Statistical Analysis Plan

TRIAL FULL TITLE	An international, open label, randomised controlled trial comparing rituximab with azathioprine as maintenance therapy in relapsing ANCA-associated vasculitis
EUDRACT NUMBER	2012-001102-14
SAP VERSION	Maintenance Phase SAP v2.0
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TRIAL STATISTICIAN	Dr Simon Bond
TRIAL CHIEF INVESTIGATORS	Dr David Jayne and Dr Peter Merkel
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1 SAP Signatures

I give my approval for the attached SAP entitled RITAZAREM – Maintenance Phase SAP v2.0 dated 25th January 2021.

Chief Investigators

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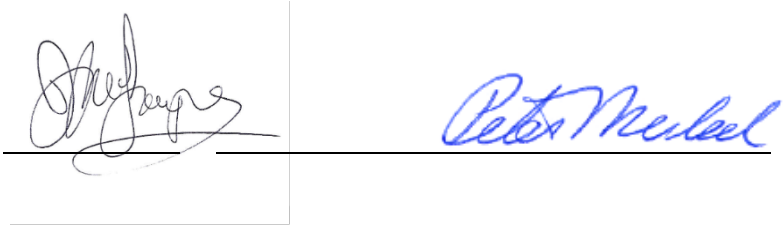
Signature: 

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3 Abbreviations and Definitions

3.1 Abbreviations

AAV	ANCA-associated vasculitis
AE	Adverse event
ALT	Alanine aminotransferase
ANCA	Auto-antibodies to neutrophils
anti-MPO	Myeloperoxidase antibodies
anti-PR3	Proteinase 3 antibodies
AST	Aspartate aminotransferase
ATG	Anti-thymocyte globulin
AUC	Area under the curve
BVAS/WG	Birmingham vasculitis activity score for Wegener's
CA	Competent authority
CCTU	Cambridge clinical trial unit
CD19	B-lymphocyte antigen CD19
CDA	Combined damage assessment index
CF	Conversion factor
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
CRF	Case report form
CRP	C-reactive protein
CVD	Cerebro-vascular disease
CYC	Cyclophosphamides
DSMB	Data safety monitoring board
ELISA	Enzyme-linked immunosorbent assay
ENT	Ear, nose, throat
EQ5D	A standardised instrument for use as a measure of health outcome
ESR	Erythrocyte sedimentation rate
EUDRACT	European Clinical Trials Database
EUVAS	European Vasculitis Study Group
FBC/CBC	Full/Complete blood count
GC	Glucocorticoids
GFR	Glomerular filtration rate
GEE	Generalised estimating equation
GPA	Granulomatosis with polyangiitis
HCG	Human chorionic gonadotrophin

IgG, IgA, IgM	Immunoglobulin G, A, M
IHD	Ischemic heart disease
IMP	Investigational medical product
IV	Intravenous
IVIG	Intravenous immunoglobulin
MedDRA	Medical dictionary for regulatory activities
MPA	Microscopic polyangiitis
PI	Principal investigator
PROMIS	Patient-reported outcomes measurement information system
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SF-36	Short form (36) health survey
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
VCRC	Vasculitis Clinical Research Consortium
WBC	White blood cell count
WG	Wegener's granulomatosis

3.2 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

4 Introduction

4.1 Preface

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.

4.2 Purpose of the analysis

This analysis will report on the maintenance phase of the trial (from randomisation to month 48 of follow-up). It will address the efficacy of rituximab compared to azathioprine in the prevention of disease relapse in patients with ANCA-associated vasculitis with relapsing disease.

5 Study Objectives and Endpoints

5.1 Study Objectives

(ICH E3; 8)

5.1.1 Primary objective

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

5.1.2 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.

5.2 Endpoints

(ICH E9; 2.2.2)

The final analysis will assess primary, secondary, and exploratory endpoints, which are described below for completeness. All endpoints to be assessed in the maintenance phase are described in sections 9 to 12.

5.2.1 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 (Table 1).

In the efficacy analysis, the date of the month 4 visit will be used as time-zero (i.e. randomisation). According to the protocol, patients might be randomised in advance of the month 4 visit (provided they achieved disease remission by the month 3 visit), however maintenance therapy (with either treatment) was not allowed to be administered before the month 4 visit[1].

[1] For a more in-depth description of randomisation procedures and trial's timelines, including definitions of the induction and maintenance phase, see Induction Phase SAP, section 9.1.1, and refer to the protocol, section 10.4.

Treatment duration is taken to be strictly 20 months post-randomisation, i.e. date of the month 4 visit + 20 months, and not the actual time of the month 24 visit when the last visit was administered. This affords a common timeline for all patients, irrespective of time slippages in the schedule of visits.

In the analysis, the censoring rules detailed in Table 1 will be implemented. Censoring time will be taken from the last assessment with no documented relapse (scheduled visit), the date of death (unscheduled visit) or the common close date. The time of relapse will be taken from the relapse form (unscheduled visit). Further particulars are detailed in section 10.3.

Table 1: Censoring rules

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

5.2.2 Secondary endpoints

1. Proportion of patients who maintain remission at 24 and 48 months[2].
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.

[2] Time measured from enrolment.

5.2.3 Exploratory endpoints

1. Health economic assessment based on EQ5D. 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.
2. 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.

The analysis of the following exploratory endpoints is not planned in this Statistical Analysis Plan; these endpoints may be explored in future analyses:

3. Serum rituximab levels and correlation with circulating B cell counts including key subsets and immunoglobulin levels.
4. Changes in ANCA titres (both anti-MPO and anti-PR3 subsets) in relation to treatment, response, and relapse.
5. HACA rate and level.
6. Serum will be stored for future biomarker studies.
7. mRNA will be stored for disease and inflammatory gene activation.
8. DNA will be stored for various studies.

6 Study Methods

6.1 General Study Design and Plan

(ICH E3; 9)

This is an international, multi-centre, open label, two-arm parallel study in patients with vasculitis. Following an induction phase where patients receive rituximab only, patients who have achieved remission in the induction phase will be randomised, 1:1, to receive fixed interval repeat rituximab dosing or azathioprine maintenance therapy. Those not in remission after the induction phase will not be randomised. The group receiving azathioprine will act as the control group.

Patients will be randomised using stratified block randomisation. 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).

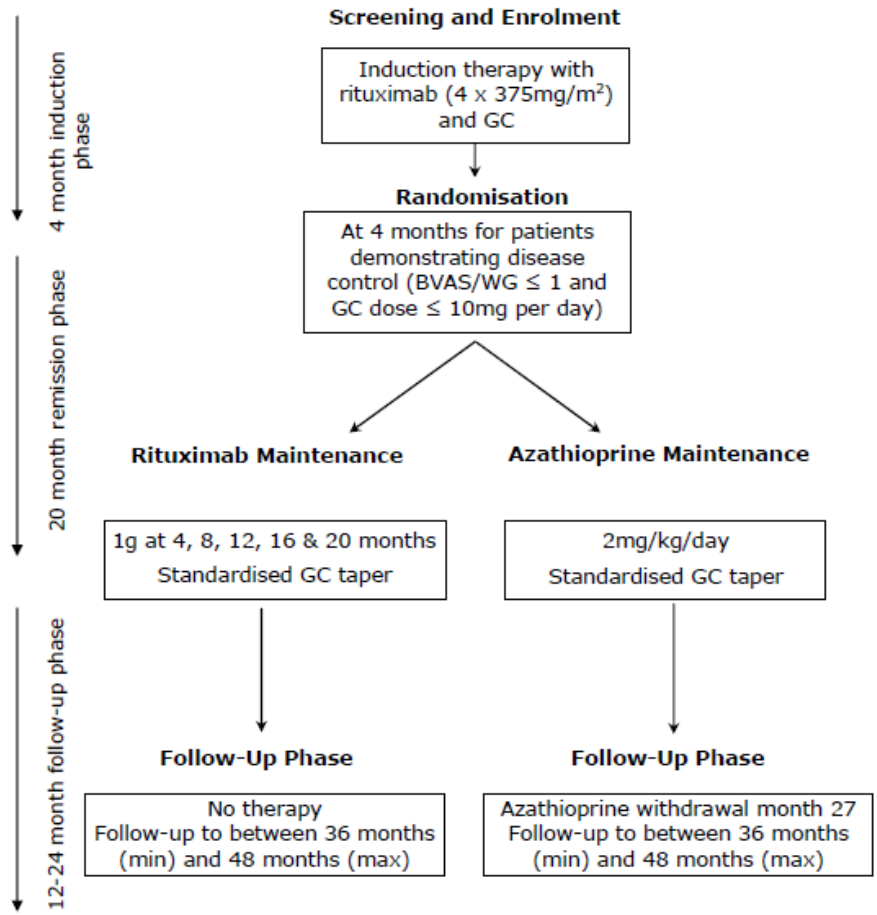


Figure 1: Study design flowchart

6.2 Inclusion-Exclusion Criteria and General Study Population

(ICH E3; 9.3. ICH E9; 2.2.1)

6.2.1 Inclusion Criteria

To be included in the trial the patients 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).

6.2.2 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 x109/l, haemoglobin < 7 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.

6.3 Randomisation and Blinding

(ICH E3; 9.4.3, 9.4.6. ICH E9; 2.3.1, 2.3.2)

This is an open-label (unblinded) study. Patients who achieved disease control by month 4 (BVAS/WG ≤ 1 and daily prednisone dose $\leq$ 10mg) will be randomised 1:1 to receive either rituximab or azathioprine. A blocked randomisation will be performed, using a block size of 6. 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).

Randomisation will be performed using a web-based system (TENALEA). This will be accessed by the principal investigator (PI) and suitably trained site staff though a secure, person specific log-in.

6.4 Study Schedule

(ICH E3; 9.5.1. ICH E9; 2.2.2)

Table 2 illustrate the schedule of events for the entire trial. The induction phase of the trial comprises the first 4 months from enrolment. At month 4 patients who have achieved remission are randomised to either maintenance therapy with rituximab or azathioprine. The maintenance phase of the trial, comprising 20

months of treatment and a 12-24 months follow up phase, commences at month 4 from enrolment.

Completed Case Report Forms (CRFs) are expected to be returned to the trial coordinating centre within 2 weeks of evaluation and the Data Manager routinely queries sites for missing/delayed forms.

Important notes regarding the schedule of events:

- The Screening and Month 0 visits must take place within 2 weeks of each other.
- The Treatment Form at Month 0 visit is completed by the PI at weeks 1, 2, 3 and 4 for rituximab infusion.
- Laboratory tests results are permitted to be within ± 2 weeks of the date of the study evaluation.
- Unscheduled assessments are performed at the time of relapse or study termination/withdrawal. Unscheduled assessment are retained for safety reviewing and not incorporated in the summary statistics of the scheduled visits.
- Biomarker research samples are taken prior to rituximab infusion.

Table 2: Time and events schedule

	Screening	Month 0	Month 1.5	Month 3	Month 4 (R)	Month 8	Month 12	Month 16	Month 20	Month 24	Month 27	Month 30	Month 36	Month 42	Month 48	Unscheduled Visit
Forms																
Enrolment	X															
Demographics	X															
Weight	X				X											
Height	X															
Urinary HCG		X														
Baseline Medical History	X															
Comorbidities	X															
Concomitant Medication	X	X	X	X	X											X
Follow Up		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Treatment		X			X	X	X	X	X							
BVAS/WG		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CDA		X			X		X			X			X	X	X	X
SF-36, EQ5D		X			X		X			X			X	X	X	X
PROMIS questionnaires	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event review		X	X	X	X											

	Screening	Month 0	Month 1.5	Month 3	Month 4 (R)	Month 8	Month 12	Month 16	Month 20	Month 24	Month 27	Month 30	Month 36	Month 42	Month 48	Unscheduled Visit
Clinical Labs																
FBC/CBC	X	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	X
Chemistry (electrolytes, creatinine, LFTs)	X	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	X
ANCA	X	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	X
Lymphocyte markers		X	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	X
Hepatitis B	X															
Research samples																
Serum		X			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	X
DNA		X														
RNA		X			X					X			X			

7 Sample Size

(ICH E3; 9.7.2. ICH E9; 3.5)

Enrolment will be ongoing until 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.

8 General Considerations

8.1 Timing of Analyses

The trial is planned to close 36 months after the final patient is enrolled. All those eligible who have been randomised and entered into the maintenance phase of the trial will be followed until the last patient to be enrolled has completed 36 months from study entry. The maintenance phase analysis will be performed after the last enrolled patient (excluding drop-outs) has reached Month 36 visit, this is the common close of the trial.

The statistical analysis plan (SAP) will be approved according to the requirements of CCTU/SOP023 before database lock. Permission to lock the database will be requested from the chief investigator (CI) using CCTU/FRM094, and the data programmers will deposit the data in a folder to which the trial statistician is given restricted access (following CCTU/SOP057).

An independent adjudication committee (blinded to treatment) will review all relapses prior to analysis and any changes deemed necessary will be recorded and included into MACRO database[3]. Data queries will be referred to the data management team for resolution (using CCTU/TPL064).

8.2 Analysis Populations

(ICH E3; 9.7.1, 11.4.2.5. ICH E9; 5.2)

Prior to database lock, each patient will be included or excluded from each analysis population defined below. The trial management team will agree on inclusion to each population prior to the analysis.

8.2.1 Safety Population

The safety population comprises all consented subjects enrolled in the trial, regardless of whether they achieved remission and were randomised at month 4. The treatment group will be analysed as randomised (rituximab or azathioprine), patients who were enrolled but not randomised will be classified as belonging to the induction group (induction).

8.2.2 Full Analysis Population (randomised patients)

The full analysis population is defined as all participants who achieved remission in the induction phase of the trial and were randomised to the maintenance phase, regardless of whether they actually received any maintenance treatment. The treatment group will be analysed as randomised (rituximab or azathioprine).

8.2.3 Per Protocol Populations (maintenance and follow-up)

The per-protocol populations includes all randomised patients who have not deviated from protocolised treatment either during the maintenance phase of the trial (from randomisation to month 24) or follow-up (from randomisation to end of

[3] Details of data utilised in the formal relapse adjudication process can be found in a separate document [reference].

trial). Thus two per-protocol populations will be defined: maintenance compliant and follow-up compliant. It is assumed that maintenance compliance is necessary for follow-up compliance, and the two per-protocol populations will be defined using this inclusive criterion. Patients who withdraw from trial or from protocolised treatment will be assessed for compliance up to the point of their withdrawal.

Compliance to the protocol of all trial treatments (rituximab, azathioprine, methotrexate, and mycophenolate Mofetil) will be considered, according to the randomised treatment allocation (rituximab or azathioprine schedules). Compliance to prednisolone schedule is not considered. In the case of treatment of relapse, what treatments are in accordance with the protocol are detailed in Section 11.6 of the protocol:

> *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.*

Due to the complexity of the data involved, each patient course of treatments will be assessed individually and an independent adjudication committee (blinded to subject ID) will determine each patient's inclusion/exclusion in the per protocol population base on data taken from the Treatment Form, Follow-Up Form and Relapse Form. It is expected that these data be reviewed concurrently with the formal adjudication of relapses and incorporated into the trial's database prior to hard lock[4].

[4] Details of data used to assess inclusion in the per-protocol populations can be found in document "Medication Compliance v 1.0" and a separate report will be produced by the independent adjudication committee detailing each patient's assessment and outcome.

8.4 Covariates and Subgroups

(ICH E3; 9.7.1, 11.4.2.1. ICH E9; 5.7)

In all formal hypothesis testing, the models will be adjusted for the following covariates:

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

the same stratifying variables used for randomisation.

8.5 Missing Data

(ICH E3; 9.7.1, 11.4.2.2. ICH E9; 5.3. EMA Guideline on Missing Data in Confirmatory Clinical Trials)

The sample size of non-missing values will be reported for summary tables. It is expected that the incidence of missing data will be low. Missing data will be assumed to be missing at random. In practice, missing values will be ignored for calculation of summary statistics. The number of non-missing values will be reported and used instead of the population or subgroup size as a denominator as needed. The overall size of the population, including missing values will be reported within the title of the table or figure to convey the amount of missing data.

Due to logistic reasons, the PROMIS questionnaire was not administered to the full study population. The number of sites and patients not taking part will be noted.

8.6 Interim Analyses and Data Monitoring

(ICH E3; 9.7.1, 11.4.2.3. ICH E9; 4.1, FDA Feb 2010 “Guidance for Industry Adaptive Design Clinical Trials for Drugs and Biologics”)

No interim analyses are planned.

An independent Data Monitoring Committee (Data and Safety Monitoring Board, DSMB) will be convened to review efficacy and safety data on a quarterly basis, 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.

8.8 Multi-centre Studies

(ICH E3; 9.7.1, 11.4.2.4. ICH E9; 3.2)

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. Plans are for approximately 50-60 centres to recruit patients.

Data is recorded in a single MACRO database across all study centres. Study centre will form part of the information recorded, so that it can be identified during the statistical analysis. Recruitment and patient's retention rate will be reported by site and grouped by country.

8.9 Multiple Testing

(ICH E3; 9.7.1, 11.4.2.5. ICH E9; 2.2.5)

For the primary outcome of the trial, 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).

9 Summary of Study Data

All continuous variables will be summarised using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. Summary tables will be structured with a column for each treatment arm ("Azathioprine", "Rituximab",), as well as a total column. Additionally some summary tables (e.g. baseline demographic) will also be presented split by induction regimen ("1A", "1B"). All tables will be annotated with the total population size relevant to that table/treatment, including any missing observations. In general, where appropriate, data will be listed sorted by site, subject and visit.

Only deviations from the general overview will be noted in the subsequent sub-sections within section 9.

9.1 Subject Disposition

9.1.1 Visit dates

The three phases of the trial are defined as follows:

1. Induction phase: enrolment to Month 4 (inclusive)
2. Maintenance phase: Month 4 to Month 24 (inclusive)
3. Follow-up phase: Month 24 (exclusive) to Month 36/42/48 (common close)

A target randomisation date (*RandomDate*) four months in the future was generated at enrolment to help local sites organise rituximab or azathioprine supply for the maintenance phase. Patients could be randomised from 14 days before to 14 days after Month 4 visit. If patients attended their Month 3 visit and were in remission, then they could be randomised up to 14 days before Month 4. Those not in remission at Month 3 were reassessed at Month 4 and, if they entered remission, were then randomised and commenced allocated therapy within the next 14 days. Those not in remission at Month 4 were not randomised (even if they had been considered in remission at Month 3 visit) and treated at the investigator's discretion, follow-up data continued to be collected unless consent was withdrawn. **Maintenance therapy (with either treatment) was not administered before the Month 4 visit.** Consequently, the month 4 visit will be considered as both the end of the Induction Phase of the trial and the beginning of the Maintenance Phase of the trial. It will be used as time zero for the primary endpoint of the Maintenance Phase (time to disease relapse from randomisation).

When calculating time elapsed in days, months or years (e.g. when calculating time from randomisation), full dates (yyyy-mm-dd) appropriately formatted, will be converted to the number of days since 1970-01-01, with negative values for earlier dates, following the default representation of dates in the R language[5]. A full year is taken to be 365.25 days long, a standardisation that approximates for the

[5] https://stat.ethz.ch/R-manual/R-devel/library/base/html/Dates.html

occurrence of leap years. A month is taken to be 1/12th of a full year. First day of the month/year will be used for fuzzy dates.

9.1.2 Subject disposition

Patient disposition will be determined using information collected in the following CRF forms:

- Withdrawal Form (v2)
- Withdrawal from Trial Form (v3)
- Withdrawal from Protocolised Treatment Form (v3)
- Death Form
- End of Trial Form.

The Withdrawal Form v2 in version 2.0 of the CRF was superseded by two new forms (Withdrawal from Protocolised Treatment v3 and Withdrawal from Trial Form v3) in version 3.0 of the CRF, approved 16 Dec 2015. This allowed a clearer distinction between those patients discontinuing protocolised treatment, who remain under long term follow up, and those withdrawing from the trial completely, who have no further data collected.

Table 3 lists the criteria used to reconcile the two types of withdrawal forms, based on the reason of discontinuation given in v2 of the form. V3 criteria will be used in the report.

When either “Investigator decision” or “Other” was selected in the v2 form, sites were asked to confirm whether the patient was withdrawn from study or from protocolised treatment by adding the text “STUDY” or “PROTOCOL” respectively in the relevant “Please Specify” text box.

When “Participant decision” was selected, sites were asked to confirm that this indeed meant the patient withdrew consent to further participation in the study, or otherwise to reclassify the withdrawal reason as “Other” and add “PROTOCOL” in the relevant text box.

Table 3: Withdrawal forms harmony

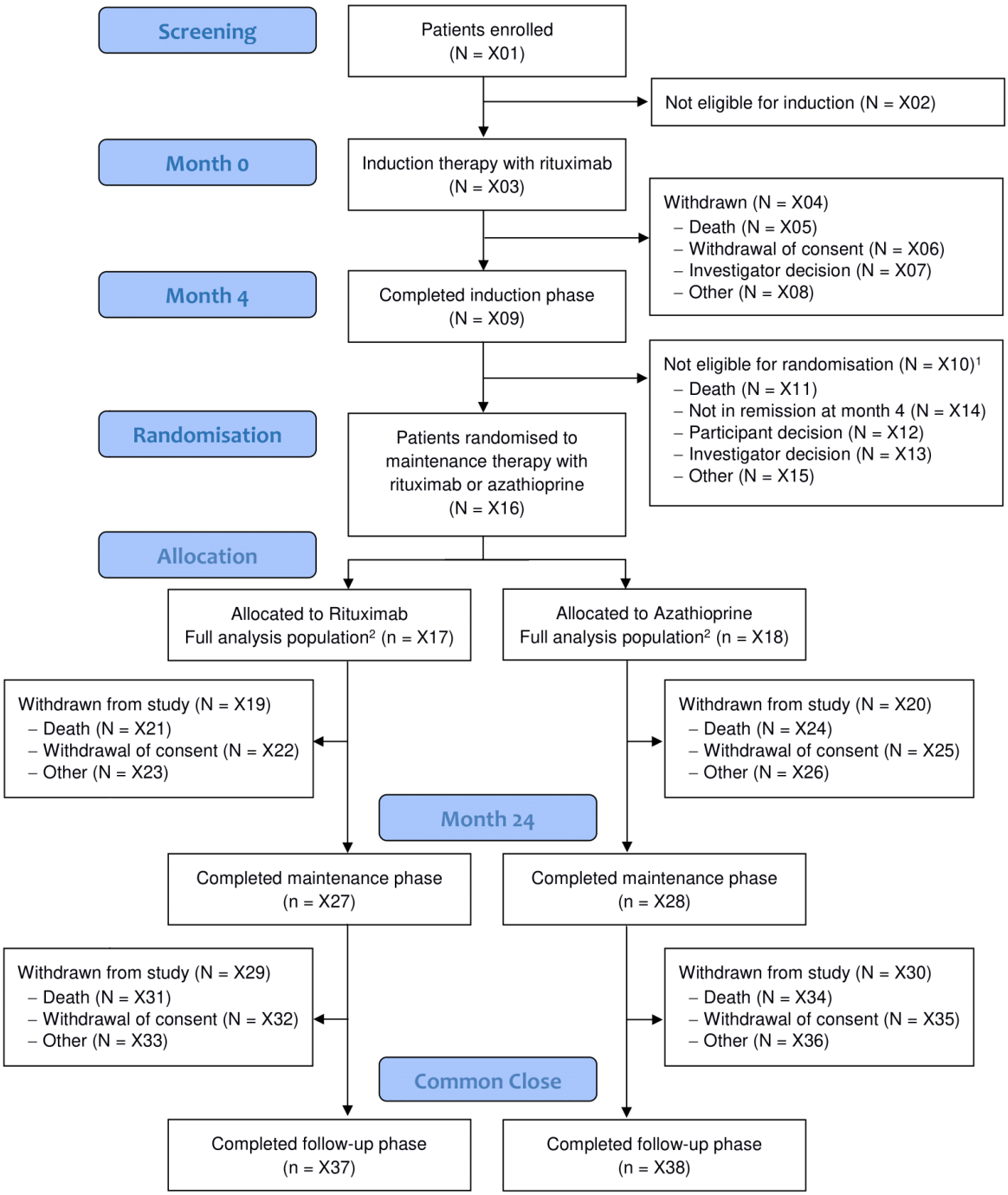
V2		V3	
Withdrawal		**Withdrawal from Study**	**Withdrawal from Protocolised Treatment**
WDReason	*Text box*	*WDRea1*	*WDPRO2*
1-Not in Remission at Month 4			1-Not in Remission at Month 4
2-Participant decision		2-Withdrawal of consent	
3-Investigator decision	"STUDY"	3-Other	
	"PROTOCOL"		3-Investigator decision
4-Relapse			2-Relapse
5-Death		1-Death	
6-Other	"STUDY"	3-Other	
	"PROTOCOL"		4-Other

Data management will check each form to ensured consistency and completeness across all the forms.

9.1.3 CONSORT diagram

A CONSORT diagram (Figure 2) will be presented to show patient disposition within the study.

Figure 2: Example CONSORT diagram for the trial



[1] Patients not eligible for randomisation remain under long-term follow up, unless they withdraw consent.
[2] The full analysis population includes all randomised patients, including those subsequently withdrawn.

9.2 Derived variables

The following derived variables will be calculated from source variables recoded in MACRO:

1. Baseline Medical History
    - **Prior disease duration (years)** – calculated from the date of diagnosis to the date of screening. First day of the month/year will be used for fuzzy dates. Date difference in years will be rounded to 1 decimal figure.
    - **Historical ANCA positivity (Positive both/anti-PR3/anti-MPO, Negative, Missing)** – a categorical variable, calculated from variables in the Enrolment Form recording historical positivity to anti-PR3 and anti-MPO ANCA. Calculated according to the following rules (if only one value is confirmed and the other is missing, the missing one is assumed to be negative):

Table 4: Historical ANCA positivity

		Anti-MPO	
		Positive	Negative
Anti-PR3	Positive	Positive for both anti-PR3 & anti-MPO	Positive for anti-PR3
	Negative	Positive for anti-MPO	Negative

    - **Total number of Body Systems affected (integer)** – a count of the number of organ manifestations reported in the Baseline Medical History Form (max count = 11). The variable will be reported both as categorical and continuous.
2. Prior treatment
    - **Cyclophosphamide (Yes/No)** – categorical variable determining whether subjects have ever received any cyclophosphamide treatment, either IV or oral. Calculated from oral and IV cyclophosphamide variables; patients can receive either treatment or both. In incomplete cases the subject will be regarded as not having received the treatment specified.
    - **Cumulative cyclophosphamide dose (g) –** continuous variable, sum of the Oral and IV cyclophosphamide doses (g); patients can receive either

treatment or both. In incomplete cases the subject will be regarded as not having received the treatment specified (i.e. dose = 0 g).

- **Rituximab or cyclophosphamide (Yes/No)** – categorical variable determining whether subjects have ever received any rituximab or cyclophosphamide treatment, either IV or oral. Calculated rituximab and cyclophosphamide variables; patients can receive either treatment or both. In incomplete cases the subject will be regarded as not having received the treatment specified.
- **Number of prior immunosuppressants (excluding glucocorticoids) (integer)** – a count of the number of prior immunosuppressants (excluding glucocorticoids) received by each subject. The following treatments are included: cyclophosphamide (Oral or IV), rituximab, azathioprine, methotrexate, mycophenolate mefotil, IVIG, anti-TNFs, and other immunosuppression listed in the Baseline Medical History Form. In incomplete cases the subject will be regarded as not having received the treatment specified. The variable will be reported both as categorical and continuous.

3. Disease Activity (BVAS/WG)
    - **BVAS/WG status (categorical)** – Disease status is determined from section 12 of the BVAS/WG form. At any given visit each patient is assigned a current disease status: "Severe flare/new disease", "Limited flare/new disease", "Persistent disease", "Remission". If multiple statuses are selected on the form a hierarchical classification is employed: "Remission" excludes all others, "Severe flare/new" trumps "Limited flare/new" and "Persistent" is trumped by all others. The data manager is responsible for the consistency of the data & raises queries accordingly (in particular it is expected that “Remission” be mutually exclusive of all other selections).
4. Disease related assessment (CDA)
    - **Total CDA score (integer)** – Accrual of damage as measured by the combined damage assessment (CDA) score. Each persistent or new occurrence of damage is recorded as “Yes” and given a score of 1. The cumulative accrual of damage is obtained by summing across the

different types of damage to get an overall score (max score = 64)[6]. The variable will be reported both as categorical and continuous.

- **Change in total CDA score between month 4 and month 12 (integer)** – difference in Total CDA score between month 4 (randomisation) and month 12, calculated for complete-case records only. The variable will be reported both as categorical and continuous.
- **Change in total CDA score between month 4 and month 24 (integer)** – difference in Total CDA score between month 4 (randomisation) and month 24, calculated for complete-case records only. The variable will be reported both as categorical and continuous.
- **Change in total CDA score between month 4 and month 36 (integer)** – difference in Total CDA score between month 4 (randomisation) and month 36, calculated for complete-case records only. The variable will be reported both as categorical and continuous.
- **Change in total CDA score between month 4 and month 48 (integer)** – difference in Total CDA score between month 4 (randomisation) and month 48, calculated for complete-case records only. The variable will be reported both as categorical and continuous.
- **Change in total CDA score between month 24 and month 36 (integer)** – difference in Total CDA score between month 24 (end of maintenance treatment) and month 36, calculated for complete-case records only. The variable will be reported both as categorical and continuous.
- **Change in total CDA score between month 24 and month 48 (integer)** – difference in Total CDA score between month 24 (end of maintenance treatment) and month 48, calculated for complete-case records only. The variable will be reported both as categorical and continuous.

5. Treatment Exposure (Treatment Form)

[6] A different scoring system from the one used in the Induction phase report is employed. This new scoring system is based on COMBIVAS's VDI (Vasculitis Damage Index) form. The new scoring system has a maximum score of 64, compared to the Induction phase report one that had a maximum score of 110. For comparison new CDA scores for the Induction phase months (visits Month 0 and Month 4) will be included in this report. Further details on how the CDA score is computed can be found in section 9.8.

- **Total maintenance rituximab dose (mg) –** cumulative rituximab dose across the maintenance phase of treatment only[7], from the Treatment Form of months 4, 8, 12, 16 and 20. Missing data (due to early withdrawal or any other reason –e.g. missing form) will be ignored (i.e. it's assumed no treatment was given, 0 mg).
- **Overall full rituximab treatment – maintenance (Yes/No)** – categorical variable, determining whether the subject has received all five full rituximab infusions as per protocol. Subjects are assumed to have followed protocol unless deviations were explicitly recorded in the Treatment form (i.e. "Treat6" = 1), any recorded deviation is considered an overall non-compliance, while missing forms are ignored.
- **Number of full rituximab infusions administered (integer) –** calculated across the maintenance phase of treatment, from the Treatment form of month 4,8,12,16 and 20. Counts explicitly the number of months when rituximab treatment was administered according to protocol. Thus "3 doses" would mean that 3 infusions administered were given as per protocol. Missing forms (NA) are ignored.
- **Total maintenance IV methylpredniso(lo)ne dose (mg)** – cumulative IV methylpredniso(lo)ne dose across the maintenance phase of treatment only[8], from the Treatment form. Missing data (due to early withdrawal or any other reason –e.g. missing form) will be ignored (i.e. it's assumed no treatment was give, 0 mg).

6. Treatment exposure (Follow Up Form)
    - **Average predniso(lo)ne dose (mg/day) –** average predniso(lo)ne dose, from randomisation to the end of trial, using the most recent daily dose as recorded in the Follow Up form at month 4, 8, 12, 16, 20, 24, 27, 30, 36, 42, and 48. If predniso(lo)ne treatment was explicitly recorded as not given in the Follow Up Form (i.e. FUp1a1= "No") then a dose = 0 mg/day will be implied, while missing data (due to early withdrawal or any other reason –e.g. missing form) will be ignored.

[7] A separate variable in the Follow Up form reports cumulative rituximab dose at 24 months, which includes doses administered during the induction phase.

[8] A separate variable in the Follow Up form reports cumulative IV methylpredniso(lo)ne dose at 24 months, which includes doses administered during the induction phase

- **Average predniso(lo)ne dose (mg/day) in the maintenance phase** – as above but calculated using the most recent daily dose as recorded in the Follow Up form at month 4, 8, 12, 16, 20, and 24 only.
- **AUC of predniso(lo)ne dose (mg)** – Area under the curve of predniso(lo)ne dose, calculated using the most recent daily dose as recorded in the Follow Up form at month 4, 8, 12, 16, 20, 24, 27, 30, 36, 42, and 48 employing a vertical step function and assuming a month to be 30 days. Missing data will be assumed to have a value of 0 mg/day.
- **AUC of predniso(lo)ne dose (mg) in the maintenance phase** – as above but calculated using the most recent daily dose as recorded in the Follow Up form at month 4, 8, 12, 16, 20, and 24 only.
- **Average azathioprine dose (mg/day)** – average azathioprine dose, from randomisation to the end of trial, using the most recent daily dose as recorded in the Follow Up form at month 4, 8, 12, 16, 20, 24, 27, 30, 36, 42, and 48. Missing data (due to early withdrawal or any other reason – e.g. missing form) will be ignored.
- **Average azathioprine dose (mg/day) in the maintenance phase** – as above but calculated using the most recent daily dose as recorded in the Follow Up form at month 4, 8, 12, 16, 20, and 24 only.
- **Average methotrexate dose (mg/week)** – average methotrexate dose, from randomisation to the end of trial, using the most recent daily dose as recorded in the Follow Up form at month 4, 8, 12, 16, 20, 24, 27, 30, 36, 42, and 48. Missing data (due to early withdrawal or any other reason –e.g. missing form) will be ignored.
- **Average methotrexate dose (mg/week) in the maintenance phase** – as above but calculated using the most recent daily dose as recorded in the Follow Up form at month 4, 8, 12, 16, 20, and 24 only.
- **Average mycophenolate mofetil dose (mg/week)** – average mycophenolate mofetil dose, from randomisation to the end of trial, using the most recent daily dose as recorded in the Follow Up form at month 4, 8, 12, 16, 20, 24, 27, 30, 36, 42, and 48. Missing data (due to early withdrawal or any other reason –e.g. missing form) will be ignored.
- **Average mycophenolate mofetil dose (mg/week) in the maintenance phase** – as above but calculated using the most recent daily dose as recorded in the Follow Up form at month 4, 8, 12, 16, 20, and 24 only.

- **Number of oral immunosuppressants (azathioprine, methotrexate and mycophenolate mofetil) (integer)** – counts the number of treatments of oral immunosuppressants (either azathioprine, methotrexate and mycophenolate mofetil) administered per patient at each visit, during the maintenance phase and overall (from randomisation to the end of trial). Missing data will be ignored.

7. Clinical Laboratory Evaluations
    - **ANCA status (Positive Both/anti-PR3/anti-MPO, Negative, Unknown)** – a categorical variable, calculated from variables in the Clinical Laboratory Test Form recording ANCA positivity (anti-PR3 and anti-MPO) at each visit. Calculated according to the following rules:

Table 5: ANCA Status

		Anti-MPO		
		Positive	Negative	Not measured
Anti-PR3	Positive	Positive PR3 & MPO	Positive PR3	Positive PR3
	Negative	Positive MPO	Negative	Unknown
	Not measured	Positive MPO	Unknown	Unknown

Table 6: Details of formulas for derived variables

Variable name	Label	Type	Original variables (MACRO ShortCode)	Formula
MHDuration	*Prior disease duration*	Real	MHDat1, Visit1	Date difference (years)
HisANCA	*Historical ANCA positivity*	Category	MHEli1, MHEli2	See Table 4 for details
BLM_Score BLM_Score_cat	*Total number of Body Systems affected*	Integer/ Category	BLM_* variables	Sum
MHCycl	*Total cyclophosphamide*	Category	MHTre3, MHTre4	if either = 1 then => 1 (Yes) else => 0 (No)
MHCyclDose	*Cumulative cyclophosphamide dose*	Real	MHCyc1, MHIVC1	Sum
MHRitCyc	*Previous treatment with rituximab or cyclophosmaphide (either IV or oral)*	Category	MHTre5, MHCycl	if either = 1 then => 1 (Yes) else => 0 (No)
MHImmN MHImmN_cat	*Number of prior immunosuppressants*	Integer/ Category	CumCyclo, MHTre5, MHTre6, MHTre7, MHTre8, MHTre11, MHTre12, MHImS1, MHImS2, MHImS3, MHImS4, MHImS5, MHImS6	Sum
BVASStatus	*Disease status*	Category	BVAS12a, BVAS12b, BVAS12c, BVAS12d	Hierarchical order, categories evaluated in order, from the most specific to the most general: 1. Remission 2. Severe flare 3. Limited flare 4. Persistent
CDAScore CDAScore_cat CDAScore_grp	*Total CDA score*	Integer/ Category	selected variables of CDA Form (see section 9.8)	Sum
CDADiff CDADiff_cat	*Change in total CDA score between month 4 and month 12, month 24, month 36 & month 48. Change in total CDA score between*	Integer/ Category	CDAScore	Difference

	month 24 and month 36 & month 48			
TreatRituxSum	*Total rituximab dose (mg)*	Real	TreatTotalRitux	Sum
TreatRituxPrtcol	*Overall full rituximab treatment*	Category	TreatAdmnProtcol	Yes if sum(TreatAdminProtocol="Yes")=5
TreatRituxMonths	*Number of full rituximab infusions*	Integer/ Category	TreatAdmnProtcol	count(TreatAdminProtocol="Yes")
TreatMPredDose	*Total IV methylpredniso(lo)ne dose (mg)*	Real	TreatMPredDose	Sum
PredMean PredMean24	*Average predniso(lo)ne dose (mg/day) - (Overall /Maintenance)*	Real	FUp1aPredDose	Average If FUp1a1 then Fu1aPredDose=0
PredAUC PredAUC24	*AUC of predniso(lo)ne dose (mg) - (Overall /Maintenance)*	Real	FUp1aPredDose	Vertical step function, assumes month=30days
AZAMean AZAMean24	*Average azathioprine dose (mg/day) - (Overall /Maintenance)*	Real	FUp1cAzathiDose	Average
MTXMean MTXMean24	*Average methotrexate dose (mg/week) - (Overall /Maintenance)*	Real	FUp1dMTXDose	Average
MMFMean MMFMean24	*Average mycophenolate mofetil dose dose (mg/week) - (Overall /Maintenance)*	Real	FUp1eMMFDose	Average
N.Month N.overall N.maint	*Number of oral immunosuppressants*	integer	Azathioprn follwup FUp1dMTX FUp1eMMF	group by subject & month
ANCA	*ANCA Status*	Category	CLAnt5 & CLAnt7 CLAnt9 & CLAnt11 CLAnt13 & CLAnt15 CLAnt1_2 & CLAnt3_2	See Table 5 for details

9.3 Protocol Deviations

Protocol deviations in the administration of treatments (rituximab and GCs) are detailed in section 9.9.

9.4 Demographic and Baseline Variables

Demographic details and subject characteristics, as specified in the Enrolment and Baseline Medical History Forms (Demography section), will be recorded at the screening visit and entered in the MACRO database.

The following demographic and baseline variables will be summarised in accordance with section 9 using the full analysis population. Frequency tables will be presented by treatment allocation ("Azathioprine", "Rituximab") and further sub-divided by induction regimen at enrolment ("1A", "1B").

9.4.1 Demographics

- Age (years), coarsening into ranges:
  - Under 18
  - 18–64
  - 65–85
  - Above 85
- Sex (M/F)
- Race (White/Black/Asian/Hispanic/Other)
- Weight (kg), converting from imperial units if necessary (1 lb = 2.205 Kg) and rounding to 1 decimal figure
- Height (cm), converting from imperial units if necessary (1 inch = 2.54 cm) and rounding to 1 decimal figure

9.4.2 Enrolment characteristics

- Body Surface Area[9] (m^2, 2 decimal figures)
- Predniso(lo)ne induction regimen (1A/1B)
- ANCA type (anti-PR3/anti-MPO)
- Relapse type (Severe/Non severe)
- Induction dose of Rituximab (mg/infusion)

9.4.3 Stratification variables

[9] Calculated using the Du Bois formula (14)

The Enrolment Form records the stratification variables at baseline (Month 0): prednisolone induction regimen, ANCA type, and relapse severity. The following frequency tables will be summarised in accordance with section 9:

- Relapse severity (Severe/Non-severe) stratified by prednisolone regimen (1A/1B).
- ANCA type (anti-PR3/anti-MPO) stratified by prednisolone regimen (1A/1B).
- Relapse severity (Severe/Non-severe) stratified by ANCA type (anti-PR3/anti-MPO).

Corresponding mosaic plots will also be produced.

9.5 Concurrent Illnesses and Medical Conditions

Any relevant medical history, as specified in the Baseline Medical History Form, will be recorded at the screening visit and entered in the MACRO database.

The following baseline medical history variables will be summarised in accordance with section 9 using the full analysis population. Frequency tables will be presented by treatment allocation (“Azathioprine”, “Rituximab”) and further sub-divided by induction regimen at enrolment (“1A”, “1B”).

9.5.1 Baseline Medical History

- Prior disease duration (years) – derived variable, details in section 9.2
- Historical ANCA positivity – derived variable, details in section 9.2
- Historical organ involvement, broken down by Body System and abnormality type, (counts):
  - Constitutional Symptoms
  - Joints
  - Skin
  - Mucous membranes/Eyes
  - Ear/Nose/Throat
  - Heart
  - Gastrointestinal tract
  - Lungs
  - Kidneys
  - Nervous system
  - Other

  - Total number of Body Systems affected – derived variable, details in section 9.2
- Co-morbidities (counts):
  - Hypertension
  - Ischemic Heart Disease (IHD)
  - Chronic Lung Disease (COPD)
  - Cerebrovascular Disease (CVD)
  - Cancer
  - Venus Thromboembolism
  - Diabetes Mellitus

9.6 Prior and Concurrent Medications

Previous medication history to treat vasculitis as specified in the Baseline Medical History Form (Medication History section) will be recorded at the screening visit and entered in the MACRO database.

The following baseline medical history variables will be summarised in accordance with section 9 using the full analysis population. Frequency tables will be presented by treatment allocation (“Azathioprine”, “Rituximab”) and further sub-divided by induction regimen at enrolment (“1A”, “1B”).

9.6.1 Prior treatment

Number of patients who have ever received the following as a treatment for vasculitis:

- Methylprednisolone
- Prediso(lo)ne
- Oral Cyclophosphamide
- IV Cyclophosphamide
- Cyclophosphamide (CYC) – derived variable, details in section 9.2
- Rituximab
- Azathioprine
- Methotrexate
- Mycophenolate Mofetil
- Sulfamethoxazole/Trimethoprim
- Plasma Exchange

- IVIG
- Anti-TNFs
- Other immunosuppression

Doses for the following treatments:

- Rituximab (mg)
- Oral Cyclophosphamide (g)
- IV Cyclophosphamide (g)
- Cumulative cyclophosphamide dose (g) – derived variable, details in section 9.2

Total counts of the following treatments:

- Number of prior immunosuppressants (excluding glucocorticoids) – derived variable, details in section 9.2

9.6.2 Concomitant Medication

Any relevant concomitant medication prescribed during the trial will be recorded in the Concomitant Medication Form at Screening, months 0 to 48 and Unscheduled visit if applicable[10]. The data will be entered in the MACRO database and retained for safety monitoring. Data will be reported as table listings per patient, per study visit. The following information, when available, will be reported:

- Medication name (generic names only)
- Category (Anticoagulant/Antiplatelet, IVIg, Antimicrobial, Other)
- Dose (units)
- Frequency (one daily, twice daily, three times daily, four times a day, alternate days, weekly, other, as required)
- Comments

9.7 Disease activity assessment (BVAS/WG)

The Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG) will be used to record disease activity (1).

[10] Concomitant medication from Screening to Month 4 visit were recorded in the Induction Phase analysis and report.

The BVAS/WG Form, automatically scored by MACRO[11], will be reported at Month 4, 8, 12, 16, 20, 24, 27, 30, 36, 42 and 48, using the full analysis population. The following variables will be summarised in accordance with section 9.

- The total count of Body Organ System involvement:
    1. General
    2. Cutaneous
    3. Mucous membranes/eyes
    4. Ear, nose & throat (ENT)
    5. Cardiovascular
    6. Gastrointestinal
    7. Pulmonary
    8. Renal
    9. Nervous system
    10. Other (all item's descriptions will be listed, by subject ID and visit)
- Total number of items:
    1. Major New/Worse
    2. Minor New/Worse
    3. Major persistent
    4. Minor persistent
- Total major items – calculated by MACRO
- Total minor items – calculated by MACRO
- Total BVAS/WG score – calculated by MACRO
- Current disease status – derived variable, details in section 9.2:
    1. Severe flare/new disease
    2. Limited flare/new disease
    3. Persistent disease
    4. Remission
- Physician's global assessment (PGA)

9.8 Disease related assessment (CDA)

The Combined Damage Assessment (CDA) Index will be used to record organ damage that has occurred in patients since the onset of vasculitis. Accrual of

[11] https://onlinelibrary.wiley.com/doi/epdf/10.1002/1529-0131%28200104%2944%3A4%3C912%3A%3AAID-ANR148%3E3.0.CO%3B2-5

damage as measured by the CDA score. Each persistent or new occurrence of damage is recorded as "Yes" and given a score of 1. The cumulative accrual of damage is obtained by summing across the different types of damage to get an overall score. CDA should never decrease, and items that are recorded at one visit should always be recorded at subsequent visits.

The CDA Form will be scored by cumulative sum of each of the Body Organ Systems detailed below, assigning a value of 1 for each item ticked as present ("Yes" checkbox ticked). Only the listed items contribute to the specified Body Organ System, non-listed items will be ignored. The "No" checkboxes will also be ignored: items are assumed to be not present unless the "Yes" checkbox has been explicitly ticked.

The CDA Form will be reported at Month 4, 12, 24, 36, 42 and 48 visits, using the full analysis population. The following CDA variables will be summarised in accordance with section 9.

- Damage to each Body Organ System, reported as a categorical variable (yes/no) surmising whether any listed sub-item is reported (i.e. "No" means a score of zero):
  a. **Musculoskeletal,** max score = 5
     1 - Significant muscle atrophy or weakness (any item)
     2 - Deforming/erosive arthritis
     3 - Osteoporosis/vertebral collapse
     4 - Avascular necrosis
     5 - Osteomyelitis
  b. **Skin/Membranes**, max score = 3
     1 - Alopecia
     2 - Cutaneous ulcers
     3 - Mouth ulcers
  c. **Ocular**, max score = 7
     1 - Cataract
     2 - Retinal changes or Retinal artery occlusion or Retinal vein occlusion
     3 - Optical nerve atrophy
     4 - Low vision or Diplopia
     5 - Blindness in one eye (left or right)
     6 - Blindness in second eye (both)
     7 - Orbital wall destruction

d. ENT, max score = 6

1 - Sensorineural hearing loss or Conductive hearing loss (Ear section)

2 - Chronic rhinitis/crusting (Nose section)

3 - Nasal bridge collapse/saddle nose or Nasal septal perforation (Nose section)

4 - Chronic sinusitis (Sinuses section)

5 - Subglottic stenosis (no surgery) (Subglottic stenosis section)

6 - Subglottic stenosis (surgery) (Subglottic stenosis section)

e. Pulmonary, max score = 7

1 - Pulmonary hypertension

2 - Pulmonary fibrosis

3 - Pulmonary infarction

4 - Pleural fibrosis

5 - Chronic asthma

6 - Chronic breathlessness

7 - Irreversible loss of lung function

f. Cardiac, max score = 7

1 - Angina or Percutaneous coronary intervention

2 - Myocardial infarction

3 - Coronary artery bypass graft

4 - Cardiomyopathy (NYHA Class I/II or NYHA class III/IV)

5 - Valvular Disease

6 - Pericarditis or Pericardectomy

7 - Hypertension (any item)

g. Vascular Disease, max score = 8

1 - Absent pulses in 1 limb

2 - 2nd episode of absent pulses in 1 limb

3 - Major vessel stenosis

4 - Claudication > 3 months

5 - Minor tissue loss

6 - Major tissue loss

7 - Subsequent major tissue loss

8 - Deep venous thrombosis or Complicated venous thrombosis

h. Gastrointestinal, max score = 4

1 - Gut infarction/resection

2 - Mesenteric insufficiency/pancreatitis

3 - Esophageal stricture/surgery

4 - Chronic peritonitis

i. Renal, max score = 3

1 - Estimated/measured GFR<50%

2 – Proteinuria (any item)
3 – End-stage renal disease or Dialysis

j. **Neuropsychiatric**, max score = 8
1 – Cognitive impairment (Psychiatric section)
2 – Major psychosis (Psychiatric section)
3 – Seizures (Neurological section)
4 – Cerebrovascular accident (Neurological section)
5 – 2nd cerebrovascular accident (Neurological section)
6 – Cranial nerve lesion (Neurological section)
7 – Sensory polyneuropathy (any item) or Motor Neuropathy (Neurological section)
8 – Transverse myelitis (Neurological section)

k. **Other**, max score = 6
1 – Gonadal failure (Premature ovarian failure or Azoospermia)
2 – Marrow failure (Refractory cytopenia or Myelodysplastic syndrome)
3 – Diabetes mellitus
4 – Chemical cystitis (any item) (Other section)
5 – Malignancy (Bladder cancer or Cervical cancer or Hemotopoetic malignancy or Solid tumour malignancy)
6 – Other (Other section)

- **Total CDA score, max = 64**[12] – derived variable, details in section 9.2. The variable will be reported both as continuous and categorical, coarsening into ranges:
  - less than 5
  - 5–10
  - 11–15
  - 16–20
  - greater than 20

- **Change in total CDA score between month 4 and month 12** – derived variable, details in section 9.2
- **Change in total CDA score between month 4 and month 24** – derived variable, details in section 9.2
- **Change in total CDA score between month 4 and month 36** – derived variable, details in section 9.2

[12] A different scoring system from the one used for the Induction Phase report is employed here to calculate an overall CDA score. The new scoring system is based on COMBIVAS VDI (Vasculitis Damage Index) form. A comparison between the old and new system for the Induction Phase will be presented.

- **Change in total CDA score between month 4 and month 48** – derived variable, details in section 9.2
- **Change in total CDA score between month 24 and month 36** – derived variable, details in section 9.2
- **Change in total CDA score between month 24 and month 48** – derived variable, details in section 9.2

9.9 Treatment Compliance

Compliance to treatment during the maintenance phase of the trial was assessed based on information collected in the Treatment and Follow Up forms. A comprehensive overview of the process involved is described in a separate document[13]. All randomised patients (full analysis population) were assessed by an independent committee for compliance to allocated treatment during the active maintenance phase (from randomisation to month 24) and during follow-up (from month 24 to end of trial). Outcomes were recorded into a spreadsheet sent to data management to be added to the main MACRO data download.

The following variables found in the spreadsheet will be summarised in accordance with section 9:

- Maintenance compliance (Yes/No) & reasons for non-compliance
- Follow-up compliance (Yes/No) & reasons for non-compliance

9.10 Treatment Exposure

In the maintenance phase, all patients allocated to rituximab treatment received rituximab 1000 mg x 1 dose at months 4, 8, 12, 16 and 20 and glucocorticoids. Patients randomised to the control arm will receive oral azathioprine, to be taken daily, with a target dose of 2mg/kg. The maximum daily dose allowed is 200mg. The maximum treatment period is 27 months, with tapering after month 24[14]. In the event of azathioprine intolerance (see section 11.2.i of the protocol), methotrexate 25 mg/week will be substituted for patients with GRF > 50 ml/min, and mycophenolate Mofetil will be substituted for patients with GRF < 50 ml/min.

9.10.1 Rituximab treatment

[13] See *Medication Compliance.docx*

[14] See section 11.2 of the protocol for further details of azathioprine administration.

The Treatment form records details of rituximab treatment, at months 4, 8, 12, 16 and 20, as recorded by the PI. The form will be reported at each time point using the full analysis population. The following variables will be summarised in accordance with section 9:

- Rituximab dose (mg)
- Rituximab administered according to protocol (Yes/No)
- Reasons for non-compliance, counts:
  a) Rituximab not administered as IgG < 3g/L
  b) Incomplete
  c) Interrupted
  d) Other

Reasons given for incomplete/interrupted/other treatment non-compliance will be listed per patient, per visit.

In addition, total cumulative rituximab dose after 24 months as recorded in the Follow Up form as well as the following derived variable (details in section 9.2) will be calculated across the maintenance therapy period[15] and summarised in accordance with section 9:

- Cumulative rituximab dose (mg) up to 24 months[16]
- Total rituximab dose in maintenance phase (mg) – derived variable, details in section 9.2
- Overall full rituximab treatment (Yes/No) – derived variable, details in section 9.2
- Number of full rituximab infusions – derived variable, details in section 9.2

9.10.2 Glucocorticoid treatment

Concomitant glucocorticoid (GC) treatment in the maintenance phase was permitted as follows. 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 (Table 7), and continues at 5 mg daily until month 16. GC dose is then reduced to 2.5mg/day and completely withdrawn at month 20.

[15] From randomisation to month 24 from enrolment inclusive.

[16] As recorded in the Follow Up form at month 24, it includes induction phase doses.

Table 7: CG Schedule 2

	Maintenance Schedule Daily Prednisolone dose (mg)
Week	
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 greater than 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.

For all patients follow-up daily dose of prednisolone was recorded at each visit in the maintenance phase (months 4, 8, 12, 16, 20, 24, 27, 30, 36, 42 and 48) in the Follow-Up Form. Section 1 and 2 of the form will be reported at each time point using the full analysis population. The following variables will be summarised in accordance with section 9:

- Number of patients receiving the following treatment since the last evaluation:
  a) Predniso(lo)ne
  b) Rituximab[17]
  c) Azathioprine
  d) Methotrexate
  e) Mycophenolate Mofetil
  f) Pneumocystis prophylaxis
     i) Co-trimoxazole

[17] Rituximab treatments as recorded in the Follow-Up Form. Includes rituximab received as part of protocol and outside of protocol.

ii) Dapsone
iii) Other
g) Aspirin
h) Warfarin

- Doses of the following treatments at each visit:
  a) Predniso(lo)ne (mg/day)
  b) Azathioprine (mg/day)
  c) Methotrexate (mg/week)
  d) Mycophenolate Mofetil (g/day)
- In addition, the following derived variables (details in section 9.2) will be calculated across the maintenance phase (from month 4 to month 24) and overall (from randomisation to the end of the trial):
  a) Average predniso(lo)ne dose (mg/day)
  b) AUC of predniso(lo)ne dose (mg/day)
  c) Azathioprine (mg/day)
  d) Methotrexate (mg/week)
  e) Mycophenolate Mofetil (g/day)

IV methylpredniso(lo)ne treatment, as recorded in the Treatment Form, will be reported at each time point using the full analysis population. The following variables will be summarised in accordance with section 9:

- IV methylpredniso(lo)ne treatment (Yes/No)
- Dose (mg)
- Cumulative IV methylpredniso(lo)ne dose (mg) up to 24 months
- Total IV methylpredniso(lo)ne dose in maintenance phase (mg) – derived variable, details in section 9.2

Reasons given for significant deviations from the GC protocol (defined as a +/- 25% of the protocol specified dose, for period greater than 2 weeks) will be listed per patient, per visit in the appendix. Additionally a frequency table of the number of predniso(lo)ne deviations per patient per visit will be provided.

A count of the number of patients whose dose of azathioprine, methotrexate, or mycophenolate was changed will be reported per visit, and overall. Details (date of dose change, clinical side effects/intolerances, laboratory abnormalities, other

reasons) as recorded in Section 2 of the form will be listed per patient per visit in the appendix.

10 Efficacy Analyses

Efficacy analyses will be performed on the full analysis population. Additionally the primary efficacy analysis will be presented for the two per-protocol populations (maintenance and follow-up compliant populations).

10.1 Primary efficacy analysis

The primary efficacy outcome measure of the trial is relapse-free survival, where a relapse is either major or minor (see definitions above). **The primary analysis will be a Cox regression model adjusted for the stratification factors (ANCA type, relapse severity and prednisone induction regimen) for the difference in the distribution of relapse-free survival between the rituximab arm and the azathioprine (control) arm (two-sided at α-level of 5%)**. Assuming a proportional hazard holds, the hazard ratio together with the 95% confidence interval will be estimated using a Cox regression model adjusted for the stratification factors.

There will be a closed testing procedure, first the null hypothesis will be teste for a hazard ratio of 1 at all time points. If this is rejected at a 5% level then two further sub-hypothesis will be examined using time-varying covariates:

1. A hazard ratio of 1 up to 20 months post-randomisation (i.e. during treatment).
2. A hazard ratio of 1 after 20 months post-randomisation (i.e. post-treatment).

Kaplan-Meier estimates for relapse-free survival at 24 and 48 months[18] and median relapse-free survival with the corresponding 95% confidence intervals by treatment allocation will be presented.

Additional analyses will consider in turn the interaction of treatment with each of the three stratification variables, i.e. ANCA type, relapse severity and induction regimen. Frequency tables and Kaplan-Meier plots, as well hazard ratios and 95%

[18] Time measured from enrolment, in reality this corresponds to 20 months and 44 months post-randomisation.

confidence intervals of a Cox proportional hazard model including interactions will be presented. These results are to be taken as exploratory only, as these analyses were not planned in the protocol, are likely under-powered and are not adjusted for multiple comparisons.

The following tables and figures will be reported, taking into account events occurring after randomisation (i.e. excluding the induction phase):

- No. of relapses:
  a) by type (major or minor)
  b) by phase (during treatment or post-treatment)
  c) per participant
- No. of participants with a relapse (major or minor)[19] by type at:
  a) All time points
  b) During treatment (up to month 20 post-randomisation)
  c) Post-treatment (after 20 months post-randomisation)
- Kaplan-Meier curve with at risk population, from randomisation
  i) Overall curve
  ii) Stratified by ANCA type, relapse severity and induction regimen
- Median relapse-free survival (95% confidence interval)
- 24-month and 48-month[20] relapse-free survival rate
- Hazard ratios[21] at:
  a) All time points
  b) During treatment (up to month 20 post-randomisation)
  c) Post-treatment (after 20 months post-randomisation).

10.2 Secondary outcomes

These analyses will mirror those described for the primary endpoint above with the secondary outcomes as the end points of the analyses. These are only intended to be exploratory given the power of the study:

1. Time to a major or second minor relapse.

[19] Primary endpoint.

[20] Time measured from enrolment, in reality this corresponds to 20 months and 44 months post-randomisation.

[21] Close testing procedure will be implemented.

2. Time to a major relapse[22].

10.3 Censoring

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:

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

In the efficacy analysis, the date of the month 4 visit will be used as time-zero (i.e. randomisation). According to the protocol patients might be randomised in advance of the month 4 visit (provided they achieved disease remission by the month 3 visit), however maintenance therapy (with either treatment) was not allowed to be administered before the month 4 visit[23].

Treatment duration is taken to be strictly 20 months post-randomisation, i.e. date of the month 4 visit + 20 months, and not the actual time of the month 24 visit when the last visit was administered. This affords a common timeline for all patients, irrespective of time slippages in scheduled visits.

In the analysis, in accordance with the protocol, the censoring time will be taken to be:

1. If no baseline assessment: time of randomisation,
2. Otherwise, the latest date between:

[22] This endpoint was not originally included in the protocol (v4.0).

[23] For a more in-depth description of randomisation procedures and trial's timelines, including definitions of the Induction and Maintenance Phase, see Induction Phase SAP, section 9.1.1, and refer to the protocol, section 10.4.

a. the last completed scheduled visit (or the last completed scheduled visit before more than two missed visits)
b. death due to other causes (unscheduled visit)
c. the common close date (for those patients whose end of trial visit, either month 42 or month 48, would have occurred after the common close)[24].

The time of relapse will be taken from the relapse form (unscheduled visit).

Patients will be considered to have had an event (e.g. first relapse) if the event occurred, either:

1. prior to the censoring date
2. within 12 months (& 14 days, allowing for a 2 weeks slippage) of the censoring date.

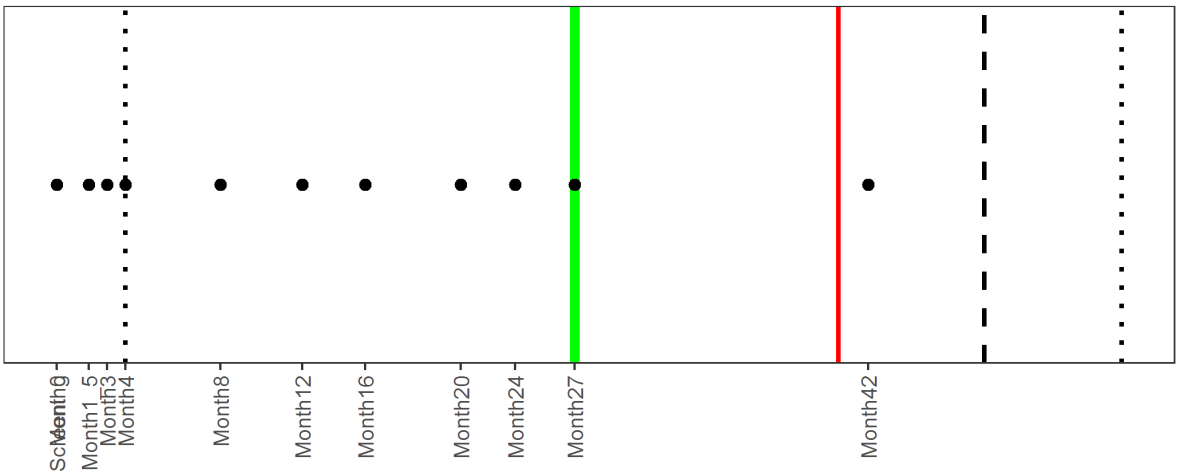
This is on account of the last censoring rule in the table above: in the case of death or progression after more than one missed visit, the patient is to be censored at the date of the last assessment with no documented relapse.

Looking at the schedule of visits in the trial, 12 months is the longest span of time for 3 consecutive visits (month 30, month 36, month 42) thus any event occurring after 12 months of the censoring date will have occurred after more than a missed visit and should be disregarded (the patient is censored instead at the last scheduled visit before the missed visits).

This is the case with patient AS3-001, who had a relapse after more than one missed visit. The relapse occurred 408 days after month 27 visit, the patient having missed month 30 and month 36 visits. The event was therefore disregarded and the patient censored at month 27. See below an illustration of the patient visits scheduled (black dots: attended visits; green line: censoring date; red line: relapse; dashed line: end of trial date; dotted lines: randomisation and common close date)[25].

[24] It was agreed with sites that patients who had not completed their month 42 or month 48 visit by the time of the common close would be followed up until the common close date.
[25] A copy of similar illustration is retained for each patient for further inspection.

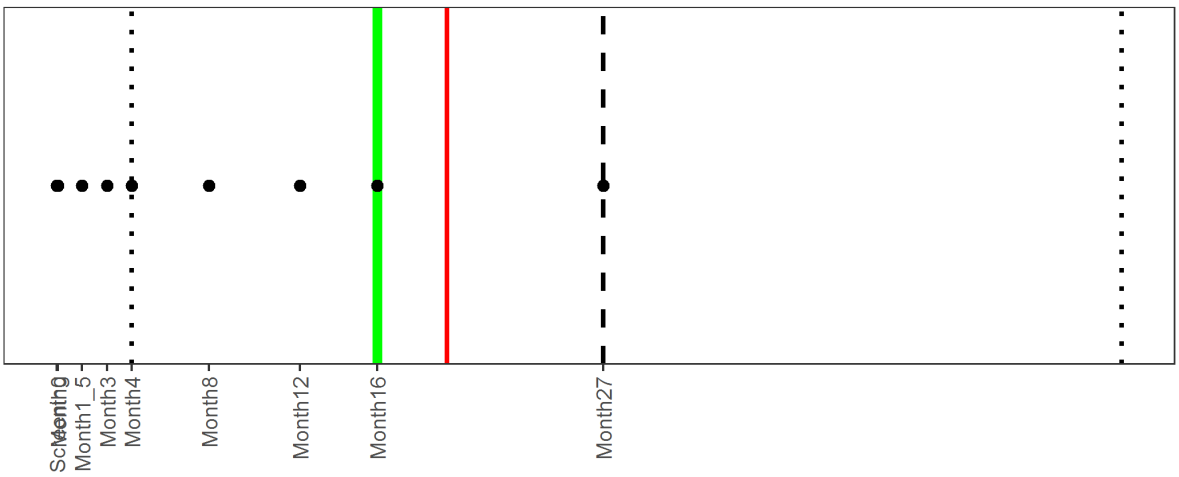
AS3001
End of Trial: 03/06/2019 (two missed visits)



The shortest time span for 3 consecutive visits (month 24, month 27, month 30) is 6 months, thus any event occurring within 6 months has occurred with no more than one missed visit and should be retained (patient relapsed).

Thus in the case of patient N15-001, who had a relapse after 108 days of month 16 visit and subsequently missed both visits month 20 and month 24, the relapse occurred within the 12 months of the censoring date and indeed was found not to have occurred after more than one missed visit. Consequently the event was retained and the patient was counted as “relapsed” on this date.

N15001
End of Trial: 19/01/2017 (two missed visits)



Events happening between 6 and 12 months of the censoring date require further investigation. Depending on the last visit before any missing gaps, these events could fall after either one or two missed visits (e.g. an event 200 days after month 30 would happen after one missed visits, while an event 200 days after month 24

would happen after two missed visits). Thus the 12 months threshold is not strong enough to determine the outcome. The analysis code explicitly checks for such instanced, which must then be adjudicated independently. None were found.

Likewise, by inspection, all deaths were by other causes and occurred before more than one missed visit, and thus no special considerations are needed (all patients who died where censored at the time of death).

An independent adjudication committee (blinded to treatment) will review all relapses and deaths. This will ensure that “deaths due to relapse” are recorded in the trial database as a relapse (i.e. there exists a corresponding relapse form). The censoring date of “deaths due to other causes” will also be verified in cases with more than one missed visit.

11 Safety Analyses

11.1 Serious Adverse Events

All serious adverse events (SAE), including serious adverse drug reactions will be reported according to guidance in sections 13.4 and 13.5 of the protocol.

All Serious Adverse Events must be reported to the central trials co-ordinator or trial physician in Cambridge within 24 hours of the investigator becoming aware of the event and will be entered in a separate database. 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. Monthly SAE listings, blinded to treatment allocation, will be reviewed by both CIs however. The Sponsor has to keep detailed records of all SAEs reported to them by the trial team.

Frequency tables for all SAEs will be reported using the safety population and stratified by both treatment arm and induction regimen as well as their interaction. Separate tables will report:

- SAEs where date of onset occurred after randomisation[26]
- SAEs occurring during treatment (up to 20 months after randomisation)

[26] SAEs occurring during the induction period (prior to randomisation) were reported separately, see Induction Phase SAP and report.

- SAEs occurring after treatment ended (from 20 months after randomisation onwards)

Additionally, counts of subjects and events stratified by relatedness (Unrelated/Related) will be reported, grouped by System Organ Class, High Level Group Term and Preferred Term based on the MedDRA code.

11.2 Adverse Events

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 hypogammaglobulinemia (IgG <5g/l)
3. Occurrence of hypogammaglobulinemia (IgG <3g/l)
4. An adverse event that results in a change in dose of trial IMPs (rituximab, azathioprine, methotrexate or mycophenolate mofetil (MMF))
5. An adverse event that results in the addition of a relevant concomitant medication (see section 13.3.1 for list)
6. An adverse event manifested by the occurrence of a relevant laboratory abnormality (see section 13.3.2 for list)
7. New malignancies

Infections are recorded using the Infection Form and entered in the MACRO database. Frequency tables for serious and non-serious infections with date of onset occurring in the maintenance phase will be reported using the safety population and stratified by induction regime. The number of patients with newly occurring IgG < 5g/L and newly occurring IgG < 3g/L will be reported. Additionally, counts of subjects and events for non-serious infections will be reported, grouped by High Level Group Term and Preferred Term based on the MedDRA code.

Individual listings of infections are reported to the DSMB and reviewed quarterly.

New malignancies are recorded using the New Malignancy Form and entered in the MACRO database. All instances of new malignancies detected during the maintenance phase will be reported as individual listings sorted per patient by site. The following detail will be reported:

- Treatment arm
- Malignancy Detection date
- Malignancy Diagnosis date
- Malignancy Site
- Malignancy Type
- Malignancy Reoccurrence
- Malignancy Treatment (Surgery, Radiotherapy, Chemotherapy, Other)
- Malignancy Associated with SAE (Yes/No)
- Malignancy Comments

11.3 Hypogammaglobulinemia

Hypogammaglobulinemia is defined as a value of IgG < 5 g/L measured at any stage of the trial (including visits occurring during the induction period). Frequency tables for hypogammaglobulinemia will be reported using the full analysis population and stratified by treatment arm and:

a) Induction regimen (1A/1B)
b) ANCA type (anti-PR3/anti-MPO)
c) Relapse type (Severe/Non severe)
d) Previous treatment with rituximab (Yes/No)
e) Previous treatment with cyclophosphamide (Yes/No)
f) Previous treatment with rituximab or cyclophosphamide (Yes/No)
g) Baseline (Screening/Month 0) IgG (g/L).

A logistic regression analysis will be carried out to predict hypogammaglobulinemia, using the above as predictor variables. Individual univariate models and a multivariate model will be considered. Outcomes (Estimate, 95% CI and P-value) will be surmised in tabular form.

These analysis are to be considered exploratory only, as they were not specified in the protocol and the data is observational.

11.4 Deaths

All deaths within the trial (whether considered a SAE or not) will be reported to the Chief Investigator and the Sponsor using the relevant Death Form. Deaths occurring in the maintenance phase will be documented and reported separately to SAEs. Total number of deaths per site will be reported in accordance with section 9 using

the full analysis population. Additionally the following causes of death will be summarised:

All causes of death that apply:

- Infection
- Active vasculitis
- Pulmonary embolus
- Withdrawal of renal replacement therapy
- Acute myocardial infarction
- Sudden death (cause unknown)
- Cerebrovascular disease
- Cancer
- Unknown
- Other

Missing data will be treated as cause of death not applicable.

11.5 Pregnancies

Pregnancy or inadequate contraception in women of childbearing potential forms one of the exclusion criteria for the study. A pregnancy test was performed at baseline for all women of childbearing potential to assess eligibility. Data was retained for safety and will not be reported.

All pregnancies within the trial (either the trial participant or the participant's partner) will 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 adverse event (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. Data from the Pregnancy Reporting Form of all pregnancies occurring in the maintenance phase will be reported as listings sorted by site.

11.6 Clinical Laboratory Evaluations

Clinical laboratory tests will be performed at baseline (either at Screening or Month 0, taking the latest value if assessment were performed at both visits), and at each visit in the maintenance phase (months 4, 8, 12, 16, 20, 24, 27, 30, 36, 42 and 48). Measured values will be recorded in the Clinical Laboratory Tests Forms and entered

in the MACRO database. Data management will ensure that any missing values are due to the test not being performed ("Not measured" thick-box).

The following variables will be summarised in accordance with section 9 using the full analysis population. Missing values will be assumed to be "not measured" without cross-referencing the relevant tick-box.

- Clinical Labs
  - Haemoglobin (g/dL)
  - Platelets (cells x 10^9/L)
  - WBC (cells x 10^9/L)
  - ESR (mm/h)
  - Creatinine (µmol/L)
  - CRP (mg/L)
  - ALT (U/L)
  - AST (U/L)
- ANCA
  - Anti-PR3 (positive/negative)
  - Anti-MPO (positive/negative)
  - ANCA status – derived variable, details in section 1.1
- Lymphocyte markers
  - CD19 (cells x 10^9/L and %)
- Immunoglobulins
  - IgG (g/L)
  - IgM (g/L)
  - IgA (g/L)

Table 8 lists the preferred unit for reporting and the multiplicative conversion factor (CF)[27] employed for those clinical labs collected in the CRF using different measurement units.

[27] Conversion factors taken from http://www.scymed.com/en/smnxfd/smnxfdac.htm

Table 8: Conversion factors

Variable	Original unit	CF	Reporting unit
Haemoglobin	g/L	0.1	g/dL
Haemoglobin	mmol/L	1.611344	g/dL
WBC	cells x 10^3/mm^3	1	cells x 10^9/L
Creatinine	g/dL	88.42 x 10^3	µmol/L
Creatinine	mg/dL	88.42	µmol/L
CRP	mg/dL	10	mg/L
CD19	cells x 10^3/mm^3	1	cells x 10^9/L
CD19	cells/µL	0.001	cells x 10^9/L
IgG	mg/dL	0.01	g/L
IgM	mg/dL	0.01	g/L
IgA	mg/dL	0.01	g/L

Laboratory values outside the ranges detailed in Table 8 will be considered un-physiological, and will be considered outliers and excluded from the analysis. All such values will be listed in a separate table (grouped by item, subject, and visit) and queried by the data manager.

Table 9: Physiological ranges for laboratory tests

Variable	Minimum	Maximum	Reporting unit
Haemoglobin	5	20	g/dL
Platelets	5	900	cells x 10^9/L
WBC	1	40	cells x 10^9/L
ESR	0	200	mm/h
Creatinine	30	1500	µmol/L
CRP	0	600	mg/L
ALT	0	1000	U/L
AST	0	1000	U/L
CD19	0	5	cells x 10^9/L
CD19	0	100	%
IgG	0	25	g/L
IgM	0	8	g/L
IgA	0	8	g/L

Values reported with a < or > sign will not be included in the analysis, except for measurements reported within the lower bounds specified in Table 10: these will be censored to "0" and included in the analysis accordingly. Excluded values will be listed in a separate table (grouped by item, subject, and visit). A table will report the number of censored values, grouped by item, subject, and visit.

Table 10: Lower bounds of clinical labs measurements

Variable	Sign	Value	Unit
CRP	<	5	mg/L
CD19	<	1	%
CD19	<	0.02	cells x 10^9/L
IgM	<	0.3	g/L
IgA	<	0.3	g/L

12 Quality of Life Analysis

Health-related quality of life and patient-reported outcomes will be assessed using questionnaires. Exploratory analyses of Quality of Life data outcomes as planned in the protocol are to be carried out by the Cambridge team. Details are outside the scope of this SAP.

12.1 EQ5D

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.

The answers to each question will be reported at Month 4, 12, 24, 36, 42 and 48 visit, using the full analysis population. EQ5Q profiles will be summarised into a utility score for each patient using the EQ-5D-3L Index Calculator[28]. Index scores are based on general population valuation surveys that use the TTO or VAS method for the UK (12). The following variables will be summarised in accordance with section 9:

1. Mobility
2. Self-Care
3. Usual Activities

[28] https://www.economicsnetwork.ac.uk/health/EQ_5D_index_calculator.xls

4. Pain/Discomfort
5. Anxiety/Depression
6. Overall index score (TTO and VAS method)

12.2 SF-36 questionnaire

The 36-Item Short Form Health Survey (SF-36) is a set of generic, coherent, and easily administered quality-of-life measures.

The answers to each question will be reported at Month 4, 12, 24, 36, 42 and 48 visit, using the full analysis population. The SF-36 questionnaire will be scored according to the scoring method of the RAND 36-Item Health Survey 1.0[29] . All 36 individual items of the questionnaire, as well as the total score of the following domains, will be will be summarised in accordance with section 9:

1. Physical Functioning (PF)
2. Bodily pain (BP)
3. Role limitations due to physical health (RP)
4. Role limitations due to emotional problems (RE)
5. Energy/fatigue (EV)
6. Emotional well-being (MH)
7. Social functioning (SF)
8. General health (GH)
9. Change in Health (CH)

Additionally, two distinct, higher order summary scores will be derived from the above domains:

1. Physical Component Summary (PCS)
2. Mental Component Summary (MCS)

calculated using the subscale scoring coefficients (Table 11) and reference populations mean and standard deviation (PCS: 82.261 and 20.867; MCS: 63.7796 and 19.582) employed in PEXIVAS study[30].

[29] https://www.rand.org/health/surveys_tools/mos/36-item-short-form/scoring.html

[30] The scoring procedure is explained in detail in [13, 14].

Table 11: factor score coefficients for PCS and MCS (14)

Subscale	PCS coefficients	MCS coefficients
Physical Functioning (PF)	0.418	-0.213
Role limitations due to physical health (RP)	0.334	-0.087
Bodily pain (BP)	0.366	-0.125
General health (GH)	0.222	0.036
Energy/fatigue (EV)	-0.017	0.286
Social functioning (SF)	-0.083	0.201
Role limitations due to emotional problems (RE)	-0.179	0.394
Emotional well-being (MH)	-0.200	0.444

Formulas to calculate the PCS and MCS scores:

- For the PCS:
  AGPHYSCO=(PF*0.456)+(RP*0.362)+(BP*0.367)+(GH*0.199)+(EV*-0.050)+(SF*-0.028)+(RE*-0.110)+(MH*-0.256)
  PCS = ((AGPHYSCO-82.261)/20.867)*10)+50
- For the MSC: : AGMENTCO=(PF*-0.227)+(RP*-0.102)+(BP*-0.130)+(GH*0.036)+(EV*0.278)+(SF*0.272)+(RE*0.329)+(MH*0.460)
  and then PCS = ((AGMENTCO -63.7796)/19.582)*10)+50

12.3 PROMIS

The Patient-Reported Outcomes Measurement Information System assessment (PROMIS) is a set of validated health-related quality of life assessments questionnaires covering the domains that include fatigue, physical function, pain and global health.

The PROMIS questionnaire will be reported for all visits (Month 4, 8, 12, 16, 20, 24, 27, 30, 36, 42 and 48) using the ITT population. The number of sites and individuals where the PROMIS questionnaire was not administered will be noted. Individual items as well as the following totals, will be will be summarised in accordance with section 9:

1. Fatigue
2. Pain
3. Physical Ability
4. Patient's Global Assessment

13 Figures

Figure 1: CONSORT diagram.
Figure 2: Tree map of recruitment, by site and country.
Figure 3-5: Mosaic plots of relapse type by induction regimen, ANCA type by induction regimen and relapse type by ANCA type.
Figure 6: Histograms of medical history at baseline.
Figure 7: Bar chart of Organ Systems involvement at baseline.
Figure 8: Bar chart of disease status by treatment arm.
Figure 9: Histograms of BVAS/WG scores by treatment arm.
Figure 10: Histogram of CDA score at month 0 and month 4 by induction regimen (**Induction phase**)[31].
Figure 11: Bar chart of CDA Score (grouped) at month 0 and month 4 (**Induction phase**).
Figure 12: Change in CDA Score (from baseline to month 4) (**Induction phase**).
Figure 13: Histogram of CDA score by treatment arm (**Maintenance phase**).
Figure 14: Bar chart of CDA score (grouped) by treatment arm (**Maintenance phase**).
Figure 15: Boxplot of CDA score by treatment arm (**Maintenance phase**).
Figure 16: Change in CDA Score (from month 4 to month 12) (**Maintenance phase**).
Figure 17: Change in CDA Score (from month 4 to month 24) (**Maintenance phase**).
Figure 18: Mosaic plot of treatment compliance (maintenance and follow up).
Figure 19: Bar chart of treatment compliance in maintenance phase by site.
Figure 20: Bar chart of treatment compliance in follow up phase by site.
Figure 21: Kaplan-Meier plot of relapse-free survival by treatment arm – Primary endpoint.

[31] Figure 8, 9 and 10 are similar to those found in the Induction phase report but obtained using a different scoring system for the CDA form. The figures are offered here as a comparison of the two scoring systems. The maintenance phase figures use the new scoring system exclusively.

Figure 65: Boxplot of SF-36 questionnaire PCS and MCS components by treatment arm.

14 Reporting Conventions

The following conventions will be adhered to in this report:

- P-values $\geq$0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001".
- The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data.
- Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

For manuscripts that use the values produced in this report, conventions detailed in [15] will be implemented.

15 Technical Details

Protocol version 4.0 (20th June 2017) was used to develop this document. No changes were made to the protocol during the development of this SAP.

The software package R version 3.6.1 (2019-07-05) will be used on a Windows computer and copies of the code employed will be stored. Medical Dictionary for Regulatory Activities MedDRA 20.0 (March 2017) is used to classify SAE/AEs.

Each report and individual table or graph will be annotated with:

- Date and time stamp
- Name of the code file that produced the analysis
- Author
- Population used

The individual code files will have comments that convey:

- Author
- Date and time of writing

- Description of any revisions
- Description of the inputs and outputs
- Reference to any parent code file that runs the code

The population to be used in a table or figure will be explicitly set at the start of a block of code that computed the output by looking up the population from the table of tables.

A reviewing statistician will have an overview of the entire analyses and will explicitly check the code producing the efficacy analysis as well as any other pieces of code as desired.

15.1 Data anomalies and corrections

Data found in MACRO database with subject ID "CN2-004" has been excluded from the analysis completely. This ID was used in error for a patient later enrolled under ID "CN2-005".

For patient "US7-003" any scheduled visit information collected after the patient's withdrawal from trial was removed in the analysis. The issue arose because the withdrawal form was handed in late by the site and the data manager, unaware, continued to enter data collected past this point into MACRO. This data was later removed from MACRO, however the empty forms and the dates of the visits persisted creating some confusion over the patient's disposition.

Two serious adverse events found in the SAE database with subject ID pre-fixed with "NR" have been excluded from the analysis completely. Patient ID "NR-N01-001" denotes a patient who was enrolled in the trial but died before being consented, subject ID "N01-001" was later reused for a different patient. Patient ID "NR-NZ-001" was used for a patient who was enrolled, consented but was found to be ineligible, therefore removed from the trial and the database. The ID was not reused, as the site did not recruit further.

16 References

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17 Listing of Tables, Listings and Figures

A listing of tables and figures included in the report can be found in the following document:

meta_table.csv (Command Line)