and/or low dose CS) in most patients for at least a period of 18 months.

Table 10. RAVE Study: Summary of key efficacy endpoints at 6, 12 and 18 months

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%)
Severe flares (rate per patient-month [cumulative no. of flares])			
6 mos	0.009 (5)	0.019 (10)	
12 mos	0.014 (14)	0.020 (19)	NA
18 mos	0.016 (22)	0.017 (23)	
Limited flares (rate per patient-month [cumulative no. of flares])			
6 mos	0.026 (14)	0.026 (14)	
12 mos	0.029 (29)	0.024 (23)	NA
18 mos	0.028 (38)	0.023 (30)	

Note: remission and partial remission rates based on worst case analysis
Flares occurring after switch of therapy were excluded from analysis.
*p< 0.05

7.1.1.2. RITUXVAS Study

7.1.1.2.1. Study design, objectives, locations and dates

This was phase II, open-label randomized trial of 44 patients from 8 centres in Europe (Britain, Germany, Sweden, Netherlands, Switzerland and Czech Republic) and Australia. The Cambridge University Hospitals NHS Foundation Trust (UK) and the European Vasculitis Study Group (EUVAS) sponsored it. The sponsor of this submission was not involved in the funding, design or conduct of the study. The trial enrolled patients between June 2006 and June 2007. Patients were to be randomized 3:1 to receive RTX + concurrent low dose IV CYC, or IV CYC followed by AZA (control group).

The main trial design differences between the RITUXVAS and RAVE studies were recency of diagnosis (newly diagnosed versus a mixture of new and relapsing disease, respectively), renal involvement (an inclusion criterion in RITUXVAS versus an exclusion if significantly impaired in RAVE), concomitant treatment with CYC (IV low dose CYC was used concurrently with RTX induction in RITUXVAS versus no concurrent CYC in the RTX arm in RAVE), and route of administration of CYC (IV CYC was exclusively used in RITUXVAS versus oral CYC as the comparator in RAVE).

7.1.1.2.2. Inclusion and exclusion criteria

The inclusion criteria required a new diagnosis of ANCA associated vasculitis, positive ANCA serology and renal involvement (as evidence by either necrotizing glomerulonephritis on kidney biopsy, or red cell casts on urine microscopy). Prior to study entry, patients were allowed to receive plasma exchange or up to 2000 mg of IV methylprednisolone, according to local practice.

Patients were excluded if they had received previous CYC therapy (for more than 2 weeks), had previous or active hepatitis B or C or HIV infection, prior malignancy, or received a live vaccine within 4 weeks of randomization.

7.1.1.2.3. Study treatments

After randomization, both treatment groups were given 1000 mg of IV methylprednisolone followed by an identical oral CS tapering regimen (starting at 1 mg/kg/day [maximum starting dose of 60 mg/day] and then reduced to 5 mg/day by 6 months). In the experimental arm, patients were to receive RTX 375 mg/m^2 weekly for 4 weeks plus IV CYC at a dose of 15 mg/kg with their 1st and 3rd RTX infusions. In the control group, patients were administered IV CYC 15 mg/kg fortnightly for the initial 3 doses, and the every 2-3 weeks for 3-6 months until remission was achieved (BVAS of 0 for 2 consecutive months). In this group CYC induction therapy could be followed by AZA (up to 2 mg/kg/day) maintenance treatment. The RTX arm did not receive any scheduled maintenance treatment apart from tapering oral CS up until 6 months. However, patients in either group were allowed to receive further RTX or CYC for disease relapse at the discretion of the investigator.

7.1.1.2.4. Efficacy variables and outcomes

The main efficacy variables were:

- BVAS score (and not the BVAS/WG, which has been specifically modified for GPA to remove some redundant evaluation items). The score range is 0-63.
- VDI (Vasculitis Damage Index), which measures vasculitis damage across multiple organs with 1 point assigned per item, and a maximum score of 64.
- Sustained Remission, defined as the absence of disease activity for 6 consecutive months.
- Remission, defined as the absence of clinical disease activity (BVAS 0) for at least 2 consecutive months.

The primary efficacy outcome was the percentage of patients achieving sustained remission at 12 months. As opposed to RAVE, the RITUXVAS study did not require patients to cease CS altogether.

- Other efficacy outcomes included:
- Median time to remission,
- Median change in BVAS score over first 3 months,
- Median change in GFR over 12 months,
- Prednisolone dose requirements,

- Disease damage assessed by change in VDI between 0 and 12 months, and
- Quality of life as per changes in the SF-36 questionnaire.

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

7.1.1.2.5. Randomisation and blinding methods

Randomization was done by a central coordinating facility that balanced variables known to influence response such as age, disease type (GPA versus MPA or renal limited vasculitis), and baseline serum creatinine between the 2 treatment groups. The trial was unblinded but some of the efficacy outcome measures (e.g. creatinine levels) were objective measurements.

7.1.1.2.6. Analysis populations

Analyses were performed on an ITT basis and included all 44 patients who were randomized into the study.

7.1.1.2.7. Sample size

Based on the results of previous uncontrolled studies of RTX use in ANCA vasculitis, the expected sustained remission rate for RTX was 95% in this trial. For patients in the control group, the assumed sustained remission rate was 65%. The estimated treatment difference of 1.5 fold would have a statistical power of at least 80%, at a 2-sided α level of 0.05, if 44 patients underwent randomization.

7.1.1.2.8. Statistical methods

Results were expressed as values and percentages for categorical variables, and medians and interquartile ranges (IQR) for continuous variables. Proportions were compared between the 2 treatment groups using chi-square test. Time-to-event analyses were performed using a log-rank test. Missing laboratory data such as GFR was imputed for patients who died using the LOCF method to provide a conservative estimate of effect.

7.1.1.2.9. Participant flow

A total of 44 patients were randomized 3:1 (33 for RTX, and for 11 control treatment) into the RITUXVAS Study. No alive patients were lost to follow-up over 12 month study period, but 6 patients (18%) in the RTX + low dose CYC group and 1 patient (9%) in the CYC group had died prior to 12 months. Another patient in the CYC group died at 19 months.

7.1.1.2.10. Major protocol violations/deviations

Two patients in the RTX + low dose CYC group received a 3rd dose of CYC dose (i.e. a protocol violation). One of those patients was classified as a treatment failure, but the other had responded to the RTX and was classified as a treatment success.

7.1.1.2.11. Baseline data

In this study patients had new-onset of ANCA-associated vasculitis with renal involvement. Subjects had a median age of 67 years (range: 20-85) and 52% (23/44) were male. Disease activity was high with the median BVAS score being 19 for the RTX group (range: 9-42), and 18 for the CYC arm (range: 12-23). At study entry, renal function was markedly impaired in both groups with the median GFR in mL/min/1.73 m^2 being 20 for the RTX group (range: 0-74) and 12 for the CYC arm (range: 0-48). A higher proportion of patients in the experimental group had GPA as their diagnosis (55% [18/33] for RTX versus 36% [4/11] for the control group). The other patients had MPA. ANCA serology status (c- or p-ANCA positivity) correlated highly with the clinical diagnosis. Other baseline disease characteristics were similar between the 2 groups with the exception of a greater proportion of renal-limited vasculitis patients in the CYC group (27% [3/11] versus 9% [3/33] for RTX) and a greater proportion of patients requiring dialysis

in the RTX + low dose CYC group (24% [8/33] versus 9% [1/11] for CYC). The use of plasma exchange was similar between the 2 groups (24% [8/33] for RTX and 27% [3/11] for CYC).

7.1.1.2.12. Results for the primary efficacy outcome

Sustained remission was achieved in 25 of 33 patients (76%) in the RTX + low dose CYC group and in 9 out of 11 patients (82%) in the CYC/AZA group. The absolute difference in sustained remission with RTX compared with CYC was -6% (95% CI: -33%, 21%), which is not statistically significant.

Among patients who reached 12 months of follow-up, 93% (25/27) of patients in the RTX + low-dose CYC group, and 90% (9/10) of patients in the CYC group achieved sustained remission. Reasons for not achieving sustained remission at 12 months included death, 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). Of these, 6 out of 8 patients from the RTX + low dose CYC group had a sustained remission, with 5 patients becoming dialysis independent. One patient from the CYC group who was dialysis dependent at the start of the study, died shortly after study entry.

7.1.1.2.13. Results for other efficacy outcomes

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. Overall, remission occurred in 30 out of 33 patients (91%) in the RTX + low dose CYC group, and 10 of 11 patients (91%) in the CYC group.

The *median BVAS score* reduced 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.

For the RTX + low dose CYC group, the *median estimated GFR* increased from 20 (IQR, 5-44) at baseline to 39 (IQR, 20-45) at 12 months. In the CYC group, the median GFR increased from 12 (IQR, 9-33) at entry to 27 (IQR, 12-47) at 12 months.

Prednisolone doses were reduced in both groups according to the study protocol, with 96% of patients from the RTX + low dose CYC group and 89% from the CYC group receiving prednisolone 5mg/day by 9 months. At 12 months, the 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.

In assessing disease damage, the *median change in the VDI at 12 months* in the RTX + low dose CYC group was 2 (IQR, 0-3), which was not significantly different from the CYC group which had a change of 1 (IQR, 0-2) (p=0.38).

In terms of *quality of life*, 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), but this difference was largely accounted for by 2 patients' scores the RTX + low dose CYC group. Exclusion of these 2 patients led to a non-significant result (p =0.32).

7.1.2. Other efficacy studies

7.1.2.1. Published Investigator Initiated Studies

A total of 162 patients with treatment refractory ANCA associated vasculitis participated in the 12 published investigator initiated studies, most (n=121) of whom received the same dose of RTX (375 mg/m^2 weekly for 4 weeks) used in the RAVE Study, as well as concurrent CS. Most patients had active systemic vasculitis, which was either refractory to CYC (56%, 90/162), or they were intolerant of CYC (4%, 6/162). Most patients (81.5%; 132/162) had a diagnosis of GPA, although 20 subjects (12.3%) had MPA, 6 (3.7%) had Churg-Strauss Syndrome, and 4 (2.5%) had an unclassified vasculitis. The median age of participants varied from 31-59 years of

age, and slightly more than half of all subjects were male. The studies used a variety of endpoints aimed at determining either complete or partial remission, but the BVAS or BVAS/WG score was the predominant method of determining efficacy response. All the studies collected data in an unblinded manner. Cumulatively, it was reported that 93% (151/162) of patients achieved either a complete or partial remission at 6-12 months of follow-up. Response rates were similar in those who received the alternative induction doses of RTX: 32 subjects were given a fixed dose of RTX 1000 mg x 2, and 9 patients were administered RTX 500 mg x 2-4 infusions.

7.1.2.2. Holle et al Study (published October 2011)

This publication was a retrospective study, using a standardized data collection methodology, for all patients who received RTX according to a standardized regimen for refractory GPA between 2002 and 2010 at a single tertiary referral centre in Germany. Its objectives were 2-fold: to investigate the overall efficacy[2] of RTX in patients with refractory GPA, and to compare the efficacy of RTX in terms of treating the granulomatous and vasculitic manifestations of GPA. There is some evidence in the literature to support the relative ineffectiveness of RTX in being able to treat the granulomatous manifestations of GPA (Aries *et al*, 2006). A total of 59 patients who received 75 cycles of RTX, and they were evaluated using the BVAS, Disease Extent Index, serum inflammatory markers (ESR/CRP), prednisolone dose requirements and clinical assessments (including ENT and opthalmological examinations). Patients in this cohort were predominately male (59%, 35/59) with a median age of 54 years (range: 22-76 years) and median disease duration of 37 months (range: 3-211 months). Most had received prior CYC (78.3%, 47/59) at a median cumulative dose of 27.75 g[3], indicating extensive prior therapy. More than half had also received previous methotrexate (58%, 34/59). Eight had also received an anti-TNF medication. Most of the subjects had positive PR3-ANCA serology (86.4%, 51/59) at baseline. Fifty (85% of 59) had generalized/systemic disease at baseline, while 9 patients (15%) had localized disease according to the EULAR/EUVAS definition. Disease manifestations prompting the use of RTX were orbital masses (n=27), renal disease (n=26, including 14 with impaired function [creatinine clearance < 60 ml/min]), meningitis[4] (n=12), pulmonary masses (n=12) and alveolar haemorrhage (n=12). Patients were given RTX at a dose of 375 mg/m^2 weekly for 4 weeks in conjunction with CS and other immunosuppressant medications (a total of 95% did so) including CYC (55%; at a dose up to 2 mg/kg/day). Some patients received a second (n=12) or third course (n=4) of RTX if they relapsed or were refractory to therapy. Refractory disease was defined according to the EULAR/EUVAS criteria – unchanged or increased disease activity after 4 weeks of treatment, or a lack of a response after 6 weeks of treatment (i.e. at least a 50% reduction in BVAS score) or chronic, persistent disease after at least 12 weeks of therapy. The median follow-up period for the entire cohort was 7 months (range: 4-58 months), and of the 36 patients who had entered some form of remission/response the median treatment follow-up period was 13.5 months (range: 3-54 months).

Complete remission was achieved in 7 (9.3%) patients. A response was documented in 61.3% of patients (52% [39/59] showed objective improvement, and 9.3% [7/59] had unchanged disease activity), and refractory disease was observed in 26.7% (20/59). However, the most interesting observation of this uncontrolled study was that granulomatous disease manifestations such as orbital masses and meningitis, were far less likely to respond than vasculitis. For example, complete remission or improvement was only recorded in 44.4% (12/27) of patients with orbital granulomas compared with 88.5% (23/26) of patients with renal disease. Furthermore,

[2] Sponsor comment: the objectives included assessment of overall efficacy and safety of RTX. [The clinical evaluator accepts this comment].
[3] Sponsor clarification: All patients had received CYC previously. Directly before treatment, 78.3% of patients (47/59) were receiving treatment with CYC at a median cumulative dose of 27.75 g. [The clinical evaluator accepts this clarification]
[4] Sponsor correction: 'meningitis' should read 'pachymeningitis'. [The clinical evaluator accepts this correction]

almost half of the patients (44.4%, 16/36) relapsed following RTX induction after a median period of 13.5 months (range: 3-54 months). This high rate of relapse was observed despite 95% of patients continuing to receive some form of maintenance immunosuppression. The prednisolone dose requirement reduced from a median of 15 mg/day to 8 mg/day following successful treatment with RTX.

7.1.3. Analyses performed across trials (pooled analyses and meta-analyses)

No pooled analysis across the studies has been performed, which is appropriate given the heterogeneity in their design, patient populations and measured outcomes.

7.1.4. Evaluator's conclusions on clinical efficacy for induction of remission in patients with severely active GPA and MPA

In support of the extension of indication for induction of remission in patients with severely active GPA and MPA, the sponsor has provided data from 1 pivotal phase II/III trial (RAVE Study) as the core evidence of efficacy for the claimed indication. Supportive evidence of efficacy is provided by a phase II, open-label, randomized trial (RITUXVAS Study) of 12 months duration, and a TGA approved literature search strategy which identified 12 relevant, uncontrolled studies involving a total of 162 patients administered RTX for treatment refractory ANCA associated vasculitis. In addition to the sponsor provided information, this reviewer has included another study examining the efficacy of RTX in patients with different disease manifestations of refractory GPA (granulomatous versus vasculitic manifestations). The submission meets the requirements of 2 EMA guidelines of relevance, both adopted by the TGA, which are CPMP/EWP/2330/99 "Points to consider on application with 1. Meta-analyses; 2. One Pivotal Study" and CHMP/EWP/83561/2005 "Guideline on Clinical Trials in Small Populations".

In the pivotal RAVE Study, a total of 198 subjects were randomised to receive either an induction course of RTX (375 mg/m^2 weekly for 4 weeks; n=99), or oral CYC (up to 2 mg/kg/day) for 3-6 months (n=98). Both groups received a protocol-determined course of CS with dose tapering to be completed by 6 months. The study also had a maintenance of remission phase between 6-18 months, whereby patients given CYC in the 6-month induction phase were switched to AZA (2 mg/kg/day), but RTX treated subjects had no specific maintenance therapy. The choice of comparator in this study is appropriate and consistent with the current standard of care for patients with a severely active ANCA associated vasculitis. However, the choice of RTX dose and regimen selected for the pivotal trial is questionable, and appears to be justified by the sponsor on the basis of what dose and regimen have been historically used. No dose-finding studies for this indication have been performed, and no dose-response relationship in terms of PD parameters of relevance (such as changes in CD19+ B-cells) has been examined. There is some evidence that lower doses of RTX may achieve the PD outcomes of interest in other autoimmune conditions.

The trial design of the pivotal RAVE Study is appropriate for the claimed indication of induction of remission in patients with severely active GPA and MPA. However, the duration of follow-up is insufficient to adequately determine relapse rate for a disease that has a natural history of involvement and treatment follow-up spanning several years. This is evident in the 18-month efficacy data for the RAVE Study, whereby more patients treated with RTX experienced severe flares between months 12-18 (8 for RTX versus 4 for CYC/AZA). Similarly, the number of limited disease flares after 6 months was higher in the RTX group (15 between months 6-12, and 9 between months 12-18) compared with the CYC/AZA arm (9 between months 6-12, and 7 between months 12-18). Although many of the supporting studies used a variety of concomitant immunosuppression medicines (particularly CYC-either IV or oral), the pivotal RAVE Study was not designed in this manner and therefore, there is limited, high quality information about the combination of RTX with other commonly used immunosuppression therapies. For the RAVE Study, randomisation procedures, strategies to maintain blinding and statistical analysis were

appropriately performed. Efficacy in the pivotal RAVE Study was primarily analysed as a non-inferiority outcome, with a secondary analysis of treatment superiority. The RAVE and RITUXVAS studies were performed according to GCP, and the minor protocol amendments in the RAVE Study did not have a significant impact upon the results.

The population examined in the RAVE and supporting studies are similar in demographics to the subjects that would be treated with RTX for GPA and MPA in Australian clinical practice. The vast majority of subjects were middle-aged, Caucasian, and near equal gender distribution. The generalizability of the results is satisfactory with some noteworthy caveats. In general, the studies only enrolled patients with severe disease who were ANCA positive, and therefore it is unclear whether the results are generalizable to those who are ANCA negative or have milder forms of GPA and MPA. The RAVE Study also excluded patients with a serum creatinine > 4.0 mg/dL or respiratory failure requiring ventilator support, so it is difficult to determine the comparative efficacy of RTX versus CYC in the most fulminantly ill patients. The RITUXVAS specifically included patients with renal vasculitis, and administered concurrent low dose CYC with RTX induction therapy.

The choice of primary efficacy endpoints was acceptable, but not ideal. For the pivotal RAVE Study, the primary efficacy outcome was the percentage of patients in each treatment group who achieved complete remission at 6 months. Complete remission was defined as the obtaining a BVAS/WG score of 0 and a successful completion of CS taper. The use of the BVAS/WG is appropriate because it is a validated instrument capable of measuring disease activity. However, the nomination of a complete CS taper by 6 months is the incorrect efficacy endpoint of interest. Moreover, it may even be counter-productive to medium-long term efficacy outcomes (beyond 12 months of follow-up) as there is evidence of significantly higher disease relapse in those who don't continue to receive continuous low dose CS until at least 18 months of treatment.[5] The primary endpoint in the RAVE Study focussed on the induction of remission (as per the sponsor's requested indication listing), but does not address the question of re-treatment with RTX (either empirical, or upon disease relapse).

All of the supporting studies used various efficacy endpoints that were relevant (and not dependent on a successful complete withdrawal of CS by a particular time point) such as changes in BVAS score, remission rates, and changes in CS dose requirements.

The primary efficacy endpoint in the pivotal RAVE trial was achieved. At 6 months, 64.3% (63/98) of patients in the RTX group achieved complete remission compared to 54.7% (52/95) of patients in the CYC group, which met the protocol-specified non-inferiority margin of treatment difference. Therefore, RTX demonstrated non-inferiority to CYC in the induction of complete remission for ANCA associated vasculitis. Treatment superiority was not demonstrated on the secondary analysis. A significantly higher proportion of patients with relapsing disease at baseline in the RTX group met the primary endpoint (66.7%, 34/51) compared with those in the CYC group (42%, 21/50; p=0.013), although, the rates of complete remission between the 2 groups in patients with newly diagnosed disease at baseline (60.4% [29/48] for RTX versus 64.6% [31/48] for CYC) were similar. Furthermore, RTX provided similar outcomes compared with CYC/AZA for patients with more severe vasculitic manifestations of GPA and MPA, such as renal disease. Various secondary and exploratory

[5] At the sponsor's request that the source of the statement be added, the clinical evaluator provided the following clarification: The references supporting this claim are Jayne *et al* 2003, Seror *et al* 2010 and de Groot *et all* 2009). All of these studies are maintenance treatment studies in ANCA vasculitis. All continued low dose prednisone for a minimum of 12-18 months (eg, de Groot had patients on prednisone 7.5 mg/day at 12 months & continued to 18 months of follow-up). The [section on study treatment for the RAVE study in the CER] contains a paragraph explaining the significance of maintaining low dose prednisolone as part of the treatment strategy in relation to the appropriateness of efficacy endpoints in RAVE Study. There are no head-to-head studies comparing the relative efficacy of short (6 months) versus persistent (12-18 months) steroid dosing. The comment made here is an opinion based on indirect data comparisons between the studies (RAVE versus the above 3 studies), as well as the majority consensus among experts in the field (eg EUVAS docs available on line).

efficacy endpoints in the RAVE Study supported the non-inferiority of RTX to conventional treatment for the induction of remission in severe ANCA associated vasculitis.

The RITUXVAS Study is supportive of the key efficacy findings of the RAVE trial by demonstrating:

- Sustained remission (BVAS of 0 for 6 months) in 76% (25/33) of patients in the RTX + low-dose CYC group, and 82% (9/11) of subjects (82%) in the CYC group at 1 year, with an absolute treatment difference of -6% (95% CI: -33%, 21%) being non-significant.
- Among patients who reached 12 months of follow-up, 93% in the RTX + low-dose CYC group and 90% in the CYC group had sustained remission.
- 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.
- Renal function improved in both groups with the median increase in GFR between baseline and 12 months being 19ml/min in the RTX + low-dose CYC group, and 15ml/min in the CYC group.

The literature search identified a total of 162 patients (121 of whom received the same dose of RTX being requested by the sponsor) with treatment refractory ANCA associated vasculitis that participated in 12 published investigator initiated studies. The majority of patients (93%, 151/162) were reported to have achieved either partial or complete remission at 6 months of follow-up. This data provides further support for the claimed indication. However, the study by Holle *et al* sheds insight into the utility and role of RTX in patients with refractory GPA. Complete remission was reported in 9.3% (7/59) of patients in this trial. Response was documented in 61.3% of patients (52% [39/59] showed objective improvement, and 9.3% [7/59] had unchanged disease activity), and refractory disease was observed in 26.7% (20/59). Of particular note in this retrospective study was that granulomatous disease manifestations such as orbital masses and meningitis, were far less likely to respond than vasculitis features. For example, complete remission or improvement was only recorded in 44.4% (12/27) of patients with orbital granulomas compared with 88.5% (23/26) of patients with renal disease. The RAVE study also showed a high rate of refractory, GPA-related laryngeal stenosis with the RTX treatment group (more details of this result are included in the safety section of this report). Furthermore, [6]almost half of the patients (44.4%, 16/36) relapsed following RTX induction after a median period of 13.5 months (range: 3-54 months). The high rate of relapse in the study by Holle *et al* was observed despite 95% of patients continuing to receive some form of maintenance immunosuppression.

Overall, the data in this submission supports the efficacy of RTX in the induction of remission in patients with severely active GPA and MPA, but there is no evidence that it is superior to the currently available standard of care unless the patient has relapsed severely active, systemic GPA. RTX offers another treatment strategy in area of medicine with a significant unmet therapeutic need.

8. Clinical safety

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

[6] Sponsor clarification. The sentence should read 'Furthermore, in the study by Holle *et al*, almost …' [The clinical evaluator accepts this clarification].

8.1.1. Pivotal efficacy studies

There is a single pivotal efficacy study (RAVE), which collected the following safety data:

- General Adverse Events (AEs) were assessed by adverse event reporting and physical examinations, both of which occurred weekly for the first 4 weeks; months 2,4, and 6 for the treatment induction period; and then every 3 months thereafter.
- Nine categories of pre-specified AEs of particular interest, including death (all cause), leucopenia (at least grade 2), thrombocytopenia (grade 2 or more), infection (grade 3 or higher), haemorrhagic cystitis, malignancy, venous thromboembolic event, hospitalization, cerebrovascular accident and infusion reaction were assessed by their overall rate and number of individual events.
- Laboratory tests, including haematology, chemistry and urinalysis with microscopy were performed at baseline, weekly for the first 4 weeks of the trial; months 2,4, and 6 for the treatment induction period; and then every 3 months thereafter.
- Chest imaging (Plain X-ray or CT Scan) was performed at baseline; months 1, 4 and 6; and then every 3 months thereafter.

All adverse events were graded according to the National cancer Institute's Common Terminology Criteria (version 3.0). Poisson regression was performed to compare the adverse event rates between the 2 treatment groups, adjusting for study centre and ANCA type (PR3 or MPO). The p-value was based on the Wald test of treatment effect.

8.1.2. Pivotal studies that assessed safety as a primary outcome

There were no studies that assessed safety as the primary outcome.

8.1.3. Dose-response and non-pivotal efficacy studies

No dose-response studies have been conducted but additional safety data was provided by the following non-pivotal efficacy studies:

- RITUXVAS (open-label, randomized study) provided data on 44 patients (33 of whom received RTX and 11 given CYC/AZA) with newly diagnosed, severe ANCA associated renal vasculitis.
- Published information from 12 investigator-initiated studies provided data on a total of 162 patients treated with RTX (all of whom received 375 mg/m^2 weekly for 4 weeks, except n=32 for a fixed dose of 1000 mg x 2, and n=9 for 500 mg x 2-4 infusions).
- Retrospective Study using a standardized data collection methodology (Holle *et al* – 2011) whereby 59 patients received a total of 75 cycles of RTX for GPA.

8.2. Patient exposure

The sponsor did not include an integrated analysis of safety data, which is appropriate because the studies used different methods of data collection. As such, in this report the safety results will be presented in 4 broad categories – RAVE Study (first 6 months, then up to 18 months, and then up to the common close out date), RITUXVAS trial, other sponsor nominated publications, and the study by Holle *et al* (published October 2011, and which was not included in the literature search).

- RAVE STUDY – First 6 months

A total of 197 patients received at least 1 dose of study medication and were included in the safety analysis (n = 99 for RTX, 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 crossover or a change to a different treatment under BMJ (86 patients in the RTX group, and 85

patients in the CYC group). The majority of patients in both groups completed the first 6 months of the study (93 of 99 [94%] for RTX, and 91 of 98 [93%] in the CYC groups). Thirteen patients in each treatment group received a different treatment as a result of the crossover protocol, or because of BMJ, or as a deviation from study drug administration. 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 patients who received RTX only and CYC only groups was 41.9 and 40.5 patient years, respectively. Since only a small proportion of patients crossed over 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 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). Therefore, safety data in these patients should be interpreted with caution.

· RAVE STUDY - Up to 18 months and Common Closeout Date

During the maintenance phase of the RAVE study, patients were followed up to a common closeout (CCO) date, corresponding to the last patient's 18-month visit. If the 18-month threshold is used as the end date, the mean follow-up periods were 1.4 years (16.8 months) in both treatment groups post-randomization. From randomization to the CCO date, mean follow-up times were 3.0 and 2.8 years in the RTX and CYC groups, respectively.

Since the study design allowed for treatment switches (blinded crossover treatment according to BMJ, or open-label RTX), many patients received therapies other than the study drug to which they were randomized. In total, 123 patients completed 18 months on their randomized treatment -61 of 99 (62%) following RTX induction, and 62 of 98 (63%) in the CYC/AZA group. Twenty-nine patients (n=16 for RTX, and n=13 for CYC/AZA) remained on their 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 to the CCO date, there were 299.2 patient-years of follow-up 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.

· RAVE: Extent of Exposure to Rituximab

All patients received at least 1 infusion of rituximab or rituximab placebo. The median cumulative dose of RTX 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 6-18, and 11 patients in the CYC/AZA group have received at least 1 open-label course of RTX. After 18 months, 1 additional patient in the RTX group and 2 additional patients in CYC/AZA group received their first open-label rituximab treatment. In addition, 7 patients in the CYC arm received RTX due to crossover or BMJ prior to 6 months.

· RAVE: Extent of Exposure to Cyclophosphamide and Azathioprine

The cumulative dose of CYC or CYC placebo during the trial was similar between the 2 treatment groups with a median 15.5 g [CYC placebo] in the RTX group, and 15.4 g [active CYC] in the CYC group. Eighty-one patients in the RTX group switched from CYC placebo to AZA placebo during the study, and 80 patients in the CYC group switched from CYC to AZA during the study. The mean (median) time to switch was 134.3 days (124 days) in the RTX group, and 129.9 days (120 days) in the CYC days. Most of these patients (74 of 81 in the RTX group, and 75 of 80 in the CYC group) switched before 6 months.

· RAVE: Exposure to Glucocorticoids

For the first 6 months of the RAVE Study, the mean cumulative IV and oral CS use was slightly lower in the RTX group (1316 mg of IV methylprednisolone, and 3326 mg of oral prednisone) than in the CYC group (1348 mg of IV methylprednisolone, and 3684 mg of oral prednisone) at 6 months. Between months 6-18, similar numbers of patients received IV and oral CS (as a protocol-defined treatment) in the 2 treatment groups (n=13 for IV CS in both groups, and n=40 for oral CS in RTX group and n=43 for oral CS in the CYC/AZA arm), with a numerically lower mean dose in the RTX group (2572 mg of oral prednisone for RTX versus 3187 mg of oral prednisone for CYC/AZA). Some patients received non-protocol-defined CS according to BMJ after the 18-month time point, which was not captured in the analysis.

· RITUXVAS

In this study, a total of 44 patients were randomized – 33 to RTX followed by low dose CYC, and 11 to CYC followed by AZA. Total patient-years of follow-up was not reported but the 12 month completion rates were high – 27/33 (81.8%) in the RTX/CYC group and 10/11 (90.9%) in the CYC/AZA arm. All subjects received 1000 mg of IV methylprednisolone followed by oral CS. Patients allocated to RTX also received 2 doses of IV CYC. Two patients in RTX/CYC group received a 3rd dose of IV CYC (1 because of treatment failure and the other due to a protocol violation).

· LITERATURE SEARCH STUDIES

A total of 162 subjects received RTX in 12 uncontrolled, investigator initiated studies. Most patients (n=121) received RTX at the requested dose of 375 mg/m^2 weekly for 4 weeks, however, 32 subjects were given a fixed dose of RTX 1000 mg x 2, and a further 9 patients were administered RTX 500 mg x 2-4 infusions. In 3 of the studies (n=15 subjects) it is unknown if any safety data was collected. Nearly all patients additionally received CS, most received concurrent CYC (IV or oral), and many patients (>50%) also took various other concomitant immunosuppressive medications with their RTX, including mycophenolate mofetil, methotrexate, cyclosporine and anti-TNF medications. The duration of follow-up varied widely from 3-55 months.

· HOLLE et al STUDY

A total of 59 patients received 75 cycles of RTX – all of which had at least 1 cycle, 12 patients had 2 cycles of RTX, and 4 had 3 cycles of RTX. A cycle of RTX treatment was 4 weekly doses at 375 mg/m^2 plus 100 mg of prednisolone on the day of infusion. Conventional immunosuppression was continued after the commencement of RTX, and for the vast majority of patients this involved CYC, either orally administered at up to 2 mg/kg/day or IV (15-20 mg/kg of body weight). A standardised tapering regimen of CS was also undertaken.

8.3. Adverse events

8.3.1. All adverse events (irrespective of relationship to study treatment)

8.3.1.1. Pivotal studies

· Baseline to 6 months

The overall AE profile was similar between the 2 treatment groups in the first 6 months of follow-up with likewise proportions of patients experiencing any AE, any severe (Grade ≥ 3) AE, and any serious AE – refer to Table 11.

Table 11. Overall summary of safety in RAVE Study at 6 months

	Rituximab n=99	Cyclophosphamide n=98
Patient-years of follow-up	47.60	47.01
No. of patients experiencing		
Any AE	**94 (94.9%)**	**97 (99.0%)**
Grade 3	20 (20.2%)	30 (30.6%)
Grade 4	8 (8.1%)	3 (3.1%)
Grade 5	1 (1.0%)	2 (2.0%)
Serious AE	33 (33.3%)	33 (33.7%)
AE leading to study withdrawal	2 (2.0%)	0
AE leading to study drug discontinuation	8 (8.1%)	13 (13.3%)
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%)
AE rates/patient-year		
AE (95% CI)	20.94 (19.68–22.29)	20.81 (19.54–22.15)
Selected AE [j]	0.78	0.96
Serious AE (95% CI)	0.97 (0.72–1.29)	1.15 (0.88–1.50)
Infection (95% CI)	2.10 (1.73–2.56)	1.47 (1.16–1.86)
Serious infection (95% CI)	0.25 (0.14–0.44)	0.28 (0.16–0.48)

a-j: [Information redacted]

The majority of patients in both groups who experienced AEs, suffered AEs of mild-to-moderate intensity: grade 1 AEs accounted for 20.2% of all AEs in the RTX group, and 22.4% of all AEs in the CYC arm; and grade 2 AEs accounted for 45.5% of all AEs in the RTX group, and 40.8% of all AEs in the CYC arm. Similar proportions of patients in both treatment groups experienced grade ≥ 3 AEs. The most common type of Grade ≥ 3 AE was infection, which occurred in 10 patients in each group. The most frequent Grade ≥ 3 infection was respiratory infections in both groups, most commonly pneumonia. 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), hyperkalaemia (1 patient), and acute renal failure (1 patient) in the "RTX other" group. The "RTX other" group refers to those patients who were randomized to RTX but then received additional immunosuppression. 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. Three grade 5 (fatal) AEs occurred: 1) multi-organ failure in a RTX treated patient who received RTX followed by CYC 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.

Pre-specified AEs of special interest were numerically higher in the CYC group (34.7%, 34/98) compared to the RTX group (22.2%, 22/99). However, the rates of those selected AEs were similar between the 2 treatment groups (0.78 events/patient year in the RTX group versus 0.96 events/patient-year in the CYC group; p-value = 0.250). This difference was principally due to the higher number of CYC patients who experienced Grade ≥ 2 leucopenia (WBC <3000/mm^3),

although this did not translate into a higher number of infections during the first 6 months of treatment with CYC. More patients in the RTX group (10 [10.1%] compared to 4 in the CYC arm [4.1%]) required hospitalization considered by the investigator to be either related to disease activity or study medication. Of the 10 RTX patients who were hospitalized, 5 received RTX only, while the other 5 subjects were administered additional therapies after receiving RTX. All 4 patients who were hospitalized in the CYC group, only received CYC (i.e. without a treatment crossover or BMJ strategy). The occurrence of any infection was also comparatively higher in the RTX arm (61.6% [2.10 events/patient-year] versus 46.9% [1.47 events/patient-year]). However, the rates of serious infection were nearly identical between the 2 treatment groups (0.25 events/patient-year for RTX versus 0.28 events/patient-year for CYC). A similar proportion of patients experienced infusion-related reactions in each group (12 in the RTX group, and 11 in the CYC/RTX placebo infusion arm).

The proportion of patients with AEs leading to a permanent discontinuation of study medication was slightly higher in the CYC group (13.3%, 13/98) compared with the RTX group (8.1%, 8/99), although 1 patient who was given RTX had an infusion reaction prompting treatment cessation.

The most common type of AEs (occurring in >10% of patients in either the RTX and/or CYC groups) is summarized in Table 12. The overall number and rate of AEs were similar across the 2 groups. Events with at least a 2-fold greater incidence in the RTX group than in the CYC arm were peripheral oedema (16.2% versus 6.1%) and hypertension (12.1% versus 5.1%). Events with at least a 2-fold greater incidence in the CYC group compared to RTX included decreased WBC count (19.4% versus 4.0%), leucopenia (26.5% versus 10.1%), increased AST (11.2% versus 5.1%), and alopecia (18.4% versus 9.1%).

Table 12. Adverse events occurring in > 10% of either treatment group at 6 months in RAVE: Safety population.

Category of Adverse Events	Rituximab n=99	Cyclophosphamide n=98
Preferred term		
Nausea	18 (18.2%)	20 (20.4%)
Headache	17 (17.2%)	19 (19.4%)
Anemia	16 (16.2%)	20 (20.4%)
Leukopenia	10 (10.1%)	26 (26.5%)
Fatigue	13 (13.1%)	21 (21.4%)
Muscle spasms	17 (17.2%)	15 (15.3%)
Diarrhea	17 (17.2%)	12 (12.2%)
Increased ALT	13 (13.1%)	15 (15.3%)
Rash	10 (10.1%)	17 (17.3%)
Alopecia	9 (9.1%)	18 (18.4%)
Insomnia	14 (14.1%)	12 (12.2%)
Cough	13 (13.1%)	11 (11.2%)
Decreased white blood cell count	4 (4.0%)	19 (19.4%)
Peripheral edema	16 (16.2%)	6 (6.1%)
Arthralgia	13 (13.1%)	9 (9.2%)
Dyspnea	10 (10.1%)	11 (11.2%)
Pyrexia	8 (8.1%)	13 (13.3%)
Upper respiratory tract infection	8 (8.1%)	13 (13.3%)
Decreased hematocrit	7 (7.1%)	13 (13.3%)
Hypertension	12 (12.1%)	5 (5.1%)
Epistaxis	11 (11.1%)	6 (6.1%)
Increased AST	5 (5.1%)	11 (11.2%)

- RAVE: Up to 18 months

The overall 18-month AE profile in the RAVE safety population was consistent with the profile observed at 6 months and comparable between the 2 treatment groups – refer to Table 13. The numbers and rates per patient-year of any AE, selected AEs, Grade ≥ 3 AEs, serious adverse

events (SAEs), and serious infections were similar between the 2 treatment groups. Again, a higher proportion of patients in the RTX group experienced infection (79.8% [79/99] versus 70.4% [69/98] for CYC/AZA), the rates of infection per patient-year were similar between the groups at 18 months (1.41 events/patient-year for RTX compared to 1.24 events/patient-year for CYC/AZA). Furthermore, a higher proportion of patients reported Grade 4 events in the RTX group (10.1% [10/99] versus 4.1% [4/98] for CYC/AZA), with the difference mainly due to disease-related respiratory and renal events.

Table 13: Overall summary of safety in RAVE Study at 18 months

	Rituximab n = 99	Cyclophosphamide n = 98
Patient-years of follow-up	139.6	134.7
No. of patients experiencing		
Any AE	**98 (99%)**	**98 (100%)**
Grade ≥ 3[a]	44 (44.4%)	45 (45.9%)
Grade 3	39 (39.4%)	43 (43.9%)
Grade 4	10 (10.1%)	4 (4.1%)
Grade 5	2 (2.0%)	2 (2.0%)
Serious AE	46 (46.5%)	41 (41.8%)
AE leading to study drug discontinuation	16 (16.2%)	24 (24.5%)
AE leading to withdrawal from the study	3 (3%)	1 (1%)
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%)
AE rates/patient-year		
AE (95% CI)	10.63 (10.10–11.18)	10.92 (10.38–11.49)
Selected AE[l]	0.47	0.48
Serious AE (95% CI)	0.49 (0.39–0.63)	0.57 (0.46–0.71)
Infection (95% CI)	1.41 (1.23–1.62)	1.24 (1.07–1.44)
Serious infection (95% CI)	0.13 (0.08–0.20)	0.16 (0.10–0.24)

AE = adverse event; CYC = cyclophosphamide; MedDRA = Medical Dictionary for Regulatory Activities.

a-l: [Information redacted]

The most common AEs (occurring in >10% of patients in the RTX and/or CYC groups) are summarized in Table 14. The overall numbers and rates of AEs were similar across the 2 groups. Common AEs that occurred at an increase incidence of ≥ 5% in the RTX group versus CYC were diarrhoea (24.2% versus 17.3%), peripheral oedema (20.2% versus 12.2%), urinary tract infection (16.2% versus 6.1%), and cough (28.3% versus 18.4%). These differences are consistent with those observed at 6 months except for urinary tract infections. The higher proportion of patients with hypertension in the RTX group compared with the CYC arm that was observed at 6 months remained at 18 months but was less marked (14.1% for RTX versus 9.2% for CYC/AZA). Common AEs with an increased incidence (≥ 5%) in the CYC group compared with RTX were leucopenia (and decreased WBC), nausea, increased ALT and AST, rash, alopecia, RBC sedimentation rate increased, haematuria, haematocrit decreased, vomiting, pyrexia, and fatigue.

Table 14. Adverse events occurring in > 10% of patients in either treatment group through 18 months: Safety population.

Category of Adverse Events	Rituximab n=99	Cyclophosphamide n=98
Cough	28 (28.3%)	18 (18.4%)
Arthralgia	25 (25.3%)	20 (20.4%)
Diarrhea	24 (24.2%)	17 (17.3%)
Headache	23 (23.2%)	23 (23.5%)
Fatigue	21 (21.2%)	26 (26.5%)
Nausea	20 (20.2%)	28 (28.6%)
Anemia	20 (20.2%)	22 (22.4%)
Upper respiratory tract infection	20 (20.2%)	19 (19.4%)
Peripheral edema	20 (20.2%)	12 (12.2%)
Muscle spasms	18 (18.2%)	21 (21.4%)
Insomnia	16 (16.2%)	14 (14.3%)
Urinary tract infection	16 (16.2%)	6 (6.1%)
Epistaxis	15 (15.2%)	13 (13.3%)
Leukopenia	14 (14.1%)	38 (38.8%)
Hypertension	14 (14.1%)	9 (9.2%)
Rash	13 (13.1%)	22 (22.4%)
Increased ALT	13 (13.1%)	20 (20.4%)
Dyspnea	13 (13.1%)	12 (12.2%)
Alopecia	11 (11.1%)	20 (20.4%)
Dizziness	11 (11.1%)	12 (12.2%)
Back pain	11 (11.1%)	8 (8.2%)
Hyperglycemia	11 (11.1%)	9 (9.2%)
Pyrexia	10 (10.1%)	16 (16.3%)
Tremor	10 (10.1%)	6 (6.1%)
Nasal congestion	10 (10.1%)	5 (5.1%)
Sinusitis	9 (9.1%)	10 (10.2%)
AST increased	8 (8.1%)	14 (14.3%)
Blood creatinine increased	8 (8.1%)	10 (10.2%)
Hematocrit decreased	7 (7.1%)	15 (15.3%)
Vomiting	7 (7.1%)	12 (12.2%)
WBC decreased	6 (6.1%)	21 (21.4%)
Hematuria	4 (4.0%)	12 (12.2%)
RBC sedimentation rate increased	3 (3.0%)	11 (11.2%)

· RAVE: Up to Common Closeout Date

In general, the overall AE profile up to the CCO date was consistent with that recorded at 18 months with 1 exception: a higher proportion of patients reported SAEs in the RTX group compared with the control group (60.6% [60/99] versus 48.0% [47/98]). However, the rate of SAEs was comparable between the 2 treatment groups (0.41 per patient-year [95% CI: 0.34, 0.49] for RTX versus 0.36 per patient-year [95% CI: 0.30, 0.44] for CYC/AZA) when adjusted for drug exposure. Results of the sensitivity analysis, which excluded AEs that occurred after a switch of therapy, were consistent with those from the 18-month analysis and revealed no new trend or pattern of AEs.

8.3.1.2. Other studies

The interpretation of safety data across the treatment groups in the RITUXVAS Study is constrained by the small sample size and limited published information. In the first 12 months of follow-up, overall safety was comparable between the 2 treatment groups, with similar reported percentage incidences and rates (per patient-year) of AEs, severe (grade >3) AEs, and SAEs. Infection was the most common type of AE, with a similar overall rate between the 2 treatment groups. Two infusion reactions and 2 malignancies (1 of which occurred after 12 months) were reported in the RTX + low-dose CYC group. Preliminary unpublished data with up to 2 years of follow-up suggests a comparable safety profile between the 2 treatment groups with respect to the incidence and rates of overall AEs, SAEs and serious infections.

In the investigator initiated studies, limited safety data was reported in 9 of the 12 studies. The published data is consistent with that reported information in the controlled trial (RAVE). The most common type of AE is infection, particularly involving the respiratory tract. Of note,

additional infections included 4 cases of herpes infection and 1 case of hepatitis B virus reactivation. In the largest study reported by Jones *et al*, 16 serious infections occurred in 20% (13/65) of patients. The serious infections were pneumonia (12 events), sepsis (3 events), and cellulitis (1 event). The next most frequently reported type of AEs is mild to moderate infusion reactions. In total, 5 deaths were reported across these studies. The study by Holle *et al* only reported SAEs and this data will be presented in the section on *Deaths and other serious adverse events; Other studies*, below.

8.3.2. Treatment-related adverse events (adverse drug reactions)

8.3.2.1. Pivotal studies

- Baseline to 6 months

A higher proportion of patients in the CYC group (58.1%) compared to the RTX arm (36.4%) had at least 1 AE that was probably or definitely related to the study medication, as per the investigator's evaluation. The most frequent treatment related AEs in the CYC group were leucopenia (22.4%), decreased WBC count (11.2%), alopecia (8.1%), hyperglycaemia (6.1%), and anaemia (4.1%). The most frequent treatment related AEs in the RTX group were leucopenia (7.1%), cytokine-release syndrome (4%), and thrombocytopenia (4%).

Infections (of any severity) are a treatment related AE of interest with any immunosuppressive therapy. A greater proportion of patients in the RTX group (61.6%) experienced an infectious AE compared with the CYC group (46.9%) in the first 6 months of follow-up. The rate of infections when adjusted for patient exposure also showed the same outcome – 2.10 per patient-year (95% CI: 1.73-2.56) for RTX compared with 1.47 per patient-year (95% CI: 1.16-1.86) for CYC. A similar outcome was determined when the exposure was limited to those subjects who received only their original allocated therapy. Table 15 summarizes the most common types of infections (at least 2% incidence) that were reported in the first 6 months of the RAVE Study.

Table 15. Most frequent infections (occurring in at least 2% of patients) up to 6 months in RAVE

	Rituximab n=99	Cyclophosphamide n=98
Total number of events	100	69
No. of patients with any infection	61 (61.6%)	46 (46.9%)
Total duration of follow-up (patient-years)	47.60	47.01
Rate of events (per patient-year) (95% CI)	2.10 (1.73, 2.56)	1.47 (1.16, 1.86)
Preferred terms		
Upper respiratory tract infection	8 (8.1%)	13 (13.3%)
Nasopharyngitis	6 (6.1%)	4 (4.1%)
Pneumonia	4 (4.0%)	5 (5.1%)
Sinusitis	5 (5.1%)	4 (4.1%)
Urinary tract infection	5 (5.1%)	3 (3.1%)
Oral candidiasis	3 (3.0%)	4 (4.1%)
Bronchitis	4 (4.0%)	2 (2.0%)
Herpes zoster	5 (5.1%)	1 (1.0%)
Candidiasis	2 (2.0%)	3 (3.1%)
Fungal infection	3 (3.0%)	2 (2.0%)
Oral herpes	4 (4.0%)	1 (1.0%)
Respiratory tract infection	4 (4.0%)	0
Vulvovaginal mycotic infection	3 (3.0%)	0
Acute sinusitis	0	2 (2.0%)
Escherichia infection	2 (2.0%)	0
Gastroenteritis	0	2 (2.0%)
Viral upper respiratory tract infection	2 (2.0%)	0

The most common types of infection involved the upper respiratory tract (reported under various terms in Table 15) with 34 AEs in 22 RTX patients, and 28 AEs in 22 CYC-treated subjects. Four of the respiratory tract infections (2 in each treatment group) were classified as severe. Herpes infection (under various terms –oral herpes, herpes zoster, herpes simplex and herpes keratitis) were also common and occurred at a higher incidence in the RTX group (11%)

compared with the CYC arm (3%). This is known infectious risk with RTX, and all of the herpes related AEs were of mild-moderate severity, except the 1 case of herpes keratitis. Fungal infections (under various terms – oral, oesophageal, vulvovaginal and cutaneous) occurred more commonly in the RTX group (15% versus 11% in the CYC arm). All of the fungal infections were judged to be mild-moderate in severity.

- RAVE: Up to 18 months

By 18 months of follow-up, a higher proportion of patients in the CYC group (70.4%) than in the RTX group (42.4%) had at least 1 AE that was probably or definitely related to study medications. The most frequent treatment related AEs in the CYC group were leucopenia (31.6%), decreased WBC count (15.3%), alopecia (8.2%), hyperglycaemia (6.1%), thrombocytopenia (5.1%), anaemia (4.1%), and increased serum ALT (4.1%). The most frequent treatment related AEs in the RTX group were leucopenia (8.1%), cytokine-release syndrome (4.0%), thrombocytopenia (4.0%), decreased WBC count (4.0%) and flushing (4.0%).

Infection related AEs were more common in the RTX group (79.8%) than the CYC arm (70.4%) at 18 months of follow-up in the RAVE Study. However, the rate of overall infection per patient-year was similar with overlapping confidence intervals: 1.41 (95% CI: 1.23-1.62) for RTX, and 1.24 (95% CI: 1.07-1.44) for CYC. In both treatment groups the rate of infection declined with time compared to the initial 6 months of treatment which may be explained by the confounding effect of higher disease activity and concurrent high dose CS in the initial treatment phase. Consistent with the pattern of infections at 6 months, respiratory tract infections were the most common site with 73 AEs in 42 RTX-treated patients, and 72 AEs in 38 CYC/AZA-treated subjects. Other types of infection, such as viral or fungal, did not become more prevalent with time on treatment or extended follow-up. Table 16 summarizes the most common types of infections (at least 2% incidence) that were reported in the first 18 months of the RAVE Study.

Table 16. Most frequent infections (occurring in at least 2% of patients) up to 18 months in RAVE

	Rituximab n = 99	Cyclophosphamide n = 98
Total number of infection adverse events	197	167
No. of patients with any infection	79 (79.8%)	69 (70.4%)
Total duration of follow-up (patient-years)	139.6	134.7
Rate of events (per patient-year)	1.41	1.24
Preferred terms		
Upper respiratory tract infection	20 (20.2%)	19 (19.4%)
Urinary tract infection	16 (16.2%)	6 (6.1%)
Sinusitis	9 (9.1%)	10 (10.2%)
Nasopharyngitis	5 (5.1%)	8 (8.2%)
Bronchitis	5 (5.1%)	7 (7.1%)
Pneumonia	4 (4.0%)	7 (7.1%)
Herpes zoster	5 (5.1%)	4 (4.1%)
Respiratory tract infection	7 (7.1%)	1 (1.0%)
Viral upper respiratory tract infection	6 (6.1%)	2 (2.0%)
Oral candidiasis	4 (4.0%)	4 (4.1%)
Fungal infection	4 (4.0%)	3 (3.1%)
Oral herpes	4 (4.0%)	3 (3.1%)
Candidiasis	2 (2.0%)	4 (4.1%)
Influenza	2 (2.0%)	3 (3.1%)
Vulvovaginal mycotic infection	5 (5.1%)	0
Gastroenteritis	0	4 (4.1%)
Herpes simplex	3 (3.0%)	1 (1.0%)
Conjunctivitis infective	3 (3.0%)	1 (1.0%)
Diverticulitis	3 (3.0%)	1 (1.0%)
Laryngitis	3 (3.0%)	1 (1.0%)
Pharyngitis	1 (1.0%)	3 (3.1%)
Fungal skin infection	2 (2.0%)	1 (1.0%)
Otitis media	1 (1.0%)	2 (2.0%)
Rhinitis	2 (2.0%)	1 (1.0%)
Tooth abscess	1 (1.0%)	2 (2.0%)
Acute sinusitis	0	2 (2.0%)
Cystitis	2 (2.0%)	0
Escherichia infection	2 (2.0%)	0
Lower respiratory tract infection	2 (2.0%)	0
Oral infection	0	2 (2.0%)
Staphylococcal infection	2 (2.0%)	0

Note: Shaded cells indicate preferred terms meeting criteria of ≥ 2% incidence since the 6-month analysis

- RAVE: Up to Common Closeout Date

The analysis of safety data collected through the CCO date was consistent with the 18-month data. The cumulative incidence of infection through to the CCO date was 89.9% in the RTX group and 78.6% in the CYC arm which corresponded to declining incidence rates (0.99 [95% CI: 0.88-1.11] for RTX and 0.91 [95% CI: 0.80-1.03] for CYC/AZA). No change in the type of infections was observed.

8.3.2.2. Other studies

It was not specifically stated whether or not AEs were judged to be treatment related for any of the supporting studies.

8.3.3. Deaths and other serious adverse events

8.3.3.1. Pivotal studies

8.3.3.1.1. Deaths

For the RAVE Study assessment at 18 months (and also at the CCO date), 2 deaths were recorded in each of the treatment groups. For the CYC group, both deaths occurred before 6 months of treatment (day 55 and 123) in patients with newly diagnosed ANCA associated vasculitis, and both deaths were due to infection (septic shock, preceded by pneumocystis

pneumonia despite appropriate prophylaxis; and the other due to pneumonia). There were also 2 deaths in the RTX group (1 due to multi-organ failure, and the other due to pulmonary alveolar haemorrhage). The 1 death in the RTX group before 6 months occurred in a patient with relapsed GPA and renal involvement who was switched to BMJ on day 16 after developing acute renal failure. The patient was switched to open-label CYC after receiving 3 infusions of RTX, developed pancytopenia on day 36, and died of multi-organ failure due to sepsis 1 month later. All 3 deaths in the first 6 months of the RAVE Study occurred in older patients (65-80 years of age), compared with the mean age of 53 years for the overall study population. The other patient (77 year old women) who died in the RTX group suffered a disease relapse with pulmonary haemorrhage on day 499, which was treated with

IV CS, plasmapheresis and a second course of 4 RTX infusions while being intubated. She succumbed to respiratory failure on day 514. She was considered to be in remission at 6 months.

8.3.3.1.2. Serious Adverse Events

At 6 months of follow-up in the RAVE Study, the overall incidence of SAEs was comparable between the RTX (33/99) and CYC groups (33/98) at 33-34%. The most commonly reported type of SAE was infection, with a similar incidence between RTX and CYC. Infection related SAEs affected a total of 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. Two grade 5 (fatal) infections (1 case each of pneumonia, and septic shock complicated by multi-organ failure) and 1 grade 4 infection (pneumocystis jiroveci pneumonia) occurred in 2 patients treated with CYC only.

The overall rate of SAEs per patient-year was numerically lower in the RTX arm (0.69) compared with the CYC group (0.94). The most frequent individual types of SAEs were deep venous thrombosis (10 patients, 5.1%), pneumonia (8 patients, 4.1%), anaemia (5 patients, 2.5%), acute renal failure (5 patients, 2.5%), and pulmonary embolism (4 patients, 2.0%). The only notable imbalance between the RTX and CYC arms was in the incidence of serious DVT (2 patients in the RTX group versus 8 patients in the CYC arm).

Three episodes of serious leucopenia were reported in the RTX group. However, grade 2 or higher leucopenia, which includes non-serious events, occurred in a greater proportion of patients in the CYC group than the RTX group (17.3% versus 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 adverse gastrointestinal events included diarrhoea (2 patients, 2.0%), and individual cases of ischemic colitis and upper gastrointestinal haemorrhage.

The overall profile of SAEs reported over 18 months of follow-up in RAVE Study was similar to those reported in the first 6 months of the trial. The proportions of patients who reported any SAE were comparable between the RTX (46.5%) and CYC (41.8%) groups. The rate of serious adverse events per patient-year was 0.49 and 0.57 in the RTX and CYC groups, respectively. These rates were lower than those reported for the first 6 months of the study and this may be due to lower disease activity and CS use later in the study.

By 18 months of follow-up, the most common type of SAE was infection, with similar incidences and rates in the RTX and CYC groups (15.2% and 0.13/patient-year in the RTX group versus 15.3% and 0.16/patient-year in the CYC group). The most common types of serious infections were pneumonia (4% for the RTX group, and 5.1% for the CYC group) and urinary tract infection (2.0% in the RTX, and 1.0% in the CYC group). Other common types of SAEs included respiratory disorders (9.1% for RTX versus 11.2% in the CYC group; mainly attributable to GPA relapse, PE, pulmonary haemorrhage and laryngeal stenosis) and blood/lymphatic system disorders (overall 6.1% in each arm; which encompassed anaemia [2.0% in the RTX group

versus 4.1% in the CYC group] and leucopenia [3.0% in the RTX group versus no patients in the CYC group]).

Consistent with the 6 month data was a higher incidence of serious DVT in the CYC group (8.2%; versus 1.0% in the RTX group), and a higher number of events affecting the gastrointestinal system in the RTX group (5; versus 2 in the CYC group). Gastrointestinal events occurring in the RTX group (ischaemic colitis, diarrhoea, gastritis, and upper gastrointestinal haemorrhage) had no clear unifying etiology. There were 2 serious gastrointestinal events in the CYC group, both were cases of acute pancreatitis. No other pattern of SAEs grouped by SOC was observed by 18 months. Two serious cardiac events were recorded in the RTX group, both of which were atrial fibrillation. There were also 2 cardiac SAEs in the CYC group: myocardial infarction and supraventricular tachycardia.

In the analysis to the CCO date, the cumulative incidence of SAEs was higher in RTX-treated patients (60.6%) than in the CYC-treated patients (48.0%). This difference in incidence may be partly explained by a longer period of follow-up in the RTX group (299 patient-years in the RTX group versus 275 patient-years in the CYC group). The overall rates of SAEs per patient-year were comparable between the RTX (0.41/patient-year) and CYC (0.36/patient-year) groups at the CCO date.

8.3.3.2. Other studies

8.3.3.2.1. Deaths

A total of 8 deaths occurred in the RITUXVAS Study: - 6 (18% of 33) occurring in the RTX group prior to 12 months, and 2 (18% of 11) in the CYC group. Only summary data about the deaths has been reported in the literature, and data on 1 of the deaths in the CYC group is unpublished. The majority of deaths occurred within 3 months of randomization, and the median time to death was 81 days (range of 22-330 days in the RTX group compared with a range of 2-610 days in the CYC arm). Compared with the overall study population, the patients who died were older (median age of 76 years; range 63-84 years) and had very low glomerular filtration rates (median GFR at baseline of 9 ml/min/1.73m^2). Both of these patient factors are known risk factors for death in ANCA associated vasculitis. Four deaths were related to infections (n=3 for RTX, and n=1 for CYC). The other causes of death were cardiovascular disease (n=1 for both treatment groups), and complications of end stage renal failure (2 subjects in the RTX group). Another patient in the CYC arm died more than 12 months after study entry due to a cardiovascular AE.

A total of 5 deaths were reported in the published investigator-initiated studies. These deaths occurred between 3 and 17 months after the commencement of RTX. Three of the deaths were associated with infection: pneumonia in a patient with severe pre-existing bronchial stenosis due to granulomatous tracheobronchial disease involvement who was receiving concomitant cyclosporine; hepatitis B reactivation in a patient receiving concomitant AZA who developed end stage renal failure, and a case of fulminant adenoviral infection in a patient with a long history of refractory GPA who received concomitant adalimumab. In all 3 cases, the patients had received extensive prior, as well as concomitant, immunosuppressive therapies that might have contributed to an overall susceptibility to infection. The other 2 deaths were reported by Jones *et al* (2009) in a case series of 65 patients with a total of 129 patient-years of follow-up. One case involved a 59-year-old patient in disease remission who suddenly died 3 months after a course of RTX for unclear reasons. A post-mortem examination was not performed. The other case was a 7-year-old boy with severe pulmonary fibrosis who died 8 months after a course of RTX. The cause of death was reported to be disease related.

Two patients (of 59) died in the Holle *et al* (2011) Study but no specific details about the deaths were in the published report.

8.3.3.2.2. Serious Adverse Events

At 12 months of follow-up in the RITUXVAS Study, 16 of 33 (48%) patients experienced 35 SAEs in the RTX arm (including 6 patients with fatal events). Six of these patients had serious infections and 2 developed malignancies (melanoma and breast cancer). Four of 11 (36%) patients experienced 11 SAEs in the CYC arm, including 3 serious infections in 2 patients. Identical proportions of patients in each of the 2 treatment groups experienced hospitalizations or life threatening events, serious infections or death. The rate of SAEs per patient-year was not reported. However, SAEs and death were common in the 9 subjects who were dialysis dependent at study entry: 3 (33%) of those patients died, and 7 (78%) of them developed at least 1 SAE.

Unpublished data with up to 2 years of follow-up in the RITUXVAS Study revealed that 20 of 33 (61%) patients treated with RTX experienced 50 SAEs (including the 6 patients with fatal events). Twelve of these patients had serious infections and 3 developed malignancies (melanoma, breast cancer and basal cell carcinoma). Four of 11 (36%) patients experienced 15 SAEs in the CYC arm, including 5 serious infections in 2 patients. Three patients in the CYC arm had fatal events, one of which was infection.

The incidence of SAEs was not systematically reported in most of the investigator initiated studies. In the largest study of 65 patients with 129 patient years of follow-up, 45 SAEs occurred in 25 patients (38%). Sixteen of the 45 events (36%) were serious infections. The median time to serious infection was 8 months from the first course of RTX treatment. Seventeen events, including 1 of 2 deaths, were related to active vasculitis (median time to event: 6 months from the first course of RTX).

Twenty-four SAEs were documented in the Holle *et al* study. Infection was the most common SAE affecting 21 patients, and pneumonia was the most prevalent type of infection (11 cases). Four opportunistic infections were reported – 2 cases of herpes zoster, 1 case of CMV reactivation and 1 patient experienced pneumocystis pneumonia. Immunoglobulin (Ig) G and M levels declined after RTX, but there was no association between low IgG or IgM levels, and infection.

8.3.4. Discontinuation due to adverse events

8.3.4.1. Pivotal studies

In the RAVE Study, permanent discontinuations of study medication due to AEs affected more patients in the CYC group compared with the RTX group at both 6 months (13.3% [13/98] versus 8.1% [8/99]); and by 18 months - 24.5% [24/98] versus 16.2% [16/99]. At 6 months, the most frequent reported AEs leading to discontinuation of study medication were leucopenia (3 patients in CYC group only), drug hypersensitivity (2 patients in the CYC arm, and 1 in the RTX group) and acute renal failure (2 subjects in treatment groups). Other AEs leading to treatment discontinuation were a mixture of singular events with no clear pattern, apart from 2 infections in the RTX group (1 case each of herpes simplex infection and pneumonia). By 18 months of follow-up, the profile of AEs leading to treatment discontinuation was consistent with that reported at 6 months, with further cessations due to either leucopenia (another 4 patients in the CYC group only), infection (1 case of febrile neutropenia in the CYC group) and GPA-related respiratory symptoms in both groups (4 relapses of GPA in the RTX group, 2 GPA relapses in the CYC arm, plus 2 cases of laryngeal stenosis in the RTX group). No infusion reactions occurring within 24 hours of IV drug administration led to treatment discontinuation, although 1 hypersensitivity reaction which was initially reported as an infusion reaction occurred 2 days after the third RTX infusion. This led to discontinuation of study drug.

8.3.4.2. Other studies

No patient in the RTX + low-dose CYC group of the RITUXVAS Study was reported to have stopped RTX treatment early (course of 4 infusions).

In the published investigator-initiated studies, only 1 patient was reported to have prematurely stopped their RTX treatment course. The completeness of the reporting is unknown. The patient who did stop prematurely was involved in the study reported by Seo *et al*. The patient received 2 of 4 planned RTX infusions and treatment was discontinued because of the development of anterior neck swelling several hours after the second infusion. The event was transient, resolved spontaneously, and no clear etiology was reported. The patient was subsequently re-treated with 3 additional courses of RTX without AEs, or the recurrence of her previous symptoms. In the study by Holle *et al*, 1 patient discontinued RTX because of an infusion reaction.

8.4. Laboratory tests

Haematological toxicity, particularly lymphopenia, neutropenia and thrombocytopenia, are known major potential safety concerns with RTX for other indications, and were pre-specified areas of special interest in the safety analysis of the RAVE Study. This will be the focus in this report. No significant treatment related changes occurred for haematocrit and haemoglobin levels.

In the 18-month study period of the RAVE Study, the median values and median changes from baseline of standard hematologic and biochemistry parameters were similar across the 2 treatment groups for most laboratory parameters. Decreases in median WBC counts, platelet counts, and neutrophils were observed in both treatment groups, with a numerically larger decrease in the CYC group. A decrease in median lymphocyte counts was observed only in the CYC group.

8.4.1. Liver Function

8.4.1.1. Pivotal studies

At 18 months of follow-up in the RAVE Study, only 1 patient (1.1% of 91) treated with RTX was recorded to have a significant change in liver function tests (asymptomatic rise in serum transaminases). In the control group, 3 subjects (3.4% of 87) recorded increased serum transaminases over 18 months of treatment and follow-up.

8.4.1.2. Other studies

Laboratory evaluations of liver function from the RITUXVAS, investigator initiated, and Holle *et al* studies are not available.

8.4.2. Kidney function

8.4.2.1. Pivotal studies

No increased incidence of impaired renal function or electrolyte disturbances were seen in the RTX group compared with the control group in the RAVE Study.

8.4.2.2. Other studies

Summaries of clinical laboratory evaluations from the investigator initiated, and Holle *et al* studies are not available. In the RITUXVAS Study whereby patients with significant renal impairment were the target population, changes in kidney function on trial were assessed as an efficacy outcome, and have been discussed earlier in this report.

8.4.3. Other clinical chemistry

8.4.3.1. Pivotal studies

In the RAVE Study, hyperuricaemia (> 10 mg/dL) occurred more frequently in the RTX group (30.3%; 20/66) than in the CYC group (15.9%; 11/69). This is in keeping with the known risk profile of RTX in other indications. The hyperuricaemia was transient and without clinical consequence. It is probably due to purine metabolism resulting from lysis of B-cells.

8.4.3.2. Other studies

Not specifically reported in any of the other studies.

8.4.4. Haematology

8.4.4.1. Pivotal studies

8.4.4.1.1. Leucopenia

At 6 months in the RAVE Study, the number of patients with at least grade 2 leucopenia (a pre-specified AE of special interest) was higher in the CYC group than in the RTX group (17 versus 5 patients). However, the incidence of grade 3 or greater leucopenia was similar in the 2 treatment groups (2 x grade 4 and 2 x grade 3 AEs were reported in 3 patients in the RTX group, compared with 3 x grade 3 AEs in 3 patients in the CYC arm).

Consistent with the 6-month analysis, the number of patients reporting grade 2 or higher leucopenia by 18 months in the RAVE Study was higher in the CYC group than in the RTX group (20 [20.4%] versus 7 [7.1%] patients). However, the incidence of grade 3 or higher leucopenia was low and similar in the 2 treatment groups (3 patients in the RTX group, and 5 patients in the CYC group). The 3 cases of leucopenia in the RTX group were reported as serious, and all occurred prior to 6 months. These three events (2 x grade 4 and 1 x grade 3) required hospitalization and temporary suspension of study treatment. One of the 3 patients developed pneumonia, and another subject received granulocyte-colony-stimulating factor (G-CSF) treatment. While no serious events of leucopenia were reported in the CYC group, 1 patient developed serious (grade 4) febrile neutropenia that required IV antibiotics, G-CSF, and interruption of CYC treatment 39 days after the first dose of study drug.

The median duration of leucopenic episodes was 24 days in both treatment groups, with a range of 7-125 days in the RTX group, and 8-121 days in the CYC group. The majority of leucopenic episodes led to a discontinuation of study drug either temporarily (23 of 44 episodes) or permanently (4 of 44 episodes).

The CYC group had a higher incidence of grade 3 or 4 lymphopenia (88.5%) and grade 4 neutropenia (18.4%) compared with the RTX group (48.1% and 10.7%, respectively) on the basis of routine laboratory values collected during the 18-month period.

Despite the higher incidence of leucopenia in the CYC group, the overall number of patients with grade 3 or greater infections through to 18 months were the same across the 2 treatment groups (13 patients in each arm). Six serious or severe (grade>3) infections occurring after the onset of leucopenia were reported in 5 patients. In the RTX group, 1 patient experienced 2 events of grade 3 pneumonia associated with concurrent grade 2 and grade 4 leucopenia; and another patient experienced grade 4 pneumonia 1 week after resolution of grade 4 leucopenia. In the CYC group, 1 patient experienced a grade 3 skin infection 6 weeks after resolution of grade 2 leucopenia, 1 patient reported a grade 3 pneumonia 2 weeks after resolution of a grade 2 leucopenia, and 2 patients experienced grade 3 urinary tract infections associated with grade 3 leucopenia.

The occurrence of leucopenia is consistent with the known safety profiles of both RTX and CYC.

However, the lack of a clear association between the occurrence of leucopenia and significant infections may be explained, at least in part, by the close study monitoring, and prompt dose modification or discontinuation of treatment. The episodes of leucopenia had relatively short durations compared to clinical practice.

Leucopenia AEs reported after 18 months and up to CCO were limited to 2 events of grade 2 leucopenia in 2 CYC patients who had reported grade >2 leucopenia previously. Thus, the cumulative incidence of grade >2 leucopenia through to the CCO date remained unchanged from the 18-month time point (7 patients in the RTX group, and 20 patients in the CYC group).

8.4.4.1.2. Thrombocytopenia

In the RAVE trial, 4 patients in the RTX group and 1 subject in the CYC arm reported grade > 2 thrombocytopenia by 18 months. The thrombocytopenia occurred in 4 patients prior to 6 months, and the fifth patient (75 year old man with newly diagnosed vasculitis) from the RTX group had grade 4 autoimmune thrombocytopenia between months 6 and 18, while receiving AZA and Bactrim. The patient was initially treated with RTX and crossed over to CYC on study day 60. Nine months after crossover, the patient developed autoimmune thrombocytopenia (grade 4; platelet count of 5,000/mm3). The patient's AZA maintenance therapy was permanently discontinued as a result of the AE, as were the co-medications of Bactrim, aspirin, and hydrochlorothiazide because of the potential interference with platelet activity. The patient did not experience any significant bleeding, but petechial spots were noted on his lower extremities. The patient was treated with IV immunoglobulin and prednisone, and subsequently underwent an elective splenectomy. The AE completely resolved, and the patient was discharged from hospital with a platelet count of 139,000/mm3.

Of the 4 patients with thrombocytopenia in the RTX group, 2 had concurrent bleeding episodes (1 patient taking warfarin had a serious upper gastrointestinal bleed; and 1 patient who had crossed over from RTX to CYC had a case of lower extremity petechial bleeding). Study medication was discontinued in 3 patients (temporarily in 2 cases; and permanently in 1 case), and the thrombocytopenia resolved in all 4 cases, with the duration of thrombocytopenia ranging from 5 to 67 days.

The single case of thrombocytopenia in the CYC group was associated with pancytopenia and pneumonia, and the thrombocytopenia resolved after 6 days. Since the study protocol required that patients receive pneumocystis prophylaxis (Bactrim), concomitant therapies may have contributed to this patient's pancytopenia. No further events of grade >2 thrombocytopenia were reported after 18 months of follow-up.

8.4.4.2. Other studies

8.4.4.2.1. Leucopenia

In the RITUXVAS trial, 2 patients (6%) in the RTX + low-dose CYC group, and 1 (9%) in the CYC group developed neutropenia related AEs. No information regarding the leucocyte counts was provided.

In the investigator-initiated studies, the incidence of leucopenia was not consistently reported. There were 2 cases of leucopenia, and 2 cases of neutropenia reported across the studies. In the 4 cases reported, concomitant medications may have contributed to their etiology. In the study by Jones *et al*, 2 of 65 patients reported SAEs of neutropenia (<0.5 x 10 9/L). These events occurred at 3 months and at 5 months after the second RTX course. Both episodes were short-lived, and there was spontaneous recovery of the neutrophil count without sepsis. Although concomitant medications might have been responsible (trimethoprim/sulfamethoxazole and AZA in 1 patient; and cyclosporin in the other subject), the events were considered likely to be related to RTX.

In another study, transient leucopenia was observed in 2 patients at 2 and 11 weeks after the initiation of RTX. In 1 of these 2 patients, leucopenia (neutrophils < 100/µL) was later attributed to daily use of metamizole, an analgesic associated with bone marrow suppression, and concurrent medication with mycophenolate mofetil. White cell counts normalized after both medications were stopped. In the second patient, leucopenia (2500 leukocytes/µL with 1200/µL neutrophils and 600/µL lymphocytes) was believed to be due to concomitant treatment with trimethoprim/sulfamethoxazole, and WBC counts normalized after the drug was stopped.

The Holle *et al* study did not report any significant leucopenic AEs.

8.4.4.2.2. Thrombocytopenia

In the RITUXVAS Study, 1 of 33 (3%) patients in the RTX + low-dose CYC group recorded thrombocytopenia (versus no patients in the CYC group). No other information has been published.

In the investigator-initiated studies, Keogh *et al* reported 1 of 11 patients developing grade 3 thrombocytopenia. However, the timing and duration of the AE suggested that it may have been associated with concomitant dapsone. Thrombocytopenia was not reported in any of the other trials. The Holle *et al* study did not report any significant thrombocytopenic events.

8.4.5. Serum Immunoglobulin Levels

8.4.5.1. Pivotal studies

At baseline in the RAVE Study, up to 21.3% of patients in both treatment groups had low serum levels of IgM, IgG and IgA –refer to Table 17. As expected, median Ig concentrations declined from baseline with treatment and follow-up (both at 6 and 18 months). The median decline in Ig concentrations was most pronounced for IgG (particularly at 6 months) with no significant difference by treatment regimen (RTX or CYC) being observed. However the decline in Ig levels had no clinical relevance as the rate of overall and serious infections were similar in patients with low serum Ig levels (at any time point) compared to subjects who maintained normal serum Ig levels.

Table 17. Change from Baseline and Proportion of patients with low Immunoglobulin (< lower limit of normal) at 6 and 18 months in the RAVE Study

	Rituximab N=99	Cyclophosphamide N=98
Baseline (no of evaluable patients)	99	94
IgM <LLN	16 (16.2%)	6 (6.4%)
IgG <LLN	18 (18.2%)	20 (21.3%)
IgA <LLN	5 (5.1%)	10 (10.6%)
6 Months (n)	83	77
IgM		
Median Change from baseline (mg/dL)	-42.0	-42.5
< LLN	49/83 (59.0%)	36/77 (46.8%)
newly occurring < LLN	35/69 (50.7%)	31/68 (45.6%)
IgG		
Median change from baseline (mg/dL)	-259	-252
< LLN	54/83 (65.1%)	43/77 (55.8%)
newly occurring < LLN	40/69 (58.0%)	30/60 (50.0%)
IgA		
Median change from baseline (mg/dL)	-48	-59
< LLN	25/83 (30.1%)	24/77 (31.2%)
newly occurring < LLN	21/79 (26.6%)	17/67 (25.4%)
18 Months (n)	69	60
IgM		
Median Change from baseline (mg/dL)	-38.0	-23.5
< LLN	27/69 (39.1%)	17/60 (28.3%)
newly occurring < LLN	18/59 (30.5%)	15/55 (27.3%)
IgG		
Median Change from baseline (mg/dL)	-185	-131
< LLN	31/69 (44.9%)	19/60 (31.7%)
newly occurring < LLN	23/61 (37.7%)	11/45 (24.4%)
IgA		
Median Change from baseline (mg/dL)	-44	-42
< LLN	19/69 (27.5%)	16/60 (26.7%)
newly occurring < LLN	15/65 (23.1%)	10/53 (18.9%)

LLN: IgM 23 mg/dL (16 – 19 yrs), 40 mg/dL (≥20 yrs); IgG 549 mg/dL, 700 mg/dL; IgA 61 mg/dL, 70 mg/dL
Newly occurring from normal value at BL

8.4.5.2. Other studies

The study by Holle *et al* reported a clinically and statistically significant ($p<0.05$) decline in serum IgM and IgG levels after RTX therapy. The median (range) IgM levels in g/L were 0.51 (0.1-1.8) before treatment and 0.2 (0.1-1.4) following RTX. The median (range) IgG levels in g/L were 8.6 (4.5-13.6) before treatment and 6.9 (2.1-13.1) following RTX. However, there was no significant association between low serum IgM or IgG levels, and the occurrence of infection.

8.4.6. Vital signs

8.4.6.1. Pivotal studies

In the RAVE Study, median body weight increased in both treatment groups over the first 6 months, and then stabilized thereafter up until 18 months of follow-up. The median change from baseline to 6 months in body weight was similar in both arms – 3.9 kg increase in the RTX arm (baseline of 80.5 kg to 84.4 kg), and 3.4 kg increase in the CYC/AZA group (baseline of 80.5 kg to 83.9 kg). It is likely that the high initial dose of CS and control of active systemic disease (catabolic state) are the main explanations for this observation. Other vitals signs (e.g. respiration rate and temperature) did not significantly change in either treatment group over the 18 months of study follow-up.

8.4.6.2. Other studies

Not reported for all other studies.

8.4.7. Hospitalization (due to ANCA vasculitis or study medication)

8.4.7.1. Pivotal studies

Hospitalization due to either ANCA related disease manifestations or complications of study drug treatment was a pre-specified safety outcome of special interest in the RAVE Study. More patients in the RTX group (10 of 99) were hospitalized because of active disease or study drug problems by 6 months compared to the CYC group (4 of 98 subjects). Of the 10 patients in the RTX group, 5 were in the "RTX other" group (i.e. they had not just received RTX and CS, but also other study immunosuppression): 3 patients had initial hospitalizations occurring before or at the time of treatment switch, 1 patient was receiving concomitant treatment with CYC (a protocol violation), and the remaining patient had a hospitalization occurring after crossing over to CYC treatment. The reasons for hospitalization in both the RTX and CYC groups were typical for this population and included respiratory tract infections in 7 patients (pneumonia in 5 patients, upper respiratory tract infection in 1 patient, and bronchitis in 1 patient); and singular cases of Adult Respiratory Distress Syndrome (ARDS), pulmonary haemorrhage, pulmonary embolism, renal failure, osteomyelitis, and a hypersensitivity reaction (all with 1 patient each). Several of these hospitalizations appeared to be related to active vasculitis or concomitant therapies such as CS rather than to study drug. Two of the patients with pneumonia also had significant leucopenia and/or neutropenia. Of note, these events are a subset of SAEs, which were equally distributed across the 2 treatment groups. Six of the 10 patients hospitalized in the RTX group were > 65 years old, compared with 0 of 4 subjects in the CYC group.

The data at 18 months and through the CCO date was consistent with outcome observed at 6 months in that more patients were hospitalized for reasons related to disease activity or study drug (as per the investigator's assessment) in the RTX group. By 18 months, 13 patients had experienced 14 hospitalizations in the RTX group, and 5 patients had 5 hospitalizations in the CYC group. Cumulatively, by the CCO date, 16 patients suffered 18 hospitalizations in the RTX group, and 7 patients required 9 hospitalizations. This difference was mainly attributable to the increased number of patients hospitalized in the RTX group during the first 6 months (10 in the RTX group versus 4 in the CYC arm). Between 6 and 18 months, 4 hospitalizations were reported in the RTX group, and 1 hospitalization was reported in the CYC group. After 18 months of follow-up, 4 additional hospitalizations were reported in each treatment group.

Of the 27 hospitalizations associated with disease or study medication up to the CCO date, 19 (15 in the RTX group and 4 in the CYC group) occurred before the time of treatment switch. In general, the hospitalizations occurring prior to 6 months were most commonly related to infections, whereas those occurring after 6 months were more commonly related to disease relapse. Overall, the reasons for these hospitalizations in both treatment groups were typical for this patient population and included the following:

- Infections (7 events in the RTX group, including 5 respiratory tract infection, 1 case of osteomyelitis, and 1 report of cellulitis; and 4 events in the CYC group, including 3 respiratory infections and 1 viral infection)
- Renal failure (2 in the RTX group, and no events in the CYC group)
- Laryngeal stenosis due to vasculitis (4 in the RTX group, and 1 in the CYC group)
- Other respiratory diagnoses (3 events in total, including single cases of pulmonary haemorrhage and pulmonary embolism in the RTX group, and ARDS in the CYC arm)
- Other individual types of events (including hypersensitivity reaction, pyrexia, and atrial fibrillation in the RTX group; and acute pancreatitis, febrile neutropenia, and anaemia in the CYC group).

Newly occurring hospitalizations associated with either underlying disease or study medication in the RTX group reported after the initial 6-month period were predominantly related to exacerbations of vasculitis. The type of AEs consistent with a disease flare in the RTX group included 3 patients with GPA who developed laryngeal stenosis, and 1 patient with GPA who experienced pulmonary haemorrhage.

Six of the 14 (43%) patients in the RTX group who were reported to have been hospitalized due to active disease or study drug were 65 years of age or older, and had baseline renal function below the median creatinine clearance of 74.71 mL/min/1.73m^2. In contrast, no patients in the CYC group who were hospitalized were > 65 years of age, and only 1 had impaired renal function (i.e. below the median value of 74.71 mL/min/1.73m^2).

8.4.7.2. Other studies

In the RITUXVAS Study, 12 (36.4% of 33) patients in the RTX + low-dose CYC group, and 4 (36.4% of 11) in the CYC arm experienced SAEs that were life threatening or requiring hospitalization. However, additional specific details were not reported.

In the published study, investigator initiated studies the incidence of SAEs leading to hospitalization was not systematically reported. In the Holle *et al* study, hospitalizations were not specifically reported.

8.4.8. Haemorrhagic Cystitis

8.4.8.1. Pivotal studies

By 6 months in the RAVE Study, 3 patients (2 in the RTX group, and 1 in the CYC group) had developed grade 2 haemorrhagic cystitis. One of the RTX patients was switched over to CYC and CS under BMJ because of a presumed AE (acute renal failure) to RTX after 3 infusions. Five months after commencing CYC, the subject developed haemorrhagic cystitis in association with BK virus bladder infection. The BK virus is a polyomavirus related to JC virus which infects the majority of children but is not associated with a specific clinical illness in childhood. The virus remains latent in the body and reactivates in the setting of significant immunosuppression. The other patient in the RTX group had 2 episodes of haemorrhagic cystitis (first event before 6 months, and the other at 18 months). This patient also crossed over treatment early (before 3 months) from RTX to CYC. The third patient with haemorrhagic cystitis received CYC from the study outset, and this resolved within 1 week of ceasing the medication.

8.4.8.2. Other studies

Not specifically reported in these studies.

8.5. Post-marketing experience

RTX was approved for the induction treatment of severe GPA and MPA in the USA in April 2011, and the sponsor has maintained a global safety database. Up until 31 August 2011, the database had received a total of 99 case reports (94 in patients with GPA, 4 in MPA and 1 not specified ANCA vasculitis) with 81 serious AEs. Expectedly, the most common categories of AEs by SOC were infections, followed by respiratory/ thoracic/mediastinal disorders. Of particular note, 4 patients who received RTX (concurrent with CS and other immunosuppressant drugs) experienced pneumocystis jiroveci pneumonia (PJP). It is unclear if any of those patients received appropriate prophylaxis for PJP, which is the standard of care. Another 4 opportunistic infections with fatal outcomes have also been recorded. These cases involve 1 unconfirmed case of Progressive Multifocal Leukoencephalopathy (PML), disseminated cytomegalovirus infection, Kaposi's varicelliform eruption, and bronchopulmonary aspergillosis. It is difficult to ascertain the incidence of these AEs as the specific overall treatment numbers are unknown. However, the above type of AEs is not unexpected given the underlying disease (ANCA vasculitis) and the known side-effect profile of RTX.

8.6. Safety issues with the potential for major regulatory impact

8.6.1. Liver toxicity

This is not a key issue for RTX given its mechanism of action and elimination pathway.

8.6.2. Haematological toxicity

This is a major issue for RTX and has already been discussed in detail earlier in this report.

8.6.3. Infusion-related reactions

Infusion reactions are characterized by fever, chills/rigors, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticarial, rash, vomiting, myalgia, dizziness and/or hypertension. In the RAVE Study no serious Infusion-Related Reactions (IRRs) were reported during the initial course of 4 RTX infusions. Expectedly, the incidence of IRRs (of any severity) was highest during the first infusion, and decreased with subsequent infusions. This is consistent with previous observations in other populations treated with RTX. In the RTX group, the proportion of patients who experienced an IRR was 12.1% (12/99), 5.1% (5/99), 4.1% (4/98) and 1.1% (1/91) from the first to fourth RTX infusion, respectively. An IRR was defined as any AE occurring within 24 hours of an infusion and considered by the investigators to be related to the infusion. In the RAVE trial, the proportion of patients experiencing any IRR was similar in the RTX (39 IRRs in 12/99 [12.1%] subjects) and CYC groups (28 IRRs in 11/98 [11.2%] patients). All IRRs were mild to moderate (rated as grade 1 or 2). One IRR of the hypersensitivity type led to the discontinuation of RTX, but occurred 2 days after the infusion and therefore was outside of the pre-defined time window to meet the criteria for an IRR. Another 2 patients experienced Grade 1 IRRs (single cases of throat tightness and chills) following the first infusion that required modification or interruption of RTX administration, but both patients received all 3 remaining infusions without any further IRRs.

The most frequent type of IRRs was cytokine release syndrome, and flushing. More patients in the RTX group experienced cytokine release syndrome than in the CYC group. Overall, 5 patients treated with RTX (5.1% of 99) reported symptoms consistent with a cytokine release syndrome, and these events all occurred on the day of the first infusion, recurred with the second infusion in 4 of 5 patients, and recurred with the third infusion in 1 patient. In contrast,

cytokine release syndrome was reported in 2 patients in the CYC group (2.0% of 98), and both occurred on study Day 1.

After the initial infusion course, 16 patients received a second course of open-label RTX in the RTX group, and a total of 20 patients have received RTX (resulting from treatment cross-over, or open-label RTX) in the CYC group. Two of these 36 patients reported an IRR. One patient experienced grade 1 flushing at the first and third infusions, which did not require dose modification or interruption. The second patient experienced grade 2 hyperhidrosis after the first and second infusions, as well as grade 2 diarrhoea following the second infusion. This did not result in dose modification, interruption or discontinuation.

In the RITUXVAS Study, 6.1% (2/33) of patients in the RTX + low-dose CYC group, and no patients in the CYC group reported IRRs. The severity of these events, the definition of an IRR and subsequent treatment in these patients were not reported.

In the published investigator-initiated studies, 7 of 12 studies made reference to the occurrence of IRRs. The definition of IRR was not reported across these studies and infusion pre-medication was not specified in the majority. However, many of these patients also received concomitant CS, which itself reduces the risk of RTX induced IRRs. Most reported IRRs were of mild-to-moderate severity. One event (anterior neck swelling several hours after the second infusion) led to stopping of further infusions within the treatment course, however the patient received further courses without complication. In 2 cases, symptoms recurred with subsequent infusions. One patient experienced an urticarial rash with the second, third and fourth infusions and no other details were provided. A second patient experienced mild angioedema following the first infusion, which was followed by polyarthritis after the fourth infusion. The polyarthritis was attributed to serum sickness and responded to short-term CS treatment. In the study by Holle *et al*, 1 significant IRR was reported (1.5% of 59) but no further details were provided.

In the RA pooled all exposure population, 25% of RTX treated patients experienced an acute IRR following their first infusion, but <1% of these were serious. Rates of IRRs in the RAVE Study were lower than those seen in the RA and lymphoma populations, which may be partly due to the different definitions of IRR across the studies. Moreover, the types and pattern of IRRs observed in the RAVE Study and other ANCA vasculitis trials are consistent with the expected risk with RTX.

8.6.4. Cardiovascular safety

In the RAVE Study, the overall incidence of any cardiac AE at 18 months was higher in the RTX group (18.2%; 18/99) than in the CYC arm (12.2%; 12/98). The difference was less pronounced at 6 months of follow-up but evident (12.1% in the RTX group versus 8.2% in the CYC group). The imbalance at 18 months was mainly attributable to grade 1 or 2 tachycardia and atrial fibrillation AEs. The incidence of cardiac SAEs was similar between the RTX and CYC groups (2.0%, or 2 cases each) at 18 months. Up to the CCO date, 1 serious cardiac SAE (myocardial infarction) was reported in a patient in the CYC group.

With respect to vascular AEs, at 18 months of follow-up in the RAVE Study, the overall incidence of venous thromboembolic events (a pre-defined AE of special interest) remained higher in patients treated with CYC (9.2% [9/98]) compared with 5.1% (5/99) in the RTX group. The AEs included 3 cases of deep vein thrombosis (DVT) and 2 of pulmonary embolism (PE) in the RTX group, and 8 DVTs and 2 cases of PE in the CYC group. Most of these events were rated as serious (3/5 in the RTX group, and 10/10 in the CYC arm).

In the RITUXVAS Study, 2 patients (1 in each treatment group) died from cardiovascular disease. In the trial by Jones *et al* (2009) 1 of 65 patients was identified as having suffered PE.

8.6.5. Immunogenicity (Human Anti-Chimeric Antibody Formation)

As of the CCO date in the RAVE Study, 28 patients (out of a potential total of 124) tested positive to Human Anti-Chimeric Antibodies (HACA) after exposure to RTX. The clinical relevance of positive HACA remains uncertain, as there has been no clear previous association between AEs, including IRRs, with HACA positivity. Furthermore, HACA results should be interpreted with caution as detectable RTX levels, as well as HACA assay variability, affects the quality of the results.

A total of 31 patients tested positive for HACA (defined as > 5 RU/ml, and immunodepletable with RTX) at any time in the RAVE Study: 25 from the RTX group, and 6 from the CYC arm. Of the 6 patients from the CYC group who tested HACA positive during the study, 3 tested positive after exposure to RTX (received either as a cross-over treatment or under BMJ, or open-label RTX). Hence, a total of 28 (22.6% of 124) patients tested HACA positive after exposure to RTX. The maximum HACA titre 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, 88% (22/25) of HACA-positive patients in the RTX group tested positive after 6 months (time points at which serum levels of RTX would be expected to be low, and less likely to interfere with the detection of HACA).

Of the 25 HACA positive patients in the RTX group, 7 received a second course of RTX as open-label treatment, and 4 of these subjects tested HACA positive prior to receiving their repeat course of RTX. None of these 4 patients experienced an IRR with their second course of treatment. In the RAVE Study, the overall safety profile was similar in HACA-positive and HACA-negative patients with no clear difference in the proportions of patients who experienced any AEs, SAEs, and AEs of special interest. In particular, the proportion of patients who reported IRRs was similar in the HACA-positive group (14.3%; 4/28) compared with the HACA-negative patients (11.5%; 11/96). Nonetheless, this result should be interpreted cautiously because of the small number of events that occurred within 24 hours of an infusion that were considered infusion related by the investigators. Ten IRRs were reported in the 4 patients who tested HACA positive, including 1 CYC patient who received RTX as crossover 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 SAEs or resulted in discontinuation of therapy. The events reported as IRRs in the HACA-positive patients comprised cytokine release syndrome (4 events), hyperhidrosis (2 events), and singular events of flushing, hypotension, oropharyngeal discomfort, and diarrhoea.

HACA was either not measured or reported in the RITUXVAS Study, or the majority of other published investigator initiated studies. In a study by Keogh *et al* (2005), HACA was measured in 10 (of a possible 11) patients at baseline, and then at 3, 6, and 9 months after receiving RTX. No HACA was detected. Smith *et al* (2006) reported HACA positivity in 2 of 8 tested patients. Both of these patients received a second course of RTX, and neither was reported to have experienced a significant IRR. No comment about HACA testing or status was made in the published study by Holle *et al* (2011).

Overall, the number of HACA-positive patients is small in this treatment population. In conclusion, the clinical relevance of HACA formation in patients with vasculitis treated with RTX remains uncertain, as it is across other indications.

8.7. Other safety issues

8.7.1. Safety in special populations

Only the RAVE Study had sufficient subject numbers and a robust data collection method to provide reliable safety data with respect to special patients groups. A total of 55 patients (28%

of 197) in the RAVE Study were at least 65 years of age, of which 12 (6%) were at least 75 years. More subjects in the RTX group were in the older age categories (36/99 were at least 65 years, 8 of whom were older than 75 years) compared to the CYC/AZA control arm (19/98 were at least 65 years, 4 of whom were older than 75 years). Adverse events were analysed by treatment group (RTX or CYC) and age (< 65 years, or 65 years and older). The incidence and type of AEs did not later with length of follow-up (up to 6 months versus up to 18 months). However, older patients (>65 years) in both treatment groups had a higher incidence of severe (at least grade 3) and serious AEs compared to younger patients. Most of these additional AEs related to anaemia and leucopenia, gastrointestinal disorders, and administration reactions (chest pain and chills). All 4 deaths (2 in each treatment group) in the RAVE Study occurred in older patients. Furthermore, more hospitalizations due to either disease or study medication occurred in patients > 65 years of age, particularly in those who received RTX (due to acute renal failure, pulmonary haemorrhage, CS-induced diabetes mellitus, and 3 cases of pneumonia – 2 of which were associated with leucopenia). Cardiac events also occurred more frequently in older patients who were given RTX induction therapy, mainly attributable to grade 1-2 atrial fibrillation and tachycardia. For younger patients (<65 years), grade 2 or greater leucopenia was predominately recorded in those receiving CYC. Table 18 shows the safety profile summary data at 6 and 18 months, analysed by age and treatment in the RAVE Study.

Table 18. Safety Profile by age and initial treatment in the RAVE Study up to 6 and 18 months

	6 Month				18 Months			
	Patients < 65 Years		Patients ≥ 65 Years		Patients < 65 Years		Patients ≥ 65 Years	
	RTX (n = 63)	CYC (n = 79)	RTX (n = 36)	CYC (n = 19)	RTX (n = 63)	CYC (n = 79)	RTX (n = 36)	CYC (n = 19)
Patient years of follow-up	30.30	38.22	17.30	8.79	90.20	111.11	49.37	23.60
No. of patients experiencing								
Any AE	58 (92.1%)	78 (98.7%)	36 (100%)	19 (100%)	62 (98.4%)	79 (100.0%)	36 (100.0%)	19 (100.0%)
Grade 3	11 (17.5%)	24 (30.4%)	13 (36.1%)	9 (47.4%)	21 (33.3%)	33 (41.8%)	17 (47.2%)	10 (52.6%)
Grade 4	4 (6.3%)	3 (3.8%)	4 (11.1%)	1 (5.3%)	5 (7.9%)	3 (3.8%)	5 (13.9%)	1 (5.3%)
Death	0	0	1 (2.8%)	2 (10.5%)	0	0	2 (5.6%)	2 (10.5%)
Serious AE	17 (27.0%)	25 (31.6%)	16 (44.4%)	8 (42.1%)	25 (39.7%)	33 (41.8%)	21 (58.3%)	8 (42.1%)
AE leading to study drug discontinuation	2 (3.2%)	11 (13.9%)	6 (16.7%)	2 (10.5%)	7 (11.1%)	22 (27.8%)	9 (25.0%)	2 (10.5%)
Selected AE								
Death (all causes)	0	0	1 (2.8%)	2 (10.5%)	0	0	2 (5.6%)	2 (10.5%)
Hospitalization [a]	4 (6.3%)	4 (5.1%)	6 (16.7%)	0	7 (11.1%)	5 (6.3%)	6 (16.7%)	0
Grade ≥ 3 infection	7 (11.1%)	7 (8.9%)	3 (8.3%)	3 (15.8%)	9 (14.3%)	11 (13.9%)	5 (13.9%)	3 (15.8%)
Malignancy	0	2 (2.5%)	1 (2.8%)	0	0	1 (1.3%)	2 (5.6%)	0
IRR resulting in cessation of further infusions	1 (1.6%)	0	0	0	1 (1.6%)	0	0	0
Venous thromboembolic event [b]	2 (3.2%)	7 (8.9%)	3 (8.3%)	1 (5.3%)	2 (3.2%)	7 (8.9%)	3 (8.3%)	1 (5.3%)
Hemorrhagic cystitis [c]	0	1 (1.3%)	1 (2.8%)	0	1 (1.6%)	1 (1.3%)	1 (2.8%)	0
Grade ≥ 2 leukopenia	0	13 (16.5%)	5 (13.9%)	4 (21.1%)	1 (1.6%)	19 (24.1%)	6 (16.7%)	4 (21.1%)
Grade ≥ 2 thrombocytopenia	1 (1.6%)	0	2 (5.6%)	1 (5.3%)	1 (1.6%)	0	3 (8.3%)	1 (5.3%)
Other AEs of special interest								
Any infection	38 (60.3%)	35 (44.3%)	23 (63.9%)	11 (57.9%)	48 (76.2%)	55 (69.6%)	31 (86.1%)	14 (73.7%)
Serious infection	7 (11.1%)	7 (8.9%)	4 (11.1%)	3 (15.8%)	9 (14.3%)	11 (13.9%)	6 (16.7%)	4 (21.1%)
Serious cardiac AE	1 (1.6%)	1 (1.3%)	0	1 (5.3%)	2 (3.2%)	1 (1.3%)	0	1 (5.3%)
AE rates/patient-year								
AE	18.74	20.36	24.80	22.76	10.13	10.81	11.52	11.44
Serious AE	0.63	0.99	1.56	1.82	0.37	0.53	0.73	0.76
Infection	2.18	1.44	1.97	1.59	1.51	1.26	1.24	1.14
Serious infection	0.23	0.24	0.29	0.46	0.11	0.14	0.16	0.25

AE = adverse event; IRR = infusion-related reaction.
[a] Resulted either from the disease or from a complication in study treatment.
[b] Includes deep venous thrombosis or pulmonary embolism.
[c] Grade 2 hemorrhagic cystitis was confirmed by cystoscopy.

The RAVE Study also demonstrates that subjects with impaired renal function (i.e. less than the median GFR of 74.71 mL/min compared to those greater than the median) at baseline have an increased risk of many AE types, including all infections (especially pneumonia and urinary tract infections), serious infections, death, hospitalization, and anaemia. This outcome is regardless of treatment strategy (RTX or CYC induction therapy). In contrast, all 4 (serious) cases of pulmonary embolism occurred in patients with higher creatinine clearance at baseline (2 in each treatment group).

Safety outcomes at 6 and 18 months assessed by disease onset (newly diagnosed [48.7%, 96/197] versus relapsed disease) in the RAVE trial showed comparable incidence and patterns of AEs, apart from a higher incidence of grade 2 or more leucopenia and thrombocytopenia for patients with newly diagnosed ANCA vasculitis, particularly for those who received CYC. Most of the relapsed disease patients (78.2%, 79/101) had received previous CYC, suggesting possible selection bias for haematological tolerance of CYC.

During the RAVE Study, the partner of 1 patient became pregnant. This subject had received RTX and id not crossover to CYC during the first 6 months of the trial. His partner had a miscarriage with no specific details being available.

8.7.2. Safety related to drug-drug interactions and other interactions

No formal drug interaction studies have been performed with RTX. This is to be expected given its elimination is mediated by a specific CD20 receptor-mediated pathway and non-specific IgG clearance. In patients with RA, PK studies do not indicate any interaction between co-administration of CYC, methotrexate or CS on the PK of RTX.

8.7.3. Progressive Multifocal Leukoencephalopathy (PML) and other infections of Special Interest

No confirmed cases of PML have been reported in the ANCA associated vasculitis studies or the Global Safety Database (GSD) as of the cut-off date of 17 May 2011. However the GSD contains 1 suspected (but unconfirmed) case of PML in a patient with GPA onset ~2 months after the last dose of RTX. This patient (71 year old female) had concurrent diabetes mellitus and renal impairment, and was receiving multiple immunosuppressant medications including CS, CYC and adalimumab. The patient's CSF was negative for JC virus, and the patient died soon thereafter of pneumonia.

The GSD also contains 22 reports of confirmed PML in patients receiving RTX for various autoimmune diseases, including 6 in the treatment indication of RA. On the basis of the estimated exposure (approximately 168,000 patients), the incidence of PML is very rare (<1 of 10,000) in the approved RA indication. The other confirmed cases of PML in patients exposed to RTX include 9 in patients with Systemic Lupus Erythematosus, and % in other autoimmune indications including 1 in a subject with ANCA-negative vasculitis and Sjogren's syndrome.

In summary, no confirmed cases of PML have, to date, been reported in patients with ANCA associated vasculitis receiving RTX. However, PML has been reported to occur in this patient population when treated with other therapies, and is a known risk associated with RTX. Surveillance for PML is part of the sponsor's proposed pharmacovigilance plan.

Patients with a history of Hepatitis B or C were excluded from the RAVE and RITUXVAS studies. However, there are 2 reports (1 in the literature and 1 in the GSD) of hepatitis B virus reactivation in association with RTX therapy for patients with ANCA vasculitis. There is limited specific information about these 2 cases, but hepatitis B reactivation is a small but major risk known to occur with significant immunosuppression (including CYC and high dose CS). Hepatitis C virus reactivation with immunosuppression is a smaller risk compared with hepatitis B virus.

Three patients in the RAVE Study developed significant opportunistic infections including 1 patient with pneumocystis pneumonia (given CYC), another experienced fungal laryngitis (CYC group) and the third subject treated with RTX developed infection with mycobacterium avium complex as well as oesophageal candidiasis. The other studies did not report specific opportunistic infections apart from Holle *et al*. Four opportunistic infections were reported – 1 case of pneumocystis pneumonia, 1 case of cytomegalovirus reactivation and 2 cases of herpes zoster.

8.7.4. Malignancies

A total of 6 malignancies in 5 patients treated with RTX, and 2 cancers in 2 patients treated with CYC were reported in the RAVE Study from randomization until CCO. Two of the cases in the RTX group had received significant prior CYC therapy. There was no particular pattern in the type of malignancies observed. Two cases of prostate adenocarcinoma (1 in each group) were diagnosed within 3 months of trial commencement and therefore, are likely to be prevalent cases. One additional patient in the CYC group was diagnosed with prostate intraepithelial neoplasia before 6 months of treatment, but upon repeat biopsies this was shown to be benign

and therefore excluded from the malignancy analysis. Between 6 months and the CCO period, another 4 patients in the RTX group (2 had significant prior CYC exposure) and 1 in the CYC/AZA arm developed malignancies. The patient from the CYC group was administered open label RTX 11 months prior to the cancer diagnosis (papillary thyroid carcinoma). One patient (69 year old female) in the RTX group developed 2 cancers – bladder cancer (study day 811) and adenocarcinoma of the colon (study day 1180). She had a past history of cervical cancer. The other malignancies observed in patients who received RTX included uterine cancer, metastatic colon cancer and malignant lung cancer. The patients who developed malignancy were generally older in age (mean of 68 years; and range: 53-78 years), and more than half had a history of significant tobacco use. Up to the CCO date, the rates (with 95% CI) of malignancy in the RTX and CYC groups were 2.00 (0.90 – 4.46) and 0.73 (0.18-2.91) per 100 patient-years, respectively. The standardized incidence ratio (SIR) for malignancy, based on incidence in an age- and sex-matched USA population according to 2000-2007 data from the Surveillance Epidemiology and End Results (SEER) database, were 2.02 (95% CI: 0.74-4.39) for the RTX group, and 1.02 (95% CI: 0.11-3.70) for patients in the CYC arm. The SIRs for the RAVE Study population lie within the expected range of 1.6- to 6-fold increase in the risk of overall malignancy among patients with ANCA associated vasculitis treated with conventional therapy (CYC/AZA/MTX/CS) compared with the general population.

No melanoma cases were reported in the RAVE Study but 2 patients treated with CYC developed squamous cell skin cancers. A further 5 patients (3 treated with RTX and 2 given CYC/AZA) experienced non-serious skin cancers.

Four of 33 (12.1%) patients treated with RTX + low dose CYC in the RITUXVAS Study developed malignancies between 8-29 months after commencing treatment. The cancer types were single cases of melanoma, breast cancer, ovarian cancer and basal cell carcinoma of the skin (x2) in another subject. None of the 11 patients in the CYC group developed cancers. The investigator initiated studies, and the trial by Holle *et al*, did not report malignancies.

In conclusion, because the malignancy event rates are low in the reported studies, within comparative expectations and affected by several potential confounding factors, it is unclear if RTX alters the cancer potential of patients with ANCA associated vasculitis.

8.8. Evaluator's overall conclusions on clinical safety

The total clinical safety data (CCO date for RAVE Study is 27 January 2010, and the cut-off date for the Global Safety Database is 31 August 2011) consists of a patient exposure of 374 patients in 15 studies, of which 266 received RTX. Most of the RTX-treated subjects only received a single course of RTX therapy, at the sponsor's requested dose of 375 mg/m^2 weekly for 4 weeks. In the current submission, less than 40 subjects in total have been reported to be exposed to a repeat course of RTX.

At 18 months of follow-up, the pivotal RAVE Study safety dataset provides a total of 139.6 patient years of observation for RTX, and 134.7 patient years of observation for CYC/AZA. For the analysis through to the CCO date, there were 299.2 patient-years of follow-up 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. The current safety dataset provides sufficient information about the short-term risk with RTX in this population such as haematological toxicity, infections, infusion reactions, and discontinuations due to adverse events. However, the extent of long-term follow-up is not adequate to assess for some potential AEs of concern that may have a long latency between drug exposure and AE occurrence, particularly malignancy, some opportunistic infections (e.g. PML) and cardiovascular safety. The study populations had baseline characteristics, disease activity and concomitant medications indicative of the intended target population for the claimed indication.

Key safety conclusions identified in the pivotal RAVE Study safety dataset are as follows:

- At 6 and 18 months, the overall incidence and rates per patient-year of exposure of any AE, AEs of pre-specified interest, grade 3 or higher AEs, and serious infections were similar in the RTX and CYC/AZA treatment groups.
- However, infections (of any severity) were numerically greater and occurred at higher rate in patients who received RTX compared with control treatment (CYC/AZA) for both the 6-month (61.6% for RTX versus 46.9% for CYC/AZA) and 18-month analysis (79.8% for RTX versus 70.4% for CYC/AZA) time points.
- The most frequent type of infectious AE in both treatment groups involved the respiratory tract (For example, there were 34 respiratory tract AEs in 22 RTX patients, and 28 corresponding AEs in 22 CYC subjects, at 6 months of follow-up).
- Various types of herpes (11% for RTX versus 3% for CYC) and fungal infections (15% for RTX versus 11% for CYC) were also more common at 6 months in the RTX versus CYC treatment group.
- Most common individual types of AEs (occurring in >10% of patients in either treatment group) showing a differential treatment related occurrence (>5% differential incidence) were diarrhoea, peripheral oedema, urinary tract infection and hypertension for RTX; and leucopenia, increased serum transaminases, and alopecia for CYC.
- Permanent discontinuations of study medication for AEs were more frequent in the CYC group (13.3% at 6 months) than the RTX arm (6.1% at 6 months).
- At 6 and 18 months of follow-up, the incidence of overall SAEs were similar in the 2 treatment groups (33-34% at 6 months) with the most frequent type of SAE being infection (overall, 10.7% at 6 months; and 15.2% at 18 months).

The RAVE Study also clearly identifies a subset of patients at the highest risk of AEs from RTX (or any other treatment strategy). Older patients (aged > 65 years) or those with significant renal impairment are the most vulnerable to a broad spectrum of AEs, particularly infections.

In the supportive studies, a total of 254 subjects received treatment with RTX (mostly, a single fixed induction course of 375 mg/m^2 x 4 infusions), and treatment follow-up was limited to 6-12 months. It is unclear for most of these studies how systematic the reporting of safety outcomes was to detect any potential safety concerns, but SAEs appeared to be recorded. In the RITUXVAS Study, 48% (16/33) patients who received RTX experienced 35 SAEs. Similarly, the largest of the studies identified by literature search (Jones *et al* Study) reported 45 SAEs in 25 subjects (38% of 65 affected) with 129 patient years of follow-up. The study by Holle *et al* reported 24 SAEs in 59 individuals. The consistent, key safety finding from all of these supportive studies is that infections were the most common type of SAE, and that the respiratory tract was the most common site of those infections.

Death has been reported in at least 15 subjects with ANCA associated vasculitis exposed to RTX (2 in the RAVE Study, 6 in RITUXVAS, 5 in the published investigator initiated studies plus a further 2 deaths were reported in the Holle *et al* trial). Five deaths (and 2 unknown) have resulted from infections. Disease progression despite treatment appears to explain at least 5 of the other deaths and 2 RTX treated patients from cardiovascular disease. However, the mortality rates and types of deaths observed in the RAVE, RITUXVAS and other studies is consistent with those expected in the target population of ANCA associated vasculitis. A total of 6 malignancies in 5 RTX treated patients in the RAVE Study, and 4 patients treated with RTX + low dose CYC in the RITUXVAS trial developed cancers. No specific type of malignancy was observed. This result is within expectations for the target population.

RTX is associated with an increased risk of opportunistic infection, including pneumocystis pneumonia and PML (although no confirmed cases have been reported thus far in patients

treated with GPA or MPA), as well as significant viral reactivations (individual reports of hepatitis B, CMV and fulminant adenovirus infection have been recorded in the ANCA vasculitis population).

The RAVE Study specifically examined the rate of hospitalizations due to either disease activity or study medication. More patients in the RTX group (10 of 99) were hospitalized because of active disease or study drug problems by 6 months compared to the CYC group (4 of 98 subjects). The reasons for hospitalization in both the RTX and CYC groups were typical for this population and included respiratory tract infections in 7 patients (pneumonia in 5 patients, upper respiratory tract infection in 1 patient, and bronchitis in 1 patient); and singular cases of Adult Respiratory Distress Syndrome (ARDS), pulmonary haemorrhage, pulmonary embolism, renal failure, osteomyelitis, and a hypersensitivity reaction (all with 1 patient each). Several of these hospitalizations appear related to active vasculitis, or concomitant therapies such as CS. Two of the patients with pneumonia also had significant leucopenia and/or neutropenia. The data at 18 months and through the CCO date was consistent with outcome observed at 6 months in that more patients were hospitalized for reasons related to disease activity or study drug (per the investigator's assessment) in the RTX group.

The RAVE Study demonstrates a higher frequency of leucopenia in the CYC versus RTX treatment groups at both the 6 (17.3% for CYC versus 5% for RTX) and 18-month time points (20.4% for CYC/AZA versus 7.1% for RTX). However, in both treatment groups no clear association between the occurrence of leucopenia and significant infections emerged. Thrombocytopenia of at least grade 2 severity by 18 months of follow-up was uncommon, but recorded in a higher number of RTX treated individuals (n=4; 2 with concurrent bleeding) compared with CYC/AZA managed subjects (n=1).

Infusion related reactions occurred in 11.2-12.1% of subjects in the RAVE Study, with a similar proportion of reported AEs in each of the treatment groups (RTX versus RTX placebo infusions). RTX treated patients recorded a slightly different pattern of IRRs with features consistent with cytokine release syndrome being more common in the RTX group (5 patients in the RTX group versus 2 in the CYC arm). Only 1 subject in the RTX arm had to cease treatment due to an IRR. In the supportive studies, a small number of subjects (n=5) recorded significant IRRs.

Human Anti-Chimeric Antibodies (HACA) were only assessed in the RAVE Study, and developed in 28 subjects (22.6% of 124) as of the CCO date. The clinical relevance of positive HACA remains unclear with no discernible link to the risk of infection or acute infusion reactions. However, the presence does produce changes in PK behaviour with HACA positivity being clearly associated with increased clearance of RTX and reduced exposure to the drug.

In summary, the safety data indicates that RTX has an overall comparable safety profile to the current standard of care (CYC and/or AZA) in patients with severe systemic manifestations of GPA and MPA. There are some significant safety concerns including infection (particularly, involving the respiratory tract), hospitalizations for disease activity or medication side-effects, leucopenia, and thrombocytopenia. Of note, is the limited overall exposure to RTX for the target population, and no significant safety information has been presented for repeat dose exposure (which is currently beyond the sponsor's requested indication). Significant pharmacovigilance would be required if approval is granted for ANCA vasculitis. This would include vigilance for opportunistic infections, malignancy, all cause death, and cardiovascular AEs.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of RTX in the proposed usage of induction therapy for severe ANCA associated vasculitis are:

- RTX is non-inferior to the current standard of care treatment (CYC/AZA) for achieving the induction of remission in most patients with severe systemic GPA and MPA, particularly those with renal or pulmonary disease manifestations. Granulomatous disease manifestations of GPA such as orbital masses and tracheobronchial stenosis may be less responsive to RTX.
- RTX is superior to the current standard of care treatment (CYC/AZA) for the induction of remission in patients with relapsed, severely active GPA.
- RTX offers an alternative treatment strategy for life-threatening diseases (GPA and MPA) which currently have limited treatment options and a significant unmet therapeutic need.

9.2. First round assessment of risks

The risks of RTX in the proposed usage are:

- RTX has an equivalent safety profile to the current standard of care (CYC/AZA) in short-medium term follow-up with a moderately high incidence of SAEs, death and hospitalizations, particularly for those of older age (>65 years) and with significant renal impairment.
- Significant risk of infections, including a variety of opportunistic infections (e.g. PML and PJP) with RTX therapy for patients with ANCA associated vasculitis.
- Optimal dose and scheduling for RTX infusions has not been adequately defined, nor has the role of concomitant or maintenance immunosuppression been delineated.
- Sufficient numbers of treated patients with long-term (multi-year) follow-up has not been achieved. This may be important for issues such as malignancy development and cardiovascular disease.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of RTX, given the proposed usage (induction of remission) in the target population (severely active systemic forms of GPA and MPA), is favourable. However, the efficacy and safety of re-treatment with RTX has not been adequately evaluated to determine its role in this scenario. The natural history of ANCA associated vasculitis is that a significant proportion of patients will relapse and require additional treatment in the future (2-7 years after diagnosis).

10. First round recommendation regarding authorisation

I recommend acceptance of the sponsor's proposed indication for RTX subject to satisfactory response to the questions, below, and regular periodic safety update reports.

11. Clinical questions

11.1. Pharmacokinetics

Could the sponsor please provide PK data (other than historical use) justifying the dose/regimen of RTX utilised in the pivotal RAVE Study? In particular, have any dose-ranging studies been performed, or are they being considered for the future?

ANCA associated vasculitis has a significant rate of disease relapse which may require re-treatment for induction of remission. Dosing studies after repeat courses of RTX (including

those with extended intervals between dosing) have not been performed thus far for the requested indication. Is the sponsor considering further studies to examine the PK of RTX with repeat course of RTX in patients with ANCA associated vasculitis?

Furthermore, it is biologically plausible that increased rates of HACA development may occur with repeat courses of RTX and/or extended dose intervals, which may then have significant implications for the PK characteristics of RTX. Could the sponsor please comment if there is a plan to examine this issue?

11.2. Pharmacodynamics

Could the sponsor please elaborate on the utility of using a PD marker (such as CD19+ B-cells) to determine the likelihood of disease relapse? If so, can the same marker be used as an indicator for re-treatment including upon disease relapse (whereby a further induction course of RTX may be considered)?

Could the sponsor please comment on whether or not genetic-related differences in PD response (e.g. polymorphisms of Fc gamma receptors) have been examined in the target population?

Could the sponsor comment on the evidence in other autoimmune conditions whereby significantly lower doses of RTX have achieved the primary PD (and clinical outcome) effect of CD19+ B-cell depletion, and how this may relate to the proposed indication in systemic vasculitis?

11.3. Efficacy

Given the small number (n=41) of patients in the published, investigator-initiated studies who received significantly lower doses of RTX were reported to obtain the same rate of remission as the proposed dose of 375 mg/m^2 x 4 infusions, has the sponsor explored the relationship between dose (over at least a limited dose range) and clinical outcomes?

Could the sponsor please comment further on the literature (e.g. Holle *et al* trial) and study findings in the RAVE trial whereby patients with vasculitic versus granulomatous disease manifestations of GPA appear to have a differential treatment response?

11.4. Safety

Could the sponsor please provide an update on the patient with GPA in the Global Safety Database who experienced suspected (but unconfirmed) PML, in particular, clarifying whether or not the case remains unconfirmed?

12. Second round evaluation of clinical data submitted in response to questions

The sponsor responded (dated 2 November 2012) to 9 questions that were raised in the first round clinical assessment. Each of these responses will be assessed in order.

Question 1. Could the sponsor please provide PK data (other than historical use) justifying the dose/regimen of RTX utilised in the pivotal RAVE Study? In particular, have any dose-ranging studies been performed, or are they being considered for the future?

The sponsor response reiterates that the population PK analysis of the RAVE Study data indicates that the key PK parameters for RTX therapy in patients with GPA and MPA are similar to that observed in adult patients with rheumatoid arthritis. No dose-ranging studies have been

performed for RTX in patients with systemic vasculitis, and none are planned by the sponsor. The sponsor acknowledges that some centres around the world and in some published case studies, beneficial efficacy outcomes have been achieved with RTX using alternative (i.e. lower) dose regimens. I agree with the sponsor in that the assessment of alternative dose regimens for RTX requires additional controlled prospective trials.

Question 2. ANCA associated vasculitis has a significant rate of disease relapse which may require re-treatment for induction of remission. Dosing studies after repeat courses of RTX (including those with extended intervals between dosing) have not been performed thus far for the requested indication. Is the sponsor considering further studies to examine the PK of RTX with repeat course of RTX in patients with ANCA associated vasculitis?

The sponsor acknowledges that a significant proportion of patients with GPA and MPA experience disease relapse (up to half within 2 years), and there is interest in evaluating the utility of maintenance RTX therapy for these patients. The MAINRITSAN Study is a prospective, open-label, investigator-initiated trial which has enrolled 114 patients in France to receive either RTX 500 mg every 6 months, or daily oral AZA (2 mg/kg) for up to 18 months, following induction of remission in newly diagnosed or relapsed GPA and MPA. The data was accepted as an abstract at the recent American College of Rheumatology meeting in November 2012. At the cut-off date for the report, 73.7% (84/114) of patients had completed 28 months of follow-up with an interim analysis showing that major disease relapse had occurred in 3.6% (2/55) of patients in the RTX group, and 27.1% (16/59) of subjects in the AZA arm. The abstract conclusion states that the study demonstrates that treatment with RTX 500 mg every 6 months is superior to AZA for the maintenance of remission. However, no statistical analysis was provided in the abstract presentation. The incidence of SAEs and infection were similar in the 2 treatment groups. No PK or immunogenicity data has been reported for this study.

An additional, investigator-initiated trial (RITAZAREM Study) is proposed to commence in October 2012. This 24-month study, which aims to recruit 160 patients, will investigate the efficacy and safety, PK and rate of HACA development with RTX 1000 mg given every 4 months compared to oral AZA 2 mg/kg/day in the maintenance of GPA and MPA remission.

Question 3. Furthermore, it is biologically plausible that increased rates of HACA development may occur with repeat courses of RTX and/or extended dose intervals, which may then have significant implications for the PK characteristics of RTX. Could the sponsor please comment if there is a plan to examine this issue?

The sponsor re-affirms that in the RAVE Study dataset the overall number of HACA-positive patients is small (n=28; 22.6% of a possible 124 tested subjects), and the clinical relevance of HACA development in patients with vasculitis treated with RTX remains uncertain, as it is across other indications. The sponsor has provided an additional published report by Cartin-Ceba *et al* (Arthritis & Rheumatism, 2012) as supportive information in addressing this issue. The report pertains to a single centre, 10-year historical study of patients with treatment refractory, severe GPA treated with at least 2 course of RTX between January 2000 and May 2010. A total of 233 RTX courses were administered to 53 subjects over the follow-up period, with a median number of courses per patient of 4 (range of 2-12 courses; 38 patients received 3-5 courses). Most RTX courses (209; 90% of 233) consisted of 4 weekly doses at 375 mg/m^2, and 10% of courses were the 2 fixed RTX doses of 1000 mg given 2 weeks apart. The study authors report that they found no evidence of patients developing clinical resistance (i.e. non-response in terms of clinical outcomes) to RTX over time with repeat courses of therapy. The rates of HACA development were not reported in this study.

Question 4. Please elaborate on the utility of using a PD marker (such as CD19+ B-cells) to determine the likelihood of disease relapse? If so, can the same marker be used as an indicator for re-treatment including upon disease relapse (whereby a further induction course of RTX may be considered)?

The sponsor opines that changes in CD19+ B-cells are an exploratory PD response biomarker, which when considered in isolation does not possess predictive value for determining disease relapse. I concur with that opinion. The RAVE Study data does not provide evidence to justify the use of CD19+ B-cells in isolation as a predictive biomarker for relapse. At 18 months of follow-up in those patients who obtained remission by 6 months, 31 relapses were recorded in the RTX group and 23 relapses were identified in the CYC/AZA group. In the relapse population, 48% of those who received RTX and 61% of those in the CYC/AZA arm had evidence of B-cell reconstitution (CD19+ B-cell count >10 cells/μL) prior to clinical relapse. However, the RAVE Study does indicate that when the achievement of B-cell depletion and ANCA seronegativity are considered together, the risk of disease relapse is low (10% in the RTX group, and 9% in the CYC/AZA arm). The sponsor acknowledges that there are conflicting opinions in the published literature as to the utility of B-cell depletion and reconstitution as a predictive biomarker of clinical response. The report by Cartin-Ceba *et al* (Arthritis & Rheumatism, 2012) suggests that pre-emptive, re-treatment with RTX in patients with relapsing GPA can be individualised based on serial B-cell and PR3-ANCA monitoring.

Question 5. Pease comment on whether or not genetic-related differences in PD response (e.g. polymorphisms of Fc gamma receptors) have been examined in the target population?

The sponsor indicates that investigation into genetic-related differences in PD response to RTX is planned by the Immune Tolerance Network, but this work has not yet commenced.

Question 6. Please comment on the evidence in other autoimmune conditions whereby significantly lower doses of RTX have achieved the primary PD (and clinical outcome) effect of CD19+ B-cell depletion, and how this may relate to the proposed indication in systemic vasculitis.

The sponsor is aware that several investigator-initiated studies have been performed in patients with autoimmune conditions (e.g. SLE and Sjogren's syndrome) using various RTX dosing regimens. The sponsor concurs that peripheral B-cells are depleted at relatively low doses of RTX, but only a minority of the whole body B-cell population resides in the peripheral blood. Furthermore, the sponsor considers peripheral blood B-cell depletion to be an unreliable PD marker correlating with clinical efficacy. As outlined in Section 5.2.5 (Relationship between PD effects and efficacy) of this report there is a limited relationship between B-cell depletion and efficacy outcomes in the first 6 months following induction therapy with RTX (RAVE Study). However, the data beyond 6 months suggests a different relationship outcome, in that many RTX treated patients had a significant return of CD19+ B-cell counts between 6 and 12 months. Peripheral B-cell repletion did not appear to impact upon the rate of complete remission over time (up to 18 months), but showed a signal towards recurrence of ANCA disease. The number of disease flares between 6 and 18 months were 17 severe and 24 limited flares for the RTX group compared with 13 severe and 16 limited for the CYC/AZA arm. This result suggests the loss of RTX treatment effect beyond 6-12 months, which may be associated with B-cell recovery.

Question 7. Given the small number (n=41) of patients in the published investigator initiated studies who received significantly lower doses of RTX were reported to obtain the same rate of remission as the proposed dose of 375 mg/m² x 4 infusions, has the sponsor explored the relationship between dose (over at least a limited dose range) and clinical outcomes?

The sponsor concurs that no relationship between RTX dose and clinical outcomes has been explored in dose ranging studies. The original submission explored the relationship between RTX $AUC_{0\text{-inf}}$ at or above the median value (10.2 mg/mL.day) and efficacy (complete remission) at 6 months in the RAVE Study. No correlation was observed in 94 PK-evaluable individuals who received RTX as per-protocol. The sponsor has included an additional analysis in the response to a TGA request for further information, whereby the rates of remission outcomes (complete remission; and remission according to BVAS/WG score=0) at 6 months were assessed according to $AUC_{0\text{-inf}}$ quartiles (n=24 for each quartile). Table 19 shows the newly presented data and has been taken without amendment from the sponsor's response. Complete remission rates were

numerically lower in the first quartile (54.2%; 13/24), highest in the third quartile (75.0%; 18/24) and equivalent in the second and fourth quartiles (66.7%; 16/24). However, this relationship was not statistically verified as indicated by a Spearman correlation coefficient of 0.08.

Table 19. Remission Outcomes at 6 months in RAVE Study by AUC Quartiles in RTX treated patients

	PK $AUC_{0\text{-inf}}$ <7.85 (n=24)	PK 7.85 ≤ $AUC_{0\text{-inf}}$ <10.16 (n=24)	PK 10.16 ≤ $AUC_{0\text{-inf}}$ <13.34 (n=24)	PK $AUC_{0\text{-inf}}$ ≥13.34 (n=24)
Complete Remission	13 (54.2%)	16 (66.7%)	18 (75.0%)	16 (66.7%)
Remission (BVAS/WG=0)	15 (62.5%)	22 (91.7%)	19 (79.2%)	21 (87.5%)

BVAS = Birmingham Vasculitis Activity Score; PK = pharmacokinetics; WG = Wegener's granulomatosis.
The WOCF imputation was used for the as-defined definition of the primary endpoint.

Question 8. Please comment further on the literature (e.g. Holle et al trial) and study findings in the RAVE trial whereby patients with vasculitic versus granulomatous disease manifestations of GPA appear to have a differential treatment response.

The sponsor opines that there are conflicting opinions in the published literature as to the effectiveness of RTX in treating vasculitic versus granulomatous disease manifestations of GPA, but that the weight of evidence suggests that RTX is effective for both granulomatous and vasculitic disease manifestations. I concur that the issue remains unclear and requires further investigation. The reasons for the differential efficacy observations in the literature are hypothesized to include patient-specific resistance mechanisms, use of lower RTX dosing regimens and the difficulty in histopathologically confirming granuloma formation versus fibrous tissue reaction at sites of granulomatous disease manifestation such as the orbit. The sponsor indicates that the results of the Cartin-Ceba *et al* Study (Arthritis & Rheumatism, 2012) are supportive of no significant differential treatment response to RTX according to predominant disease organ manifestation. Of the 53 patients in this study, all of whom achieved complete remission with RTX, 39% (21) had granulomatous disease and 61% (32) had vasculitic disease manifestations. The RAVE Study was not powered to determine a differential treatment response to RTX for granulomatous versus vasculitic disease presentations.

Question 9. Please provide an update on the patient with GPA in the Global Safety Database who experienced suspected (but unconfirmed) PML, in particular, clarifying whether or not the case remains unconfirmed.

The sponsor has not received any additional information on this case to verify the validity of the report.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of RTX in the proposed usage are unchanged from those identified in Section 9.1 of this report. The sponsor response to the list of questions highlights that there is conflicting and limited literature on the relative benefit of RTX in inducing remission in patients with granulomatous versus vasculitic disease manifestations.

13.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of RTX in the proposed usage are unchanged from those identified in Section 9.2 of this report.

13.3. Second round assessment of benefit-risk balance

The benefit-risk balance of RTX, given the proposed usage (induction of remission) in the target population (severely active systemic forms of GPA and MPA), is favourable. However, as per the first round assessment (Section 9.3 of this report), the efficacy and safety of re-treatment with RTX has not been determined and the natural history of ANCA associated vasculitis is that a significant proportion of patients will relapse and require additional treatment in the future.

14. Second round recommendation regarding authorisation

I recommend acceptance of the sponsor's proposed indication for RTX subject to regular periodic safety update reports[7].

[7] Note that discussions of recommendations relating to the draft PI and CMI are not included in this Extract.

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