

## Clinical Trial Protocol

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Trial Title: An international, open label, randomised controlled trial comparing rituximab with azathioprine as maintenance therapy in relapsing ANCA-associated vasculitis

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I give my approval for the attached protocol entitled "An international, open label, randomised controlled trial comparing rituximab with azathioprine as maintenance therapy in relapsing ANCA-associated vasculitis" Version 5.1 dated 12<sup>th</sup> July 2019.

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### Site Signatures

I have read the attached protocol entitled "An international, open label, randomised controlled trial comparing rituximab with azathioprine as maintenance therapy in relapsing ANCA-associated vasculitis" Version 5.1, dated 12<sup>th</sup> July 2019 agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice CPMP/ICH/135/95; the Declaration of Helsinki and all applicable regulatory requirements and laws (The European Clinical Trials Directives 2001/20/EC and 2005/28/EC in Europe, The National Research Act 1974 in the United States and the Therapeutic Goods Regulations 1990 in Australia).

Japanese investigators agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice, the Declaration of Helsinki, and the Ethics Guideline for Clinical Studies promulgated on 2008 by Ministerial Notification No. 415 of Ministry of Health, Labour Welfare of Japan.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

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## 4 Abbreviations and Definitions

### Abbreviations

AAV	ANCA-associated vasculitis
ANCA	Anti-neutrophil cytoplasmic antibody
BVAS/WG	Birmingham Vasculitis Activity Score for Wegener's
CA	Competent Authority
CCTU	Cambridge Clinical Trials Unit
CDA	Combined Damage Assessment Index
CMV	Cytomegalovirus
COPD	Chronic obstructive pulmonary disease
CRF	Case Report Form
CRO	Clinical Research Organisation
DNA	Deoxyribonucleic acid
DSMB	Data Safety and Monitoring Committee
EC	Ethics Committee (encompassing Institutional Review Board (IRB) and Independent Ethics Committee (IEC))
EQ5D	EuroQol 5D Quality of Life Questionnaire
FDA	The Food and Drug Administration
GC	Glucocorticoids
GP	General Practitioner
GPA	Granulomatosis with polyangiitis (Wegener's)
HACA	Human Antichimeric antibodies
IB	Investigator's Brochure
ICH-GCP	International Conference on Harmonisation – Good Clinical Practice
IEC	Independent Ethics Committee
IRB	Independent Review Board
IV	Intravenous
MHRA	Medicines and Healthcare products Regulatory Agency
MMF	Mycophenolate Mofetil
MPA	Microscopic Polyangiitis
mRNA	Messenger RNA
NHS	National Health Service
PROMIS	Patient Reported Outcomes Measurement Information System
NIH	National Institutes of Health
R&D	Research and Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SF-36	Short Form (36) Health Survey
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMC	Trial Management Committee
TPMT	Thiopurine methyltransferase
VCRC	Vasculitis Clinical Research Consortium

### Definitions

Relapse (flare)	The occurrence of any new BVAS/WG item.
Major Relapse	The development of a new or recurrent major disease activity item using the BVAS/WG assessment tool
Minor Relapse	Any increase in disease activity that does not meet the definition of Major Relapse
Remission	BVAS/WG ≤ 1 (one minor persistent BVAS/WG item) and GC dose ≤ 10mg/day
Complete Remission	BVAS/WG = 0 independent of GC
Sustained Remission	Remission lasting more than 6 months without a relapse



## 5 Trial Synopsis

<b>Title</b>	An international, open label, randomised, controlled trial comparing rituximab with azathioprine as maintenance therapy in relapsing ANCA-associated vasculitis (AAV)
<b>Sponsor name</b>	Cambridge University Hospitals NHS Foundation Trust
<b>North American Sponsor</b>	University of Pennsylvania
<b>Japan Sponsor</b>	Okayama University
<b>Ireland Sponsor</b>	University College Cork
<b>Disease Under Investigation</b>	ANCA-associated vasculitis (AAV)
<b>Purpose of Clinical Trial</b>	To demonstrate the superiority of rituximab against azathioprine in the prevention of disease relapse in AAV patients with relapsing disease
<b>Clinical Phase</b>	III (3)
<b>Trial Design</b>	Multi-centre, international, open-label, randomised controlled trial in relapsing AAV. At least 160 participants will be randomised 1:1 to receive fixed-interval repeat rituximab dosing or azathioprine maintenance therapy. The trial has 3 phases and will last for 48 months: <i>Induction</i> – 0-4 months <i>Maintenance</i> – 4-24 months <i>Long-term follow-up</i> – patients will have a minimum of 12, and maximum of 24 months follow-up
<b>Primary objective</b>	To assess the efficacy of rituximab compared to azathioprine in the prevention of disease relapse in AAV patients with relapsing disease
<b>Secondary objectives</b>	To demonstrate: <ol style="list-style-type: none"> <li>1. Sustained disease remission beyond the 24 month treatment period</li> <li>2. Long term safety of rituximab administration</li> <li>3. The optimal remission maintenance therapy in AAV following induction of disease remission with rituximab</li> </ol>
<b>Trial Endpoints</b>	Primary: Time to disease relapse (either minor or major relapse) from randomisation.  Secondary: <ol style="list-style-type: none"> <li>1. Proportion of patients who maintain remission at 24 and 48 months</li> <li>2. Time to a major or second minor relapse</li> <li>3. Cumulative accrual of damage as measured by the combined damage assessment score (CDA)</li> </ol>

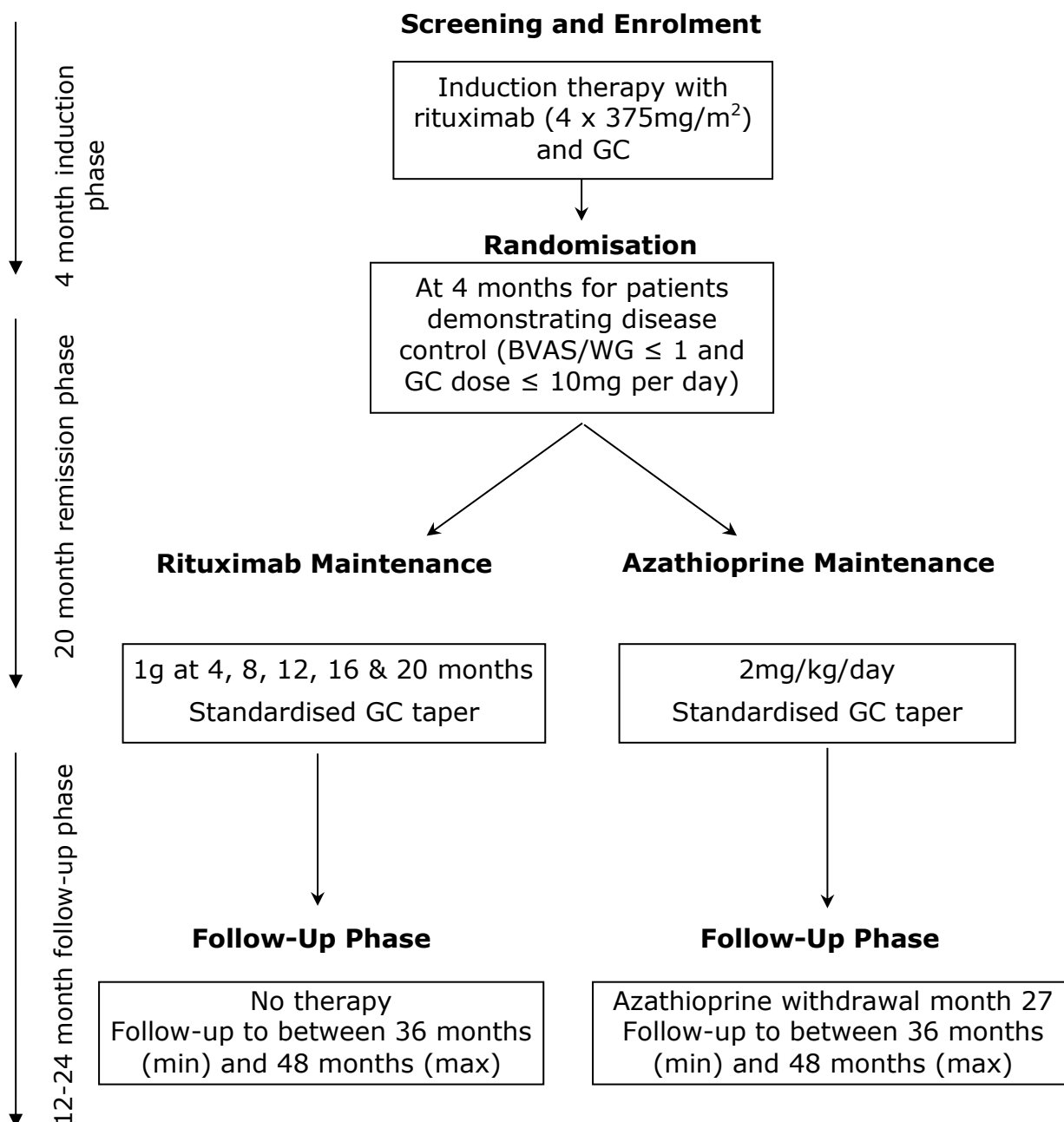
	<ol style="list-style-type: none"> <li>4. Health-related quality of life as measured using SF-36</li> <li>5. Cumulative glucocorticoid exposure</li> <li>6. Severe adverse event rate</li> <li>7. Infection (treated with either intravenous or oral antibiotics) rate</li> </ol> <p>Exploratory:</p> <ol style="list-style-type: none"> <li>1. Health economic assessment based on EQ5D</li> <li>2. Health-related quality of life and patient-reported domains as measured using PROMIS</li> <li>3. Serum rituximab levels, and correlation with circulating B cell counts including key subsets and immunoglobulin levels</li> <li>4. Changes in ANCA titres (both anti-MPO and anti-PR3 subsets) in relation to treatment, response, and relapse.</li> <li>5. HACA rate and levels</li> <li>6. Serum will be stored for future biomarker studies</li> <li>7. mRNA will stored for disease and inflammatory gene activation studies</li> <li>8. DNA will be stored for future genetic studies</li> </ol>
<b>Sample Size</b>	Enrolment will be ongoing until at least 160 patients are randomised. It is anticipated this will require 190 patients to be recruited.
<b>Summary of Eligibility Criteria</b>	<p>Subjects must meet <u>all</u> of the following criteria to be eligible for enrolment:</p> <ol style="list-style-type: none"> <li>1. Written informed consent (15 years and above)</li> <li>2. A diagnosis of AAV (granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis), according to the definitions of the Chapel Hill Consensus Conference</li> <li>3. Current or historical PR3/MPO ANCA positivity by ELISA</li> <li>4. Disease relapse defined by one major or three minor disease activity items on the Birmingham Vasculitis Activity Score for Wegener's (BVAS/WG), in patients that have previously achieved remission following induction therapy</li> </ol>
<b>Key Exclusion Criteria</b>	<ol style="list-style-type: none"> <li>1. Age &lt; 15 years (age &lt; 18 years at centres that do not treat paediatric patients)</li> <li>2. Previous therapy with any biological B cell</li> </ol>

	depleting agent (such as rituximab or belimumab) within the past 6 months
<b>Randomisation</b>	<p>Patients will be stratified at the time of randomisation (month 4) according to:</p> <ol style="list-style-type: none"> <li>1. ANCA type (anti-PR3 or anti-MPO)</li> <li>2. Relapse severity (severe or non-severe)</li> <li>3. Selected prednisone induction regimen (1A or 1B)</li> </ol>
<b>Investigational Medicinal Product and Dosage</b>	<p><b>Rituximab</b></p> <p><i>Induction Regimen</i> Patients will be recruited at the time of relapse. All will receive rituximab 375 mg/m<sup>2</sup>/week x 4 doses and glucocorticoids.</p> <p>Patients that achieve disease control (BVAS/WG ≤ 1 and daily prednisone dose ≤ 10mg) by month 4 will be randomised to the rituximab or control remission maintenance groups.</p> <p><i>Rituximab maintenance group</i> Rituximab 1000 mg at months 4, 8, 12, 16 and 20 and glucocorticoids.</p>
<b>Active Comparator Products</b>	<p><b>Azathioprine</b></p> <p><i>Induction Regimen</i> Patients will be recruited at the time of relapse. All will receive rituximab 375 mg/m<sup>2</sup>/week x 4 and glucocorticoids.</p> <p>Those patients that achieve disease control (BVAS/WG ≤ 1 and daily prednisone dose ≤ 10 mg) by month 4 will be randomised to the rituximab or control remission maintenance groups.</p> <p><i>Control maintenance group</i> Azathioprine 2 mg/kg/day from month 4 to 24. Dose reductions for intolerance, abnormal liver function tests, cytopenias, or based on abnormal TPMT genotype/activity testing (if performed) will be made. Methotrexate 25 mg/week, for patients with GFR &gt; 50 ml/min and intolerant of azathioprine even at a reduced dose of 1 mg/kg/day, or mycophenolate mofetil 2 g/day, for patients intolerant of azathioprine and with GFR &lt; 50 ml/min, and glucocorticoids. Intolerance is defined as the occurrence of an adverse</p>

	effect (see section 11.2.i) <i>NOT</i> lack of efficacy. At month 24, the azathioprine, methotrexate, mycophenolate mofetil dose will be reduced by 50% and stopped at month 27 (dose = 0 mg/day at month 27).
<b>Route of Administration</b>	Rituximab will be administered intravenously. Azathioprine and mycophenolate mofetil will be administered orally. Methotrexate can be given orally, subcutaneously, or intramuscularly.
<b>Concomitant Therapy</b>	<p><u>Glucocorticoids at induction</u></p> <p>For all glucocorticoid dosing, prednisone may be substituted for prednisolone.</p> <p>The investigator may choose one of two permitted GC regimens:</p> <p>Oral prednisone (prednisolone will be allowed), commencing at 1.0mg/kg/day (maximum 60 mg/day), <b>or</b> 0.5mg/kg/day (maximum 30 mg/day), both reducing to 10mg/day by month 3 (See schedule 1, pg. 26).</p> <p>Maximum daily dose of GC is 60 mg prednisone in week 0. Round down to the nearest 5 mg above 20 mg. Round down to the nearest 2.5 mg below 20 mg. GC to be administered in a single daily dose.</p> <p>Intravenous (IV) GCs are not mandated by the protocol. At the investigator's discretion, patients may receive up to a maximum cumulative dose of 3000mg IV methylprednisolone, between 14 days prior to enrolment and 7 days after enrolment.</p> <p><u>Glucocorticoids in Maintenance Phase:</u></p> <p>A GC dose of prednisolone 10 mg/day or less is a requirement for randomisation. GC reduces to 5 mg/day by month 6, according to schedule 2 (pg. 26). At month 16, GC dose is reduced to 2.5mg/day and at month 20 GC are completely withdrawn.</p>
<b>Maximum Treatment Duration</b>	Treatment is protocolised for the entire duration of the study, until the common close date, when the final patient recruited has completed 36 months within the study or until the patient has completed 48 months on study whichever the sooner. Patients in the rituximab arm will receive treatment until

	month 20, and those in the azathioprine arm until month 27.
<b>Summary of Study Procedures</b>	
Screening:	Procedures to establish inclusion/exclusion criteria.
Baseline:	Baseline data will include: <ol style="list-style-type: none"> <li>1. Date of birth, sex, limited medical history</li> <li>2. Medications, including prior AAV treatments</li> <li>3. Height/weight</li> <li>4. Urinary HCG in women of child bearing potential at screening or on Day 1 of rituximab treatment</li> <li>5. Disease activity assessment (BVAS/WG)</li> <li>6. Disease related damage assessment (CDA)</li> <li>7. Patient self-reported SF-36 questionnaire, EQ5D questionnaire and PROMIS questionnaires.</li> </ol>
Treatment period:	Evaluations will be performed at months 0, 1.5, 3, 4, 8, 12, 16, 20, 24, 27, 30, 36, and every 6 months until the last patient has completed 36 months in the study. The maximum duration in the study is 48 months. Assessments will also be performed at the time of relapse or study termination /withdrawal.
End of Trial:	The trial will end when the last patient has completed 36 months in the trial (from enrolment).
<b>Safety and Monitoring</b>	The NIH-sponsored VCRC Data and Safety Monitoring Board will provide independent oversight of this trial.

## 6 Trial Flow Chart



## 7 Introduction

### 7.1 Background

#### **ANCA-associated vasculitis (AAV): Disease overview and current treatment**

Granulomatosis with polyangiitis (GPA) (formally Wegener's granulomatosis (WG)) and microscopic polyangiitis (MPA) are primary systemic vasculitides, predominantly involving microscopic blood vessels with no or scanty immune deposits. Their association with circulating auto-antibodies to neutrophils (ANCA) has led to these conditions being grouped together as ANCA-associated vasculitis (AAV) (1, 2). The cause of AAV is unknown. AAV has an annual incidence of 20 per million and an approximate prevalence of 200/million (3). It is a multi-system autoimmune disease that causes tissue damage especially to the respiratory tract and kidneys, and causes early mortality, organ failure including end stage renal disease, and chronic morbidity. Prior to the availability of effective treatment, AAV was almost universally fatal, with a 93% mortality within 2 years due to pulmonary and renal failure (4). The introduction of what is now termed conventional immunosuppressive treatment transformed survival. Administration of cytotoxic immunosuppression (cyclophosphamide or methotrexate) and corticosteroids for at least one year induces remission in approximately 80% of patients. However, there are a significant proportion of patients that inadequately respond to traditional therapy. Also, relapsing disease is common with over 50% of patients experiencing a relapse within 5 years (5, 6, 7, 8). Relapse is associated with increased exposure to immunosuppressive medications and corticosteroids and at least 25% suffer severe early or late toxicity from these agents (9). The majority of relapses in the NORAM trial were minor, but were associated with a higher cumulative cyclophosphamide and glucocorticoid exposure (10). As treatment exposure is the greatest modifiable cause of damage, then prevention of relapses, minor as well as major is highly desirable. There is a major unmet need for safer therapy that leads to sustained treatment free remission in patients with relapsing disease, which will reduce drug toxicity that results from cumulative exposure to cyclophosphamide and glucocorticoids.

#### **Rituximab**

Rituximab is an IgG1 kappa, chimeric murine/human monoclonal antibody directed against the B-cell surface molecule CD20, resulting in B cell depletion. CD20 is thought to regulate an early step in the activation process for cell cycle initiation and differentiation. CD20 is not found on pro- or pre-B cells or mature plasma cells (the source of 95% of circulating IgG), so rituximab eliminates peripheral B cells without preventing regeneration of B cells from precursors and does not directly affect immunoglobulin levels. The cytotoxic effect is achieved by antibody-dependent cell-mediated cytotoxicity (ADCC), complement-mediated cell lysis and apoptosis (11). Rituximab was licensed for the treatment of non-Hodgkin's lymphoma in 1997 and for rheumatoid arthritis in 2006. Rituximab was licensed for AAV by the US FDA in 2011. In these conditions, rituximab was well tolerated with a favourable safety profile.

### 7.2 Data from Non-Clinical Studies

In vivo preclinical studies have shown that rituximab depletes >95% B cells from the peripheral blood cynomolgus monkeys. This depletion occurs presumably through complement and cell-mediated processes. The B-cell compartments within lymphatic tissue, including spleen, mandibular lymph node, and/or sub-mucosal lymphoid nodules, were also depleted within a short period of treatment, but to a lesser extent. Consistent with rituximab binding only to CD20+ B cells, T cell numbers were unaffected after treatment with rituximab.

## 7.3 Clinical Data

### 7.3.1 Efficacy

#### **Rationale for the use of rituximab in AAV**

B cells play a key role in the pathogenesis of AAV. Not only are they the precursors of ANCA secreting plasma cells, but they also act as antigen presenting cells for autoreactive T cells, providing co-stimulatory support and initiating T cell activation, as well as producing pro-inflammatory cytokines, such as IL-6 and TNF $\alpha$ . Specifically depleting B cells with targeted biological agents, such as rituximab, is therefore a promising approach to the treatment of AAV

#### **Rationale for clinical trial design and dosage**

##### Rituximab in AAV: Remission induction therapy

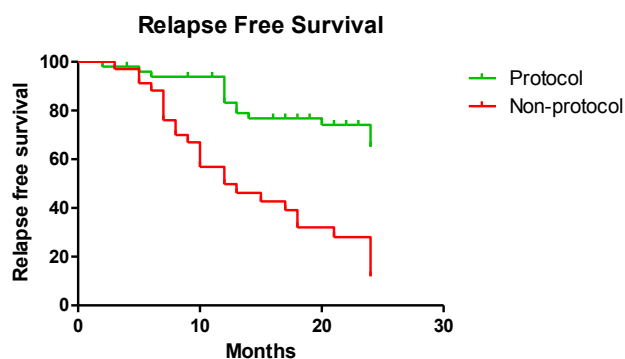
Randomised controlled trial data on the efficacy of rituximab in AAV is available from the RITUXVAS (n=44) (12) and RAVE (n=197) (13) studies. Both compared a rituximab based regimen to a cyclophosphamide based regimen as induction therapy for AAV. The RITUXVAS trial included newly diagnosed renal AAV. RAVE included patients with new and relapsing AAV. Neither trial identified differences in remission or severe adverse event rates between groups. However, the RAVE study included patients with an existing diagnosis of AAV, experiencing disease relapse, as well as those with a new diagnosis. It was in this subgroup of 101 patients that rituximab demonstrated superiority to cyclophosphamide in a prespecified exploratory analysis, with 62.2% patients in the rituximab group entering complete remission, when compared with 42% in the cyclophosphamide group (13).

##### Rituximab in AAV: Remission maintenance therapy

Results from uncontrolled studies consistently suggest that after a single course of rituximab AAV remissions occur and are sustained without the need for maintenance immunosuppression. However the majority of relapsing AAV patients treated with rituximab will relapse, with a mean time to relapse of one year (14). ANCA and B cell levels however lack the sensitivity to predict relapses and guide the timing of re-treatment.

Pilot data on the efficacy of rituximab as a maintenance agent is available from a cohort of 84 patients followed up at Addenbrooke's hospital between 2002 and 2010. Between 2002 and 2006, 34 patients received non protocolised treatment with rituximab which involved either, 2x1g doses, or 4x375mg/m<sup>2</sup> doses at the outset, and only further treatment with rituximab if a clinical relapse occurred. From 2006-2011, 50 patients received a protocolised course of rituximab therapy comprising of 2x1g or 4x375mg/m<sup>2</sup> doses initially, followed by 1g every 6 months for 2 years. Relapse free survival in the protocolised group was considerably higher than that in the non-protocolised group (Figure 1) (15). Six monthly re-treatment with rituximab resulted in prolonged B cell depletion, without a significant fall in immunoglobulin levels or an increased risk of severe adverse events or serious infections.



**Figure 1.**

At 24 months, 24% (12/50) of protocolised patients have relapsed, compared to 71% (24/34) non-protocolised patients

## 8 Rationale for Trial

Rituximab is an established induction agent in AAV, especially for those with relapsing disease. Its role as a maintenance agent is less clear. 50% will pursue a chronic relapsing course with 77% relapsing a second time within 2 years of a single course of rituximab. *Therefore the major unmet need is prevention of future relapse in relapsing patients.* Pilot data suggests that 6 monthly rituximab over 2 years is effective, safe, and leads to sustained treatment free remission. This is the platform for definitive study in a controlled trial which, if positive, will re-define remission therapy for AAV. Relapses however did still occur, the vast majority (90%) within the 2 months preceding subsequent rituximab doses, and so a 4 monthly repeat dosing strategy has been adopted for the study.

The study aims to improve outcomes for AAV patients by comparing a rituximab regimen to the current standard of care – azathioprine or methotrexate and glucocorticoids. In addition to answering the primary question of which is the superior therapy for preventing relapse in AAV, a number of key secondary questions will be addressed:

- Does sustained rituximab therapy have long-term benefit beyond the treatment period?
- Is sustained rituximab safe?
- What is the optimal remission therapy after rituximab induction?

## 9 Trial Design

### 9.1 Statement of Design

RITAZAREM is a multi-centre, international, open label, randomised controlled trial in relapsing AAV. Patients will be randomised, 1:1, to receive fixed interval repeat rituximab dosing or azathioprine maintenance therapy.

### 9.2 Number of Centres

RITAZAREM is a joint venture of the European Vasculitis Study Group (EUVAS) and the Vasculitis Clinical Research Consortium (VCRC).

RITAZAREM will occur in multiple centres internationally including Europe, North America and Australia/New Zealand and Japan. Plans are for approximately 50-60 centres to recruit patients.

### 9.3 Number of Subjects

Enrolment will be ongoing until at least 160 patients are randomised. It is anticipated this will require 190 patients to be recruited. Any patients in the induction phase when enrolment is halted will continue to follow the protocol and be randomised if the relevant criteria are met.

### 9.4 Trial Duration

The trial has 3 phases and will last for 48 months:

*Induction* – 0-4 months

*Maintenance* – 4-24 months

*Long-term follow-up* – patients will have a minimum of 12, and maximum of 24 months follow-up

### 9.5 Trial Objectives

#### 9.5.1 Primary objective

To assess the efficacy of rituximab compared to azathioprine in the prevention of disease relapse in AAV patients with relapsing disease

#### 9.5.2 Secondary objectives

To demonstrate

1. Sustained disease remission beyond the 24 month treatment period
2. Long term safety of rituximab administration
3. The optimal remission maintenance therapy in AAV following induction of disease remission with rituximab

### 9.6 Trial Endpoints

#### 9.6.1 Primary endpoint

The primary endpoint is the time to disease relapse (either minor or major relapse) from randomisation. Any patients who have not relapsed at study close will be censored. Further details of how relapse/censoring dates will be defined are given below.

A blinded Independent Adjudication Committee will be convened to look at all endpoint data.

Situation	Date of Relapse or Censoring	Outcome
No baseline assessments	Randomization	Censored
Relapse documented between scheduled visits	Unscheduled visit date	Relapsed
Drop-out with no relapse	Date of last assessment with no documented relapse	Censored
Treatment discontinuation for undocumented relapse	Date of last assessment with no documented relapse	Censored
Treatment discontinuation for toxicity or other reason, or protocol deviation	The patient will be followed up as per protocol and date of relapse or censoring observed accordingly	Relapsed/censored
Death due to relapse	Date of Death	Relapsed
Death due to other causes	Date of Death	Censored
Death or progression after More than one missed visit	Date of last assessment with no documented relapse	Censored

### 9.6.2 Secondary endpoints

1. Proportion of patients who maintain remission at 24 and 48 months
2. Time to a major or second minor relapse
3. Cumulative accrual of damage as measured by the combined damage assessment score (CDA)
4. Health-related quality of life as measured using SF-36
5. Cumulative GC exposure
6. Severe adverse event rate
7. Infection (treated with intravenous or oral antibiotics) rates

### 9.6.3 Exploratory endpoints

1. Health economic assessment based on EQ5D
2. EQ5D is a standardised instrument for use as a measure of health outcome, providing a simple descriptive profile and a single index value for health status. It is designed to be completed by patients.
3. Health-related quality of life and patient-reported outcomes as measured using the Patient-Reported Outcomes Measurement Information System assessment (PROMIS). PROMIS is a set of validated health-related quality of life assessment questionnaires covering domains that include fatigue, physical function, pain, and global health.
4. Serum rituximab levels and correlation with circulating B cell counts including key subsets and immunoglobulin levels
5. Changes in ANCA titres (both anti-MPO and anti-PR3 subsets) in relation to treatment, response, and relapse
6. HACA rate and level
7. Serum will be stored for future biomarker studies
8. mRNA will be stored for disease and inflammatory gene activation
9. DNA will be stored for various studies

## **10 Selection and Withdrawal of Subjects and Randomisation**

### **10.1 Inclusion Criteria**

To be included in the trial the patient must have:

1. Provided written informed consent (15 years and above)
2. A diagnosis of AAV [granulomatosis with polyangiitis or microscopic polyangiitis], according to the definitions of the Chapel Hill Consensus Conference
3. Current or historical PR3/MPO ANCA positivity by ELISA
4. Disease relapse defined by one major or three minor disease activity items on the Birmingham Vasculitis Activity Score for Wegener's (BVAS/WG), in patients that have previously achieved remission following at least 3 months of induction therapy, with a combination of glucocorticoids and an immunosuppressive agent (cyclophosphamide or methotrexate or rituximab or mycophenolate mofetil)

All patients will receive induction therapy with rituximab. Only those entering remission by 4 months will be randomised 1:1 to the rituximab or control groups

### **10.2 Exclusion Criteria**

The presence of any of the following will preclude patient inclusion:

1. Age < 15 years (age < 18 years at centres that do not treat paediatric patients)
2. Exclusions related to medication:  
Previous therapy with:

- a. Any biological B cell depleting agent (such as rituximab or belimumab) within the past 6 months
  - b. Alemtuzumab or anti-thymocyte globulin (ATG) within the last 12 months
  - c. IVIg, infliximab, etanercept, adalimumab, abatacept or plasma exchange in past 3 months
  - d. Any investigational agent within 28 days of screening, or 5 half lives of the investigational drug (whichever is longer)
3. Exclusions related to general health:
- a. Significant or uncontrolled medical disease not related to AAV, which in the investigators opinion would preclude patient participation
  - b. Presence of another multisystem autoimmune disease, including Churg Strauss syndrome, systemic lupus erythematosus, anti-GBM disease, or cryoglobulinaemic vasculitis,
  - c. Any concomitant condition anticipated to likely require greater than 4 weeks per year of oral or systemic glucocorticoid use and which would preclude compliance with the glucocorticoid protocol (e.g. poorly-controlled asthma, COPD, psoriasis, or inflammatory bowel disease).
  - d. History of severe allergic or anaphylactic reactions to humanised or murine chimeric monoclonal antibodies
  - e. Known infection with HIV (HIV testing will not be a requirement for trial entry); a past or current history of hepatitis B virus or hepatitis C virus infection.
  - f. Ongoing or recent (last 12 months) evidence of active tuberculosis or known active infection (screening for tuberculosis is part of 'standard of care' in patients with established AAV) or evidence of untreated latent tuberculosis. Screening for tuberculosis is as per local practice.
  - g. History of malignancy within the past five years or any evidence of persistent malignancy, except fully excised basal cell or squamous cell carcinomas of the skin, or cervical carcinoma in situ which has been treated or excised in a curative procedure.
  - h. Pregnancy or inadequate contraception in women of childbearing potential
  - i. Breast feeding or lactating
  - j. Medical, psychiatric, cognitive or other conditions that, in the investigator's opinion, compromise the patient's ability to understand the patient information, to give informed consent, to comply with the trial protocol, or to complete the study.
4. Exclusion criteria related to laboratory parameters:
- a. Bone marrow suppression as evidenced by a total white count  $< 4 \times 10^9/l$ , haemoglobin  $< 7 \text{ gm/dl}$  or platelet count  $< 100,000/\mu l$
  - b. Aspartate aminotransferase or alanine aminotransferase or amylase  $> 2.5$  times the upper limit of normal, unless attributed to vasculitis

### 10.3 Enrolment and Assignment and Trial Number

The patient will be allocated a unique trial identification number to be used on all trial related material for the patient upon enrolment. Patients will be enrolled by logging into an internet based website (TENALEA) provided by the Cambridge Clinical Trials Unit. After logging in, the investigator will confirm eligibility criteria, ANCA subtype, relapse severity and the prednisolone induction regimen followed (1A or 1B). Investigators are required to enter the height and weight of the patient. Body surface area and the dose for each of the 4 rituximab induction infusions ( $375\text{mg}/\text{m}^2$ ) will be automatically calculated within TENALEA using the Dubois and Dubois formula (17). A target date for randomisation four months in the future will be generated. This information should be recorded on the enrolment CRF page.

## 10.4 Randomisation

At the time of enrolment, a target date for randomisation (4 months from enrolment) will be generated. Randomization will be performed by the local investigator **for those patients in remission (BVAS/WG  $\leq$  1 and daily prednisone dose  $\leq$  10mg) by month 4.**

Patients can be randomised from 14 days before, to 14 days after, month 4. If patients attend their month 3 visit and are in remission, then they can be randomised up to 14 days before month 4, to enable time to organise rituximab infusion or azathioprine supply according to treatment allocation. Those not in remission at month 3 are reassessed at month 4 and if they enter remission must be randomised and commence allocated therapy within the next 14 days. Those not in remission at month 4 are not randomised, even if they had been considered in remission at the month 3 visit, and are treated at the investigator's discretion. Follow-up data will continue to be collected unless consent is withdrawn.

The randomization algorithm will then assign the patient to either the rituximab maintenance therapy or the control arm, where patients receive azathioprine, unless there is a contraindication when mycophenolate mofetil or methotrexate are alternatives (see section 11.1.4). **Maintenance therapy with rituximab or azathioprine must not be administered prior to the month 4 visit.** Notification of the treatment allocation will be forwarded to the central study co-ordinator, local investigator and local pharmacy by electronic mail (email) upon randomization. In the event that access to the internet is unavailable, the investigator may call the central study coordinator, based at Addenbrooke's Hospital, Cambridge, UK who will access the randomization program and inform the investigator of the treatment allocation and ensure randomization information reaches the appropriate study personnel.

Patients will be stratified at the time of randomisation according to:

1. ANCA type (anti-PR3 or anti-MPO)
2. Relapse severity (severe or non-severe)
3. Selected prednisone induction regimen (1A or 1B)

## 10.5 Method of Blinding

This will be an open label study.

A non-blinded, open label study has been chosen for *reasons of simplicity and practicality* in view of RITAZAREM being an international multi-centre trial. Previous EUVAS studies with similar end-points have also been unblinded yet have led to robust and reproducible conclusions.

## 10.6 Subject Withdrawal Criteria

Patients will be withdrawn from the trial immediately if they choose to withdraw their consent to participate. Otherwise subjects will be followed until the end of the trial or until death. In the event that consent to participate is withdrawn, it will be requested of patients that the study team continue to be allowed to collect vital status information from the patient and/or their family physician or general practitioner. Subjects who are withdrawn will not be replaced. Subjects will not be randomized if they do not achieve disease control (BVAS/WG  $\leq$  1 and daily prednisone dose  $\leq$  10mg) by month 4 and will

be treated at the discretion of the local investigators, although they will continue to be followed and data collected for safety purposes.

**Withdrawal is anticipated to be a rare occurrence.** Local investigators may stop the randomised treatment for appropriate medical reasons, be that individual adverse events or new information gained about a treatment. Pregnant patients will be treated with best medical practice, and continue in long term follow up. Non-compliant patients will be helped to return to protocol compliance, and continue in long term follow up. Any decision to stop the randomised treatment **MUST** be discussed with the chief investigator in order not to adversely affect the conduct of the trial. Patients will continue to be followed up, and data collected and documented as set out in the protocol, unless they withdraw their consent for this.

## 11 Trial Treatments

Rituximab, azathioprine, methotrexate and mycophenolate mofetil are all considered IMPs for the purposes of this study. Glucocorticoids are a non-IMP.

### 11.1 Rituximab

*Rationale for rituximab dosing*

#### Induction Phase:

375mg/m<sup>2</sup>/week x 4 doses, was the dose used in both the randomised controlled rituximab induction trials in vasculitis (RITUXVAS and RAVE) and will be the induction dose used in RITAZAREM.

#### Maintenance Phase:

Neither RITUXVAS nor RAVE addressed the question of repeat dosing with rituximab as a maintenance strategy. The two largest data sets presently available utilising repeat rituximab as a maintenance strategy, employed doses of 1000mg x 2 every 6 months (Mayo Clinic) (total 8000mg in 24 months) or 1000mg every 6 months (Cambridge, UK) (total 4000mg in 24 months). The selected dose for RITAZAREM, 1000mg every 4 months (5000mg in total), falls between these two regimens. In addition, 9 out of 10 relapses seen in the Cambridge cohort occurred in the 2 months prior to a scheduled rituximab dose, yet responded to further rituximab. Reducing the interval between rituximab doses to 4 months has the potential to further reduce relapse rates.

B cell depletion is a pharmacodynamic surrogate for rituximab efficacy. Because B cell return typically commences after four months, by reducing the dosing interval to four months the study aims to maintain 100% B cell depletion for the 24 month treatment phase.

No data exists for a total rituximab dose below 1000mg in vasculitis. Adopting a 375mg/m<sup>2</sup> dose every 4 months as a maintenance strategy would result in a median dose of 700mg. The MAINRITSAN study is employing a 500mg dose every 6 months. This is likely to result in under dosing, because 20% of patients relapsed using 1000mg every 6 months in the Cambridge cohort. In addition, more frequent maintenance dosing is inconvenient for patients and more expensive.

#### 11.1.1 Dosage schedules

##### Induction Regimen

Patients will be recruited at the time of relapse. All will receive rituximab 375 mg/m<sup>2</sup>/week x 4 doses and glucocorticoids. The first dose of rituximab

should be given within 14 days of enrolment into the trial. All induction doses of rituximab should be completed by week 6.

Patients that achieve disease control (BVAS/WG  $\leq 1$  and daily prednisone dose  $\leq 10$ mg) by month 4 will be randomised to the rituximab or control remission maintenance groups.

First infusion: The recommended initial infusion rate for rituximab (MabThera/Rituxan) is 50 mg/h; subsequently, the rate can be escalated in 50 mg/h increments every 30 minutes to a maximum of 400 mg/h.

Subsequent infusions: Subsequent infusions of rituximab (MabThera/Rituxan) can be started at a rate of 100 mg/h and increased by 100 mg/h increments every 30 minutes to a maximum of 400 mg/h.

Pre-medication with 100 mg IV methylprednisolone will be administered prior the first infusion to minimise infusion reactions. Sites will follow local pre-medication practice for infusions 2, 3, and 4. 100 mg IV methylprednisolone will be administered prior to *each* maintenance dose.

Infusions of rituximab in the maintenance phase should be given within 2 weeks of the randomisation at month 4 (if randomisation allocation is to the rituximab arm). Further infusions at month 8 onwards must be given within +/- 2 weeks of the assessment date.

#### Rituximab maintenance group

Rituximab 1000 mg x 1 dose at months 4, 8, 12, 16 and 20 and glucocorticoids.

**Dose of rituximab for maintenance therapy must not be administered prior to the month 4 visit.**

#### 11.1.2 Route of Administration

Rituximab will be administered intravenously.

#### 11.1.3 Maximum dosage allowed

The induction dose will vary depending on the body surface area of the patient. The maximum dose administered during the maintenance phase will be 5g.

#### 11.1.4 Maximum duration of treatment of a subject

Treatment with rituximab will cease at month 20. Patients will continue to be followed until month 36 at a minimum.

#### 11.1.5 Known Drug Reactions & Interaction with Other Therapies

Infusion reactions (within 24 hours of the infusion) occur in up to 50% of patients receiving rituximab. Pre-medication with 100 mg IV methylprednisolone will be administered prior the first infusion to minimise the effect of such reactions. Administration of 100 mg IV methylprednisolone for induction infusions 2, 3, and 4 is at the local investigator's discretion. 100 mg IV methylprednisolone will be administered prior to *each* maintenance dose. Symptoms include – fever, rigors, urticaria/rash, pruritis, flushing, angiodema, nausea, vomiting, fatigue, headache, rhinitis, throat irritation, bronchospasm and hypotension. Following treatment, sepsis, leucopaenia and neutropaenia can occur. In patients with autoimmune diseases, severe skin reactions such as Toxic Epidermal Necrolysis (TEN) and Stevens- Johnson Syndrome (SJS) with

fatal outcome have been reported very rarely with Rituximab in the post-marketing setting. For autoimmune and oncology indications, in case of the occurrence of severe skin reactions, Rituximab treatment should be discontinued. The decision to re-administer Rituximab must be carefully assessed based on the individual patient's benefit-risk profile. The cases of TEN and SJS have been reported with either first time use or with later infusions. Some of the cases occurred on the day of dosing or within a few days of dosing. In other cases, the event occurred weeks or up to four months after the dose.

Please always refer to the Investigator Brochure for expected adverse events associated with rituximab administration.

#### 11.1.6 Dosage Modifications

Rituximab will be administered at a dose of  $375\text{mg}/\text{m}^2 \times 4$ , at weekly intervals during the induction phase of the trial. Patients achieving remission and randomised to the rituximab remission maintenance group will receive rituximab 1000mg, at months 4, 8, 12, 16 and 20. The dose of rituximab does not need to be adjusted for renal function.

If the IgG level falls below 3g/l, it should be repeated in the month prior to the next scheduled dose of rituximab and the dose not administered if the IgG level remains  $<3\text{g}/\text{l}$ . If the IgG level has risen and is  $\geq 3\text{g}/\text{l}$ , then rituximab should be administered as per protocol. For those with an IgG level remaining  $< 3\text{g}/\text{l}$ , the IgG level is checked again within the month prior to the next scheduled dose of rituximab and this dose only given if the level has risen to  $\geq 3\text{g}/\text{l}$ . IgM and IgA levels are ignored for the purpose of rituximab dosing. Dosing of azathioprine (methotrexate and mycophenolate mofetil) should continue according to protocol regardless of IgG level.

#### 11.1.7 Legal Status of the Drug

Rituximab (Mabthera) has marketing authorisation numbers EU/1/98/067/001 and EU/1/98/067/002, which were granted in the EU to Roche Registration Limited. Rituximab has a license for use in stage III-IV follicular lymphoma (Non-Hodgkins lymphoma) and in chronic lymphocytic leukaemia in both untreated and relapsing/refractory patients. It has a license for use in severe active rheumatoid arthritis, in combination with methotrexate, when patients have had an inadequate response or demonstrated intolerance to other disease modifying agents, including one or more anti-TNF agents.

In the United States rituximab is licensed for use in lymphoma, rheumatoid arthritis, and induction therapy for AAV (with regimen of  $375\text{mg}/\text{m}^2 \times 4$  doses).

Rituximab is also approved for use in Canada, Switzerland, Australia, Japan and the European Union for GPA and MPA (AAV).

For further information, please refer to the Investigator Brochure (IB).



### 11.1.8 Drug Storage and Supply

Rituximab must be stored as directed by the relevant IB, and the container should be kept in the outer carton to protect from light. Rituximab (MabThera) will be supplied directly by Roche to non-US sites, and rituximab (Rituxan) to all US sites by Genentech. Trial-specific prescriptions will be used for the entirety of the trial.

## 11.2 **Azathioprine**

Azathioprine is converted in the liver to 6-mercaptopurine, which impairs purine synthesis, incorporation of purines into DNA and DNA polymerase repair activity. Lymphocyte function is reduced, B cells more than T cells, as well as the cellular component of the inflammatory response. Azathioprine is well absorbed orally, and its elimination requires hepatic metabolism by xanthine oxidase. Therefore an important interaction is with allopurinol, a xanthine oxidase inhibitor.

Patients randomised to the control arm will receive oral azathioprine, to be taken daily. The maximum daily dose allowed is 200mg. The maximum treatment period is 27 months, with tapering at month 24 as described below.

### i. Adverse Effects

Major adverse effects include nausea and vomiting, dose-dependent myelosuppression and reversible, cholestatic hepatotoxicity. An increased incidence of malignancy particularly skin cancers and lymphoma has been seen after prolonged administration in transplant recipients. There could potentially be an increased susceptibility for developing macrophage activation syndrome (MAS) with the use of azathioprine in patients with autoimmune conditions. Physicians should be attentive to symptoms of infection such as EBV and cytomegalovirus (CMV), as these are known triggers for MAS. Please always refer to the Summary of Product Characteristics (SmPC) or package insert or monograph for expected adverse events associated with azathioprine.

### ii. Administration

The target dose is 2mg/kg. The maximum daily dose is 200mg. This should be continued until month 24. The dose should then be reduced by 50% and azathioprine completely withdrawn at month 27. The dose should be rounded down to the nearest 25mg. The dose may vary on alternate days e.g. 100mg one day, 150mg the next for patients on an overall dose of 125mg daily.

**Dose of azathioprine for maintenance therapy must not be administered prior to the month 4 visit.**

### iii. Monitoring

Full blood count (FBC/CBC) and ALT or AST (for hepatotoxicity), should be measured routinely for patients taking azathioprine, more frequently in the initial period following initiation

### iv. Leucopenia related to azathioprine

Stop oral azathioprine if the white cell count (WBC)  $< 4 \times 10^9/l$   
Restart with a dose reduced by 25% when WBC  $> 4 \times 10^9/l$ . Monitor weekly for four weeks. If leucopenia is severe (WBC  $< 1 \times 10^9/l$  or  $< 4 \times 10^9/l$  for more than 2 weeks), restart azathioprine at 50mg per day, when WBC  $> 4 \times 10^9/l$ . Increase weekly to target dose as WBC allows.  
Temporary prophylaxis to prevent PJP (PCP) and fungal infection are recommended until WCC  $> 4 \times 10^9/l$ . G-CSF may be considered.  
For a falling WBC, ( $< 6 \times 10^9/l$  and a fall of  $> 2 \times 10^9/l$  over the previous count), then reduce dose by 25%.

v. Azathioprine intolerance

Dose reductions for intolerance, abnormal liver function, cytopenias, or based on TPMT genotype/activity testing (if performed) will be made. Patients homozygous for abnormal TPMT genotype/profoundly reduced enzyme activity will not receive azathioprine. Methotrexate 25 mg/week will be substituted, for patients with GFR  $> 50$  ml/min and intolerant of azathioprine even at a reduced dose of 1 mg/kg/day, Mycophenolate mofetil 2 g/day will be substituted, for patients intolerant of azathioprine and with GFR  $< 50$  ml/min, and glucocorticoids. Intolerance is defined as the occurrence of an adverse event (see section 11.2.i) NOT lack of efficacy.

### 11.3 Methotrexate

Methotrexate is a folic acid antagonist. Its cytotoxic effect is mediated by binding of dihydrofolic acid reductase, which inhibits the reduction of folic acid to tetrahydrofolate, which is essential for the synthesis of purine and pyrimidine. Methotrexate easily penetrates the tissues after oral administration, with the highest concentrations being seen in the liver and kidneys. Most methotrexate is excreted unchanged through the urine within 24 hours. Renal disease causes accumulation of methotrexate, and in rare cases methotrexate can form complexes in the kidneys leading to renal damage.

Methotrexate is to be given, in a weekly dose. The maximum dose allowed is 25mg/week. The maximum treatment period is 27 months.

i. Adverse Effects

Adverse events include myelosuppression occurring day 7-14 after a single dose, infections due to immunosuppression, stomatitis, gastrointestinal disturbance (nausea, vomiting, diarrhoea), alopecia, hypersensitivity reactions and central nervous systemic disturbance (headaches, drowsiness and blurred vision). Rare, but serious side effects include pulmonary fibrosis and a reversible hepatotoxicity manifest by increased transaminases. Patients should only drink minimal amounts of alcohol, and methotrexate should be avoided if there is pre-existing liver disease.

Methotrexate is teratogenic, and therefore adequate contraceptive methods must be employed whilst on the drug and for 6 months after stopping it. Concomitant administration of folate antagonists, such as co-trimoxazole and trimethoprim should be avoided, as acute megaloblastic pancytopenia has been reported. As it is renally excreted methotrexate should be avoided in patients with moderate to severe renal impairment. Please always refer to the Summary of Product Characteristics (SmPC) or package insert or monograph for expected adverse events associated with methotrexate.

ii. Administration

Patients commencing methotrexate after induction of remission should start at a dose of 10mg per week. This should increase by 2.5mg weekly to a target dose of 25mg weekly. This should be continued until month 24. The dose should then be reduced by 50% and methotrexate completely withdrawn at month 27. Folic acid, 5mg weekly, should also be commenced.

Methotrexate is given orally, although parenteral, intramuscular, or subcutaneous administration can be used if oral medication is not tolerated. In the case of gastrointestinal disturbance, methotrexate can be given in 2 divided doses on the same day. Metoclopramide can also be administered.

### iii. Monitoring

Full blood count (FBC) and liver function tests (LFTs) should be measured routinely for patients taking methotrexate, more frequently in the initial period following initiation.

Methotrexate dosage should be monitored per local practice if concomitant treatment with aspirin or non-steroidal anti-inflammatory drugs (NSAIDs, such as ibuprofen, indomethacin, naproxen, and many others) is commenced, as concomitant use of methotrexate and NSAIDs has been associated with fatal methotrexate toxicity.

Methotrexate should be stopped if transaminases rise > 3 fold of the normal range, or WBC <  $3 \times 10^9/l$  or platelet count < 100,000/ $\mu l$ . Methotrexate can be re-started at a reduced dose of 50%, if the abnormal parameter normalises.

## **11.4 Mycophenolate Mofetil**

MMF is a prodrug that is hydrolysed to form mycophenolic acid. Mycophenolic acid reversibly inhibits inosin-monophosphate-dehydrogenase (IMDH), a key enzyme of de novo purine synthesis. Lymphocytes are key effector cells in AAV, whose proliferation and function relies almost exclusively on de novo purine synthesis whereas most other cells use the salvage pathway.

MMF is to be taken orally, twice daily. The maximum dose allowed is 3g/day. The maximum treatment period is 27 months. Mycophenolic acid is an acceptable alternative to MMF.

### i. Adverse Effects

Adverse effects of mycophenolate mofetil include gastro-intestinal (GI) disturbance leucopenia and infection including cytomegalovirus (CMV). In a systematic review of transplant patients, leucopenia and CMV were significantly more common only at the very highest MMF dose (3g), compared with azathioprine. The frequency of malignancy in a three year transplant study where MMF was combined with other immunosuppressive drugs showed no difference compared to azathioprine. GI adverse effects may be related to accumulation of the metabolite, mycophenolic acid glucuronide, which accumulates in renal failure. Dose reduction in those with a creatinine clearance of less than 25 ml/min may be required. Hypogammaglobulinaemia and bronchiectasis in association with recurrent infections has been reported in patients receiving mycophenolate mofetil particularly in combination with other immunosuppressants. Mycophenolate mofetil is a powerful human teratogen, with an increased risk of spontaneous abortions and congenital malformations in case of exposure during pregnancy. Please always refer to the Summary of Product Characteristics (SmPC) or package insert or

monograph for expected adverse events associated with mycophenolate mofetil.

ii. Administration

Mycophenolate mofetil will be administered orally. The drug will be started at 1g per day and dose increased to the target dose of 2g per day if tolerated. The dose can be increased to 3g daily for those with a sub optimal response. This should be continued until month 24. The dose should then be reduced by 50% and mycophenolate mofetil completely withdrawn at month 27.

iii. Monitoring

The total white cell count (WBC) should be measured routinely for patients taking MMF, more frequently in the initial period following initiation. Stop if  $WBC < 4 \times 10^9/l$ . Restart with MMF dose reduced by at least 500mg when  $WBC > 4 \times 10^9/l$ . Monitor weekly for one month. If severe ( $WBC < 1 \times 10^9/l$  or prolonged ( $WBC < 4 \times 10^9/l$  for  $> 2$  weeks), MMF should be withdrawn.

## 11.5 Concomitant Therapy

### 11.5.1 Glucocorticoids

Glucocorticoids at Induction:

For all glucocorticoid dosing, prednisone may be substituted for prednisolone. The investigator may choose one of two permitted glucocorticoid regimens to allow for variabilities in disease severity and glucocorticoid prescribing.

Oral prednisone (prednisolone will be allowed), commencing at 1.0mg/kg/day (maximum of 60 mg/day), or 0.5mg/kg/day (maximum of 30 mg/day), both reducing to 10mg/day by month 3. It is advised to start at 1.0mg/kg/day (maximum 60 mg/day) initially for those with life or organ threatening manifestations, such as severe nephritis or pulmonary haemorrhage and 0.5mg/kg/day (maximum 30 mg/day) for those with less severe disease. However, this is left to physician discretion, although the initial dose MUST be specified on the randomisation form, as it will be a stratification criterion. The chosen prednisolone regimen must be commenced by the time of the first rituximab (induction) infusion. Regardless of the dose chosen the tapering must adhere to schedule 1 below.

### Schedule 1:

Week	Induction Schedule A (1 mg/kg group)		Induction Schedule B (0.5 mg/kg group)	
	<60kg	≥60kg	<60kg	≥60kg
0	50	60	25	30
2	35	45	20	25
4	25	35	17.5	20
6	20	25	15	17.5
8	15	17.5	12.5	15
10	12.5		12.5	
12	10		10	

The maximum daily dose of prednisolone is 60 mg in week 0 in Schedule A. The maximum daily dose of prednisolone is 30 mg in week 0 in Schedule B.

The dose should be rounded down to the nearest 5 mg above 20 mg and to the nearest 2.5 mg below 20 mg. Prednisolone is to be administered in a single daily dose.

Intravenous (IV) GC are not mandated by the protocol. But, at the investigator's discretion, patients may receive up to a maximum cumulative dose of 3000mg IV methylprednisolone, between 14 days prior to enrolment and 7 days after enrolment.

#### Glucocorticoids in Maintenance:

A GC dose of 10 mg/day or less is a requirement for randomisation. GC reduces to 5 mg/day by month 6, according to schedule 2, and continues at 5 mg daily until month 16. GC dose is then reduced to 2.5mg/day and completely withdrawn at month 20.

#### **Schedule 2:**

<b>Week</b>	<b>Maintenance Schedule Daily prednisone dose (mg)</b>
12	10
14	10
16 (randomisation)	10
18	7.5
20	7.5
22	5
24	5

Alternate day dosing regimens (i.e. those that use two different doses on alternate days) may be used to achieve the appropriate average daily dose required by the protocol but differences in alternative day doses may not be >5 mg. For example, a dose of 7.5 mg/day may be achieved by alternating daily doses of 10 mg/day and 5 mg/day.

#### Adverse effects

The following are expected adverse effects if GC therapy: sepsis, hypertension, fluid retention, hyperglycaemia and diabetes mellitus, peptic ulceration, osteoporosis, avascular necrosis, cushingoid appearance, striae, alopecia and hirsutism.

#### 11.5.2 Prophylactic therapies

Prophylaxis for infection, such as with low-dose sulfamethoxazole-trimethoprim and prophylaxis for osteoporosis with calcium and vitamin D supplementation are strongly recommended and treatment with bisphosphonates to be considered but implementation is left to local practice.

#### 11.5.3 Plasma exchange

Plasma exchange can be administered during the induction period following local practice at the discretion of the investigator. Rituximab will not be administered within the 48 hours prior to receiving a plasma exchange treatment.

## 11.6 Treatment of relapse

Patients experiencing their first minor relapse after randomisation and before month 24 of the treatment phase will remain on the randomised treatment (rituximab or azathioprine) and will have their oral prednisolone/prednisone increased to 20mg/day for one week decreasing in 2.5mg increments each week to reach 5mg/day after six weeks. The second minor relapse or first major relapse, occurring before month 24 of the treatment phase will result in the patient being withdrawn from protocolised treatment and returned to treatment according to local best practice. Any relapse occurring after the 24 month treatment phase will be treated according to local best medical practice.

## 12 Procedure and Assessments

### 12.1 Screening Evaluation

Patients must review and sign the ICF prior to undergoing any study-related assessment. Patients will be evaluated by their local trial investigators to ensure they meet all the inclusion criteria and none of the exclusion criteria as stated in sections 10.1 and 10.2 of this protocol. The screening visit requires confirmation of the diagnosis of AAV (ANCA positivity, current or historical and pertinent histology results) and documentation of organ manifestations of active AAV. They will then undergo a baseline assessment. Therapy with IV methylprednisolone may begin during screening.

### 12.2 Baseline Data

Baseline data will include basic demographic information, laboratory data and clinical data and will be collected prior to receiving study therapy.

This information will include:

- a) Height and weight
- b) Sex
- c) Age and date of birth
- d) Any significant past medical history
- e) Concomitant medications, including previous treatment for AAV and prior cyclophosphamide exposure
- f) Full blood count (including platelets and differential white cell count)
- g) Biochemical series (including renal function and immunoglobulin levels)
- h) Pregnancy test in females of child bearing potential
- i) Viral screen for:
  - Hepatitis B. Please ensure hepatitis B surface antigen (HbSAg) and anti-hepatitis B core antibody (anti-HBc) are checked
  - Hepatitis C (*if performed*)
- j) Disease activity assessment (BVAS/WG) (including urine sample)
- k) Damage related assessment (CDA)
- l) Patient self-reported SF-36 questionnaire, EQ5D questionnaire and PROMIS questionnaires.

### 12.3 Trial Assessments

#### 12.3.1 Timing of assessments

Evaluations will be performed at months 0, 1.5, 3, 4, 8, 12, 16, 20, 24, 27, 30, 36, and every 6 months until the last patient has completed 12 months of follow up (36 months from study entry)

Only those patients that achieve disease control (BVAS/WG  $\leq$  1 and daily prednisone dose  $\leq$  10mg) by month 4 will be randomised to the rituximab or control remission maintenance groups. Patients who are not randomised will

continue to be followed up as per protocolised assessment until the common study closure date.

#### 12.3.2 Assessment data

The following assessments will be performed at the above time points (except CDA and SF-36/EQ5D):

- a. Disease activity assessment (BVAS/WG) (including urine sample)
- b. Damage related assessment (CDA) – completed at months 0, 4, 12, 24, 36 and 48.
- c. Quality of life evaluations – Short form 36 (SF-36) questionnaire and EQ5D questionnaire at months 0, 4, 12, 24, 36, 42 and 48 months. PROMIS questionnaires at every assessment up to and including 48 months.
- d. Blood tests including a full blood count and immunoglobulin levels (refer to schedule of assessment, Appendix 1, for collection of biomarker samples for DNA, RNA and serum).
- e. Treatment exposure to prednisolone, rituximab and azathioprine
- f. Adverse event review and concomitant medication review

The above assessments will also be performed at the time of relapse or study termination/withdrawal.

### **12.4 Long-Term Follow-up Assessments**

All patients will be followed until the last patient to be recruited has completed 36 months from study entry. With a two year recruitment period the median duration of follow-up will be 48 months from entry (range 36-48 months).

### **12.5 Trial Restrictions**

There are no specific restrictions to daily activities for participants of the study. Both male and female subjects should take adequate contraceptive precautions for the duration of the interventional phase of the trial (initial 24 months). In addition, contraception should be continued for 12 months after the last dose of rituximab (Investigators in republic of Ireland ONLY, please see Ireland specific appendix, for additional details regarding contraception). No live vaccines should be given to enrolled patients during the first 27 months of the trial.

## **13 Assessment of Safety**

### **13.1 Definitions**

#### 13.1.1 Adverse event

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product.

#### 13.1.2 Adverse reaction to an investigational medicinal product (AR)

All untoward and unintended responses to an investigational medicinal product related to any dose administered. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or

argument to suggest a causal relationship.

#### 13.1.3 **Unexpected adverse reaction**

An adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product).

When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

The term "severe" is often used to describe the intensity (severity) of a specific event. This is not the same as "serious," which is based on patient/event outcome or action criteria.

#### 13.1.4 **Serious adverse event (SAE) or serious adverse reaction**

Any untoward medical occurrence or effect that:

- Results in death
- Is life-threatening
- Requires hospitalization or prolongs an existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Other important medical events that may not be immediately life-threatening or results in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered 'serious'

Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Important medical events should be reported on the serious adverse event (SAE) form under the 'other' category.

#### 13.1.5 **Suspected Unexpected Serious Adverse Reaction (SUSAR)**

A serious adverse reaction, the nature and severity of which is not consistent with the information set out in the Reference Safety Information

#### 13.1.6 **Reference Safety Information (RSI)**

The information used for assessing whether an adverse reaction is expected. RSI for rituximab is the Investigator's Brochure (IB) (Section 6 – Guidance for the Investigator).

UK sites, will use Rituximab IB version 16. Any subsequent versions will be reviewed by the trial physician. Provided there is no significant change to the safety information, which would necessitate a protocol amendment, subsequent versions will not be circulated to investigators and Version 16 of the IB will continue to be used as the RSI for the duration of the study. If there is a significant change in safety information, the protocol will be amended and the Rituximab IB version number updated.

For non UK sites, updated IBs will be circulated to country leads, and they would continue to follow current regulatory practices in their country, with regards to submission to ethics and regulatory bodies. It will be clearly



documented in site TMFs what practice should be followed, and what version of the Rituximab IB is being used as RSI.

For the comparator drugs - azathioprine, methotrexate and mycophenolate mofetil the RSI will be:

**UK & Europe:**

- Methotrexate (Concordia International) SmPC section 4.8, dated 31/08/2018
- Mycophenolate Mofetil (Accord Healthcare Ltd) SmPC section 4.8, dated 06/10/2016
- Azathioprine (Aspen) SmPC section 4.8, dated 06/04/2017

USA – Package Insert

Canada - Monograph

Japan – Package Insert

New Zealand – Data Sheet (equivalent of SmPC/Package Insert)

Australia – Product Information (equivalent of SmPC/Package Insert)

All the drugs which we use in the RITAZAREM trial are prescribed for clinical use as approved drugs.

The Package Insert, Monograph, Product Information, Data Sheet and SmPC are very close.

### **13.2 Expected Adverse Reactions/Serious Adverse Reactions (AR /SARs)**

All expected Adverse Reactions are listed in the latest version of the reference safety information as specified in section 13.1.6. This must be used when making a determination as to the expectedness of the adverse reaction. If the adverse reaction meets the criteria for seriousness, this must be reported as per section 13.4.5.

#### **Rituximab**

Infusion reactions (within 24 hours of the infusion) may occur in up to 50% of patients receiving rituximab. Pre-medication with 100 mg IV methylprednisolone will be administered prior the first infusion to minimise the effect of such reactions. Sites will follow local pre-medication practice for infusions 2, 3, and 4. 100 mg IV methylprednisolone will be administered prior to each maintenance dose. Symptoms include – fever, chills, rigors, urticaria/rash, pruritis, flushing, angioedema, nausea, vomiting, fatigue, headache, rhinitis, throat irritation, bronchospasm and hypotension. However, lower rates were observed in the two randomised controlled induction trials. In the RITUXVAS study, 2/33 patients experienced an infusion reaction and in RAVE, only 1/99 experienced an infusion reaction severe enough to prevent administration of further infusions of rituximab.

Infusion reactions – fever, chills, rash, pruritis, flushing, throat irritation, angioedema, nausea and vomiting, fatigue, headache, hypotension and bronchospasm.

Mild infusion reactions are common, and can be treated by stopping the infusion, and restarting at a lower rate, together with antihistamine, antiemetic and paracetamol.

Severe infusion reactions have occurred but are rare. Hydrocortisone and adrenaline should be available for administration if needed (as per hospital protocol). Following a moderate or severe infusion reaction, patients should be

admitted to hospital for observation.

Following treatment, bone marrow suppression including leucopaenia and neutropaenia can occur. Following rituximab treatment, severe skin reactions such as TEN (Toxic epidermal necrolysis) and SJS (Stevens Johnson Syndrome) have been reported very rarely (see section 11.1.5). Infusion reactions, skin reactions, leucopaenia and neutropaenia do not require reporting, unless they meet the criteria for a serious adverse event (SAE) – see section 13.1.4 for definition of SAE.

Infections can also occur, including very rarely, reactivation of hepatitis B, and progressive multifocal leucoencephalopathy caused by reactivation of the JC virus. All infections are being collected as adverse events of interest. See section 13.4.

If discontinuation of rituximab is being considered for any reason, then the TMC must be consulted.

### **Azathioprine**

The following expected adverse drug reactions may occur in patients taking azathioprine: hematotoxicity, hepatotoxicity, pancreatitis and gastrointestinal disturbances. Hypersensitivity reactions may also occur (including malaise, dizziness, vomiting, diarrhoea, fever, rigors, myalgia, arthralgia, rash, hypotension and interstitial nephritis) and there is increased susceptibility to infections. Macrophage activation syndrome (MAS) has also been reported in patients with autoimmune diseases taking azathioprine.

### **Mycophenolate Mofetil**

Patients receiving immunosuppressive regimens involving combinations of medicinal products, including Mycophenolate Mofetil, are at increased risk of developing lymphomas and other malignancies, particularly of the skin. Patients receiving Mycophenolate Mofetil should be instructed to report immediately any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow depression. Patients treated with immunosuppressants, including Mycophenolate Mofetil, are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal), fatal infections and sepsis. Other suspected adverse drug reactions include gastrointestinal disturbance (nausea, constipation, flatulence, anorexia, weight loss, vomiting, abdominal pain, gastrointestinal inflammation, ulceration, and bleeding, hepatitis, jaundice, pancreatitis), hypogammaglobulinaemia, bronchiectasis and blood disorders (including leucopenia, anaemia, thrombocytopenia, pancytopenia, and red cell aplasia). Mycophenolate mofetil is a powerful human teratogen, with an increased risk of spontaneous abortions and congenital malformations in case of exposure during pregnancy.

### **Methotrexate**

Acute or chronic interstitial pneumonitis, often associated with blood eosinophilia, may occur and deaths have been reported. Symptoms typically include dyspnoea, cough (especially a dry non-productive cough) and fever for which patients should be monitored at each follow-up visit. Patients should be informed of the risk of pneumonitis and advised to contact their doctor

immediately should they develop persistent cough or dyspnoea. Methotrexate may be hepatotoxic, particularly at high dosage or with prolonged therapy. Liver atrophy, necrosis, cirrhosis, fatty changes, and periportal fibrosis have been reported. Bone marrow suppression (avoid concomitant use with another anti-folate drug (e.g. trimethoprim)) and gastrointestinal disturbance (nausea and abdominal discomfort) may also be seen as adverse drug reactions with methotrexate therapy.

Please also see Summary of Product Characteristics (SmPC) or Package Insert or Monograph for expected adverse events for azathioprine, methotrexate, mycophenolate and glucocorticoids. Please see Investigator Brochure (IB) for expected adverse events for rituximab.

### **13.3 Expected Adverse Events/Serious Adverse Events (AE/SAE)**

All serious adverse events, including serious adverse drug reactions (see section 13.2) should be reported according to guidance in section 13.5.

In addition to all SAEs, the following selected adverse events (AEs) are being collected as part of the RITAZAREM trial.

1. Infections (all episodes requiring treatment with intravenous (IV) or oral antibiotics or infections that are commonly understood to be opportunistic)
2. Occurrence of hypogammaglobulinaemia (IgG <5g/l)
3. An adverse event that results in a change in dose of trial IMPs (rituximab, azathioprine, methotrexate or mycophenolate mofetil (MMF))
4. An adverse event that results in the addition of a relevant concomitant medication (see section 13.3.1 for list)
5. An adverse event manifested by the occurrence of a relevant laboratory abnormality (see section 13.3.2 for list)
6. New malignancies

#### **13.3.1 Relevant concomitant medications**

1. Any anticoagulant, including warfarin, or newer equivalent agents, aspirin, clopidogrel, dipyridamole etc. This will identify any patient who has had a venous thromboembolic event or cardiovascular event – both important comorbidities in the AAV population.
2. IVIg – indicative of hypogammaglobulinaemia or recurrent infections
3. Any antibiotic, antiviral or antifungal agent – a corresponding infection form should have been completed, so this will act as an important cross check

#### **13.3.2 Relevant laboratory abnormalities**

1. Haemoglobin < 100g/l
2. White cell count <  $3.0 \times 10^9/l$
3. Platelet count <  $75 \times 10^9/l$
4. Creatinine > 30% rise from baseline AND >  $120\mu\text{mol/l}$
5. ALT or AST > 3 times upper limit of normal

Non-serious expected or unexpected adverse events, except those listed in section 13.3, will not be collected or reported as part of this trial.

### 13.4 Recording and Evaluation of Adverse Events

The Sponsor expects that all SAEs and selected adverse events highlighted in section 13.3 are recorded from the point of informed consent regardless of whether a patient has yet received a medicinal product. Individual serious adverse events should be evaluated by the investigator, including evaluation of its seriousness, causality and any relationship between the investigational medicinal product(s). The indication for any new concomitant medication, and cause of laboratory abnormality will be captured on the AE CRF page.

#### 13.4.1 Assessment of seriousness

Seriousness is assessed against the criteria in section 13.1.4. This defines whether the event is an adverse event, serious adverse event or a serious adverse reaction.

#### 13.4.2 Assessment of causality

*Definitely:* A causal relationship is clinically/biologically certain. **This is therefore an Adverse Reaction**

*Probable:* A causal relationship is clinically / biologically highly plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product and there is a reasonable response on withdrawal. **This is therefore an Adverse Reaction.**

*Possible:* A causal relationship is clinically / biologically plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product. **This is therefore an Adverse Reaction.**

*Unlikely:* A causal relation is improbable and another documented cause of the AE is most plausible. **This is therefore an Adverse Event.**

*Unrelated:* A causal relationship can be definitely excluded and another documented cause of the AE is most plausible. **This is therefore an Adverse Event.**

Unlikely and Unrelated causalities are considered NOT to be trial drug related  
Definitely, Probable and Possible causalities are considered to be trial drug related

A pre-existing condition must not be recorded as an AE or reported as an SAE unless the condition worsens during the trial and meets the criteria for reporting as a SAE or selected adverse event (see section 13.3.)

Investigators will be prompted on the follow up form completed at each visit to complete an infection form or new malignancy form if either of these events have occurred since the last trial visit. Details regarding the changes in dose of IMPs (rituximab, azathioprine, methotrexate and mycophenolate mofetil) including new dose, date of change and reason for change will be captured on the follow up form.

The occurrence of hypogammaglobulinaemia (IgG < 5g/l) is flagged when data is entered into the trial database, and is reported to the DSMB on a 6 monthly basis.

The occurrence of a relevant laboratory abnormality or the addition of a new concomitant medication will be flagged as data is entered into the trial database. An adverse event form will be generated, and the relevant abnormality and data identified pre-filled on the form. Forms will then be sent to investigators for completion. Completed adverse event forms must be submitted to the CCTU within 2 weeks.

### **13.5 Reporting Serious Adverse Events**

Each Principal Investigator needs to record all serious adverse events and report these to the Chief Investigators. The Chief Investigators have delegated responsible for assessing all SAEs, to the trial physician, (currently) Dr Rona Smith, for expectedness and notification of all SAEs to the Sponsor immediately, but not more than 24 hours after first notification. Individual SAEs will be assessed by the trial physician, and if advice is needed, this will be sought from one of the CIs, blinding them to treatment allocation. The Sponsor has to keep detailed records of all SAEs reported to them by the trial team.

All Serious Adverse Events must be reported to the central trials co-ordinator or trial physician in Cambridge, currently Kim Mynard or Dr Rona Smith, within 24 hours of the investigator becoming aware of the event, via email ([RITAZAREM@medschl.cam.ac.uk](mailto:RITAZAREM@medschl.cam.ac.uk)). Cumulative safety reports will be generated and sent monthly to the sponsor, the TMC and the DSMB and every three months to all Principal Investigators. All single SAE case reports will also be sent to the DSMB in real-time.

The Chief Investigator is also responsible for prompt reporting of all serious adverse events to the competent authority (e.g. MHRA) of each concerned Member State of findings that could adversely affect the health of subjects, impact on the conduct of the trial or alter the competent authority's authorization to continue the trial in accordance with Directive 2001/20/EC. The Chief Investigator may delegate the responsibility for reporting serious adverse events to the competent authority of any member state outside the UK to the lead investigator for that member state.

An adverse event or reaction that meets serious criteria irrespective of consistency (expected or unexpected) with the applicable product information (e.g. investigators brochure for unapproved investigational product or summary of product characteristics) must be reported to the sponsor unless explicitly listed within the protocol that REPORTING is not necessary.

### **13.6 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)**

All suspected adverse reactions related to an investigational medicinal product (the tested IMP and comparators) which occur in the concerned trial, and that are both unexpected and serious (SUSARs) are subject to expedited reporting. Please see section 13.1.6 for the Reference Safety Information to be used in this trial.

#### **13.6.1 Who should report and whom to report to?**

The Sponsor delegates the responsibility of notification of the occurrence of

SUSARs to the Competent Authority (CA), Ethics Committee (EC)/IRB and any other investigators to the Chief Investigators. The Chief Investigators should report all the relevant safety information previously described, to the Sponsor. The Chief Investigators have delegated the responsibility for reporting to the member state Competent Authority and local EC/IRB to the lead investigator of each member state.

The Chief Investigators shall inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of subjects. Information about SUSARs will be sent to the DSMB within 24 hours of receipt by the Chief Investigators.

### 13.6.2 When and what events to report?

#### 13.6.2.1 Fatal or life-threatening SUSARs

The CA, Research Ethics Committee and Sponsor should be notified as soon as possible but no later than **7 calendar days** after the trial team and Sponsor has first knowledge of the minimum criteria for expedited reporting.

In each case relevant follow-up information should be sought and a report completed as soon as possible. It should be communicated to the CA, Ethics Committee and Sponsor within an additional **8 calendar days**.

In addition to the timelines above, investigators should be aware of, and comply with, the reporting timelines in their respective countries.

#### 13.6.2.2 Non fatal and non life-threatening SUSARs

All other SUSARs and safety issues must be reported to the competent authority and Ethics Committee in the concerned member state as soon as possible but no later than **15 calendar days** after first knowledge of the minimum criteria for expedited reporting. Further relevant follow-up information should be given as soon as possible.

### 13.6.3 How to report?

#### 13.6.3.1 Minimum criteria for initial expedited reporting of SUSARs

Information on the final description and evaluation of an adverse reaction report may not be available within the required time frames for reporting. For regulatory purposes, initial expedited reports should be submitted within the time limits as soon as the minimum following criteria are met:

- a) A suspected investigational medicinal product,
- b) An identifiable subject (e.g. trial subject code number),
- c) An adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship,
- d) An identifiable reporting source, and, when available and applicable:

- A unique clinical trial identification (EudraCT number or in case of non-European Community trials the sponsor's trial protocol code number)

- A unique case identification (i.e. sponsor's case identification number).

#### 13.6.3.2 Follow-up reports of SUSARs

In case of incomplete information at the time of initial reporting, all the appropriate information for an adequate analysis of causality should be actively sought from the reporter or other available sources. Further available relevant information should be reported as follow-up reports. In certain cases, it may be appropriate to conduct follow-up of the long-term outcome of a particular reaction.

#### 13.6.3.3 Format of the SUSARs reports

Electronic reporting, when available, is the expected method for expedited reporting of SUSARs to the CA. The format and content as defined by the CA should be adhered to.

### **13.7 Pregnancy Reporting**

All pregnancies within the trial (either the trial participant or the participant's partner) should be reported to the Chief Investigator and the Sponsor using the relevant Pregnancy Reporting Form within 24 hours of notification.

Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets serious criteria, this would be considered an SAE.

### **14 Toxicity – Emergency Procedures**

In the event of toxicity reactions, standard medical practices will be employed, including emergency care and hospitalization if needed. All medications in this study are licensed for use in medicine and their uses are familiar to the physicians and staff at all participating centres.

### **15 Evaluation of Results**

The primary endpoint is the time to relapse (including both major and minor – see definitions in section 15.1) from randomisation. This will be reported when all subjects have completed the 24 month treatment phase of the study.

#### **15.1 Response Criteria**

##### 15.1.1 Remission

For the purpose of this study, and progression to randomisation for allocation to one of the two arms of the maintenance phase of the study, remission equates to achievement of disease control (defined as a BVAS/WG  $\leq$  1 and daily prednisone dose  $\leq$  10mg) by month 4.

##### 15.1.2 Major relapse

Major relapse is defined as the development of a new or recurrent major disease activity item using the BVAS/WG that in the opinion of the investigator requires treatment with > prednisone 20mg/day for any period of time and/or increase in dose of immunosuppressive medication and/or addition or substitution of another immunosuppressive medication.

Subjects experiencing a major relapse will have met the end point of the trial. Further treatment decisions are made by the investigator and are not determined by the protocol. All patients will continue to be followed for safety purposes.

### 15.1.3 Minor relapse

Minor Relapse = "Any increase in disease activity that does not meet the definition of Major Relapse."

Although subjects experiencing a minor relapse will have met the trial end-point they will remain in the trial on the following protocol (Relapse Schedule): minor relapses will be treated with an increase in prednisone to 20 mg/day for 7 days, reducing by 2.5 mg every week back to 5 mg/day . Treatment of a minor relapse will be allowed only *once* during the trial period. At the time of a second minor relapse, further treatment decisions are made by local investigators and are not determined by the protocol. All patients will continue to be followed for safety purposes.

## 16 Statistics

### 16.1 Statistical Methods

The study will have a 24 month recruitment period. The minimum follow-up period will be 24 months of treatment plus 12 months post-treatment, totalling 36 months. The maximum follow-up period will be 24 months of treatment plus 24 months post-treatment, totalling 48 months.

The primary intention to treat analysis will be based on a Cox proportional hazard model. There will be a closed testing procedure, first the null hypothesis will be for a hazard ratio of 1 at all time points. If this is rejected at a 5% level then two further sub-hypotheses will be examined using time-varying covariates:

1. A hazard ratio of 1 up to 24 months post-randomisation (i.e. during treatment).
2. A hazard ratio of 1 after 24 months post-randomisation (i.e. post-treatment).

A detailed statistical analysis plan will be produced before the final data base lock and this plan will include sub-group analyses and handling of missing or spurious data.

### 16.2 Interim Analyses

No interim analyses are planned, but an independent Data Monitoring Committee (Data and Safety Monitoring Board) will be convened to review efficacy and safety data, and will advise on the need for any additional analyses or alterations to the conduct or even continuation of the trial if there are major safety concerns.

### 16.3 Number of Subjects to be Enrolled

Enrolment will be ongoing until at least 160 patients are randomised. It is anticipated 190 patients will be required to be recruited to meet the goal of 160 patients randomized. Any patients in the induction phase when enrolment is halted will continue to follow the protocol and be randomised if the relevant criteria are met.

A power of 90% is achieved under the alternative hypothesis of a hazard ratio of 0.42 at the 5% significance level with 58 observed relapses. Randomising 160 patients will achieve this over the course of the study assuming a drop-out rate up to 5% at 2 years and a relapse-free rate of 75% and 50% at 4 years in the experimental and control arms respectively.

Based on data from the Cambridge cohort study, the overall hazard ratio is estimated (95% confidence interval) as 0.230 (0.116, 0.458) based on 37 observed relapses. For the early period the hazard ratio estimate is 0.210 (0.098, 0.449) based on 30 observed relapses. For the late period the hazard ratio estimate is 0.323 (0.061, 1.729)



based on seven observed relapses. Hence the sample size/power calculations are robust as they are based on a hazard ratio of 0.42 under the alternative hypothesis; the value of 0.42 is at the upper end of the confidence intervals for the overall and early period hazard ratios from the pilot data. The projected drop-out rate is based on the recently published EUVAS IMPROVE trial (16). It justifies the assumption of a rate below 5% in the second year.

#### **16.4 Criteria for the Termination of the Trial**

The trial may be discontinued in the event of clear evidence of harm or benefit for one treatment regimen on the recommendation of the DMC/DSMB and in conjunction with the Trial Management Committee. Safety data will be reviewed by the DMC/DSMB on an annual basis. The trial is planned to close 36 months after the final patient is enrolled (common closing date).

#### **16.5 Procedure to Account for Missing or Spurious Data**

A detailed statistical analysis plan will be produced before the final data base lock and this plan will include sub-group analyses. The only aspect of missing data that will affect the primary analysis is the handling of patients who drop out before the scheduled study close; the process for handling such events is given in the definition of the primary endpoint in section 9.6.1.

#### **16.6 Definition of the End of the Trial**

The trial will end when the final patient has completed 12 months of follow up (has been in the trial for 36 months in total).

### **17 Data Handling and Record Keeping**

#### **17.1 CRF**

All data will be transferred into a Case Report Form (CRF) which will be anonymised. All trial data in the CRF must be extracted from and be consistent with the relevant source documents. The CRFs must be completed, dated and signed by the investigator or designee in a timely manner. It remains the responsibility of the investigator for the timing, completeness, legibility and accuracy of the CRF pages. The CRF will be accessible to trial coordinators, data managers and the investigators as required.

All CRF pages must be clear, legible and completed in black ink. Any errors should be crossed with a single stroke so that the original entry can still be seen. Corrections should be inserted and the change dated and initialled by the investigator or designee. If it is not clear why the change has been made, an explanation should be written next to the change. Typing correction fluid must not be used. Changes must not be made to the CRF pages once the original has been returned to the trial coordination centre.

Completed CRF pages should be returned to the trial coordinating centre within 2 weeks of the evaluations.

#### **17.2 Source Data**

To enable monitoring, audit and/or inspection the investigator must agree to keep records of all participating patients (sufficient information to link records e.g., CRFs, hospital records and samples), all original signed informed consent forms and copies of the CRF pages. Data sources will include patient medical records and on-line test results, patient questionnaires (SF-36, EQ5D, PROMIS) and flowsheets of blood results.

### **17.3 Data Protection**

All investigators and trial site staff involved in this trial must comply with the requirements of the EU General Data Protection Regulation and Data Protection Act 2018 or applicable local laws for sites outside the UK and Trust/Institution Policy with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

## **18 RITAZAREM Committees**

The NIH-sponsored VCRC Data and Safety Monitoring Committee will provide oversight of this study. This is a standing DSMB that provides such oversight for existing VCRC studies of vasculitis, including randomised controlled interventional studies. A comprehensive charter for this study will be drafted and implemented prior to the start of the study. It is anticipated that the DSMB will meet at least 6 monthly to discuss the study progress and more frequently, if needed.

The role of the Trial Steering Committee (TSC) (page 5) is to provide overall supervision of the study on behalf of Arthritis Research UK. The TSC will monitor the progress of the study and maximise the chances of completing the study within the agreed time scale and budget. The TSC will meet regularly via teleconference.

The Trial Management Committee (TMC) (page 5) is responsible for the design, conduct and overall management of the study. The members meet via regular teleconferences.

## **19 Ethical & Regulatory Considerations**

### **19.1 Consent**

The Informed Consent form must be approved by the EC and must be in compliance with ICH GCP, local regulatory requirements and legal requirements. The investigator must ensure that each trial participant is fully informed about the nature and objectives of the trial and possible risks associated with their participation.

The investigator or designee will obtain written informed consent from each patient before any trial-specific activity is performed. The informed consent form used for this trial and any change made during the course of this trial, must be prospectively approved by the EC. The investigator will retain the original of each patients signed informed consent form in the Investigator Site File (ISF).

Should a patient require a translation of the trial documentation by a locally approved interpreter/translator, it is the responsibility of the individual investigator to use locally approved translators.

All trial documentation in a different language (other than English), including the translation and back translation of documents must be reviewed and approved by the Sponsor prior to use. All sections of the approved documents must appear in the translation. The translated version must be appropriately dated and include version control.

### **19.2 Ethical Committee Review**

Ethical committee approval will be obtained before the start of the trial or implementation of any amendment, or use of any participant Information sheet, informed consent form and other relevant documents e.g., advertisements and GP information letters if applicable from the EC. All correspondence with the EC will be retained in the Trial Master File/Investigator Site File.

Annual reports will be submitted to the EC in accordance with national requirements. It is the Chief Investigators responsibility to produce the annual reports as required.

### **19.3 Regulatory Compliance**

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the relevant Competent Authority for example the MHRA or FDA. The protocol and trial conduct in the UK will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments. For sites outside the UK, the trial will be conducted in accordance with the applicable local regulatory requirements and laws.

Annual Safety Reports will be submitted to the relevant Competent Authority in accordance with national requirements. It is the Chief Investigators responsibility to produce the annual reports as required.

### **19.4 Trial Documentation Amendments**

Trial documentation amendments including protocol amendments must be reviewed and agreement received from the Sponsor for all proposed amendments prior to submission to the EC and/or relevant Competent Authority.

The only circumstance in which an amendment may be initiated prior to EC and/or relevant Competent Authority approval is where the change is necessary to eliminate apparent, immediate risks to the patients (Urgent Safety Measures). In the case, accrual of new patients will be halted until the EC and/or relevant Competent Authority approval has been obtained.

### **19.5 Peer Review**

The trial protocol has been designed by the Trial Management Committee. The protocol has been reviewed by representatives of Roche/Genentech. Input from members of the VCRC and EUVAS has been sought and incorporated. The DSMB also reviewed the protocol prior to finalisation.

### **19.6 Declaration of Helsinki and ICH Good Clinical Practice**

The trial will be performed in accordance with the spirit and the letter of the declaration of Helsinki, the ICH Good Clinical Practice Guidelines (CPMP/ICH/135/95), the protocol and applicable local regulatory requirements and laws.

### **19.7 GCP Training**

All trial staff must hold evidence of appropriate GCP training (or local equivalent) or undergo GCP training (or local equivalent) prior to undertaking any responsibilities on this trial. This training should be updated every 2 years or in accordance with your Trust/Institution's policy.

## **20 Sponsorship, Financial and Insurance**

The trial will be sponsored by Cambridge University Hospitals NHS Foundation Trust except in the US and Canada, where it will be sponsored by the University of Pennsylvania (North American Sponsor), Japan (Okayama University) and Ireland (University College Cork).

Funding sources for this trial include: Arthritis Research UK, U.S. National Institutes of Health, and Roche/Genentech, Japanese Ministry of Health, Labour and Welfare.

Cambridge University Hospitals NHS Foundation Trust, as a member of the NHS Clinical Negligence Scheme for Trusts, will accept full financial liability for harm caused to participants in the clinical trial caused through the clinical negligence of its employees and honorary contract holders. There are no specific arrangements for compensation should a participant be harmed through participation in the trial, but no-one has acted negligently.

## **21 Monitoring, Audit & Inspection**

The investigator must make all trial documentation and related records available should a CA Inspection occur. Should a monitoring visit or audit be requested, the investigator must make the trial documentation and source data available to the Sponsor's representative. All patient data must be handled and treated confidentially.

On-site monitoring for targeted SDV has been outsourced by the Sponsor. The Sponsor retains oversight of all trial activities via monitoring meetings with the CRO. Central monitoring and statistical analysis will be undertaken by the trial team at Addenbrooke's Hospital throughout the trial.

## **22 Protocol Compliance and Breaches of GCP**

The investigator must not implement any deviation from the protocol without formal written agreement from the Sponsor and Chief Investigator. If this necessitates a subsequent protocol amendment, or halt to the trial this should be submitted to the EC, CA & Trust/Institution for review and approval if appropriate.

Potential/suspected serious breach of GCP must be reported immediately to the Sponsor.

## **23 Publications Policy**

Ownership of the data arising from this trial resides with the Sponsor. On completion of the trial the data will be analysed and tabulated and a Clinical Study Report prepared by the Trial Management Committee. All investigators participating in the study will be credited. Anonymous Trial data will be shared with Roche/Genentech at three time points: when all patients have completed the induction phase; when all patients have completed the maintenance phase and on completion of the study. All publications need to be reviewed by the Sponsor before being submitted. The Sponsor will provide Roche with details of any publications or presentations for review 45 days in advance of submission, and 15 days in the case of abstracts.

## **24 Publications**

1. Watts RA, Suppiah R, Merkel PA, Luqmani R. Systemic vasculitis--is it time to reclassify? *Rheumatology (Oxford)*. 2011 Apr;50(4):643-5.
2. Falk RJ, Jennette JC. ANCA disease: where is this field heading? *J Am Soc Nephrol*. 2010 May;21(5):745-52. Epub 2010 Apr 15.
3. Watts RA, Scott DG. Epidemiology of the vasculitides. *Curr Opin Rheumatol* 2003;15:11-16.
4. Booth AD, Almond MK, Burns A, Ellis P, Gaskin G, Neild GH, et al. Outcome of ANCA-associated renal vasculitis: a 5-year retrospective study. *Am J Kidney Dis* 2003 Apr;41(4):776-84

5. Jayne D, Rasmussen N, Andrassy K, Bacon P, Tervaert JW, Dadoniene J, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med* 2003 Jul 3;349(1):36-44.
6. De Groot K, Harper L, Jayne DR, Flores Suarez LF, Gregorini G, Gross WL, Luqmani R, Pusey CD, Rasmussen N, Sinico RA, Tesar V, Vanhille P, Westman K, Savage CO; EUVAS (European Vasculitis Study Group). Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med*. 2009 May 19;150(10):670-80.
7. DeGroot K, Rasmussen N, Bacon PA, Tervaert JW, Feighery C, Gregorini G, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis & Rheumatism* 2005 Aug;52(8):2461-9.
8. Etanercept plus standard therapy for Wegener's granulomatosis. *N Engl J Med* 2005 Jan 27;352(4):351-61.
9. Seo P, Min YI, Holbrook JT, Hoffman GS, Merkel PA, Spiera R, Davis JC, Ytterberg SR, St Clair EW, McCune WJ, Specks U, Allen NB, Luqmani RA, Stone JH; WGET Research Group. Damage caused by Wegener's granulomatosis and its treatment: prospective data from the Wegener's Granulomatosis Etanercept Trial (WGET). *Arthritis Rheum*. 2005 Jul;52(7):2168-78.
10. Faurischou M, Westman K, Rasmussen N, de Groot K, Flossmann O, Höglund P, Jayne DR. Brief Report: long-term outcome of a randomized clinical trial comparing methotrexate to cyclophosphamide for remission induction in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum*. 2012 Oct;64(10):3472-7
11. Reff ME, Carner K, Chambers KS, Chinn PC, Leonard JE et al. Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. *Blood*. 1994; 83(2):435-445.
12. Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, Savage CO, Segelmark M, Tesar V, van Paassen P, Walsh D, Walsh M, Westman K, Jayne DR; European Vasculitis Study Group. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med*. 2010 Jul 15;363(3):211-20.
13. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, Kallenberg CG, St Clair EW, Turkiewicz A, Tchao NK, Webber L, Ding L, Sejismundo LP, Mieras K, Weitzenkamp D, Ikle D, Seyfert-Margolis V, Mueller M, Brunetta P, Allen NB, Fervenza FC, Geetha D, Keogh KA, Kissin EY, Monach PA, Peikert T, Stegeman C, Ytterberg SR, Specks U; RAVE-ITN Research Group. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med*. 2010 Jul 15;363(3):221-32.
14. Jones RB, Ferraro AJ, Chaudhry AN, Brogan P, Salama AD, Smith KG, Savage CO, Jayne DR. A multicenter survey of rituximab therapy for refractory antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum*. 2009 Jul;60(7):2156-68.
15. Smith RM, Jones RB, Guerry MJ, Laurino S, Catapano F, Chaudhry A, Smith KG, Jayne DR. Rituximab for remission maintenance in relapsing antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum*. 2012 Nov;64(11):3760-9.
16. Hiemstra TF, Walsh M, Mahr A, Savage CO, de Groot K, Harper L, Hauser T, Neumann I, Tesar V, Wissing KM, Pagnoux C, Schmitt W, Jayne DR. Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial. *JAMA*. 2010 Dec;304(21):2381-8.
17. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. *Internal Medicine*. 1916 Jun;17(6):863-71.

## 25. Appendices: 25.1 Appendix 1: Schedule of events

Study Date M=Month R = Randomisation	*Screen	**M0	M1.5	M3	M4 (R)	M8	M12	M16	M20	M24	M27	M30	M36	M42	M48
<b>Data Forms</b>															
Eligibility Review	X														
Informed Consent	X														
Demographics	X														
Weight	X				X		X			X			X		
Height	X														
Urinary HCG <sup>∞</sup>		X													
Baseline medical history	X														
Follow up			X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Comorbidities	X														
BVAS/WG		X	X	X	X	X	X	X	X	X	X	X	X	X	X
CDA		X			X		X			X			X	X	X
SF-36, EQ5D		X			X		X			X			X	X	X
PROMIS questionnaires		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event review		X	X	X	X	X	X	X	X	X	X	X	X	X	
<b>Clinical Labs ♦</b>															
FBC/CBC	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ESR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry (electrolytes, creatinine, LFTs)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CRP	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ANCA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lymphocyte markers		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunoglobulins		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatitis B <sup>≠</sup>	X														
<b>Research Specimens•</b>															
Serum		X			X	X	X	X	X	X	X	X	X	X	X
Plasma		X			X	X	X	X	X	X	X	X	X	X	X
DNA		X													
RNA		X			X					X			X		

\*\*There are also visits at weeks 1, 2, 3 and 4 for rituximab infusions, during which the Treatment Form is completed by the PI.

\*Please note, the screening visit and month 0 visit must take place within 2 weeks of each other.

♦Laboratory test results are permitted to be within  $\pm$  2 weeks of the date of the study evaluation.

•Please remember to take all biomarker samples *prior* to rituximab infusion.

The M48 assessments will be performed at the time of relapse or study termination/withdrawal

<sup>∞</sup> In women of child bearing potential

<sup>≠</sup>Hepatitis B screening by HBsAg and anti-HBcore Ab

<sup>±</sup>Withdrawn subjects will continue to follow the visit schedule