Plasma exchange and glucocorticoid dosing in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis: an international randomized controlled trial

Short title: PEXIVAS

Protocol Version: 1.1

EUDRACT number: 2009-013220-24
ISRCTN number: ISRCTN07757494
Clinicaltrials.gov registration number: NCT00987389

Trial Sponsor: Cambridge University Hospitals NHS Foundation Trust, UK

Data Management and Analysis Centre: Birmingham Clinical Trials Unit (BCTU), UK

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

Funding:
National Institutes of Health Research (UK): Number, HTA 08/56/04
Food and Drug Administration/National Institutes of Health (USA): FDA R01 FD003516 and the National Institutes of Health (USA) - National Institute of Arthritis and Musculoskeletal and Skin Diseases: U54 AR0573319
National Health and Medical Research Council (Australia): 626939
Canadian Institutes of Health Research (Canada): 211079
PEXIVAS Trial Management Group

Chief Investigators
Dr. David Jayne
Cambridge University Hospitals NHS Foundation Trust
dj106@cam.ac.uk
Dr. Peter Merkel
Boston University School of Medicine
pmerkel@bu.edu
Dr. Michael Walsh
McMaster University Health Science Centre
mwalsh@ucalgary.ca

Trial Physician
Dr. Alina Casian
Addenbrooke’s Hospital, Cambridge
alina.casian@doctors.org.uk

Clinical Trials
Professor Keith Wheatley
CRUK Clinical Trials Unit
Tel: 0121 415 9119
k.wheatley@bham.ac.uk

Statistics
Miss Natalie Ives
University of Birmingham
Clinical Trials Unit (BCTU)
Tel: 0121 415 9113
n.j.ives@bham.ac.uk

PEXIVAS Study Offices
For general queries about the study and for information on site set-up:

<table>
<thead>
<tr>
<th>Europe</th>
<th>United States of America</th>
<th>Canada</th>
<th>Australasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial Coordinator</td>
<td>Carol A. McAllear</td>
<td>Dr. Michael Walsh</td>
<td>Dr. Chen Au Peh &amp; Dr. Carmel Hawley</td>
</tr>
<tr>
<td>Vascularitis Research Office, Box 57</td>
<td>Vasculitis Center, E5</td>
<td>Dept of Clinical Epidemiology &amp; Biostatistics</td>
<td>Australasian Kidney Trials Network</td>
</tr>
<tr>
<td>Addenbrooke’s Hospital Hills Road Cambridge</td>
<td>72 East Concord Street Boston MA, 02118 USA</td>
<td>Room 2C9, 1200 West St Main McMaster University Health Science Centre, Hamilton Ontario, L8N 3Z5 Canada</td>
<td>University of Queensland</td>
</tr>
<tr>
<td>CB2 0QO United Kingdom</td>
<td>Tel: 617.414.2505 Fax: 617.414.2510 Email: <a href="mailto:ceking@bu.edu">ceking@bu.edu</a></td>
<td>905.525.9140 Fax: 905.524.3841 Email: <a href="mailto:mwwalsh@ucalgary.ca">mwwalsh@ucalgary.ca</a></td>
<td>Level 1, Building 33 Princess Alexandra Hospital Ipswich Rd, Woolloongabba QLD 4102, Australia</td>
</tr>
<tr>
<td>Tel: 441223 256731 Fax: 441223 586796 Email: <a href="mailto:biljana.jovanovska@addenbrookes.nhs.uk">biljana.jovanovska@addenbrookes.nhs.uk</a></td>
<td></td>
<td></td>
<td>Telephone: +61 732402625 E-mail: <a href="mailto:carmel.hawley@health.qld.gov.au">carmel.hawley@health.qld.gov.au</a> <a href="mailto:chen.peh@adelaide.edu.au">chen.peh@adelaide.edu.au</a></td>
</tr>
</tbody>
</table>

For queries about collection of data and data analysis:

Birmingham Clinical Trials Unit (BCTU), College of Medical & Dental Sciences, Robert Aitken Institute, University of Birmingham, Edgbaston, Birmingham B15 2TT, United Kingdom
Tel: 0121 415 9100 (answering machine outside office hours); Fax: 0121 415 9135

Trial Coordinator
Mrs Elizabeth Brettell 0121 415 9131 e.a.brettell@bham.ac.uk

Computing
Mr Nick Hilken 0121 415 9121 n.h.hilken@bham.ac.uk

Statistician
Mr Andrew Howman 0121 415 9116 a.j.howman@bham.ac.uk

Randomisation
Internet: https://www.trials.bham.ac.uk/PEXIVAS
Telephone: 0800 953 0274 (toll free in UK, available 9am to 5pm UK time)
Or +44 (0)121 415 9137 (from outside the UK, available 9am to 5pm UK time)
1 Protocol Synopsis

Title: Plasma exchange and glucocorticoid dosing in the treatment of ANCA-associated vasculitis: a multicentre randomized controlled trial

Short Title: PEXIVAS

Clinical Phase: III

Principal Investigators: David Jayne, Peter A. Merkel, Michael Walsh

Trial Sponsor: Cambridge University Hospitals NHS Foundation Trust

Sample Size: 500 participants

Accrual Period: 60 months

Study Duration: 84 months

Study Design: Multi-centre, international, open label, factorial design, randomized control trial in severe ANCA-associated vasculitis (AAV). Five hundred participants will be randomized, 1:1, to receive adjunctive plasma exchange (PLEX) in addition to standard immunosuppressive therapy and glucocorticoids (GC) or standard immunosuppressive therapy and GC without PLEX. The same 500 patients will be randomized, 1:1, to receive reduced-dose GC taper or standard-dose GC taper. There will be a minimum duration of follow-up of 2 years.

Primary Study Objectives:

1. To determine the efficacy of PLEX in addition to immunosuppressive therapy and GC in reducing death and end-stage renal disease (ESRD)
2. To determine the non-inferiority of a reduced-dose GC regimen in reducing death and ESRD

Primary Outcome Measures: Composite of i) all-cause mortality or ii) End-stage renal disease

Secondary Objectives:

For both of i) PLEX in addition to immunosuppressive therapy and GC compared to immunosuppressive therapy and GC alone; and ii) reduced-dose GC compared to standard-dose GC:

1. To determine the effect on disease activity
2. To determine the effect on mortality
3. To determine the effect on ESRD
4. To determine safety
5. To determine effects on health related quality of life

Secondary Outcome Measures
1. Sustained Remission
2. All-cause mortality
3. ESRD
4. Serious Adverse Events
5. Serious infections
6. Medical Outcomes Survey Short Form – 36 (SF-36)
7. EuroQoL EQ5D Index Score

Exploratory Objectives
For each of i) PLEX in addition to immunosuppressive therapy and GC compared to immunosuppressive therapy and GC alone; and ii) reduced-dose of GC compared to standard-dose GC:
1. To determine the cost-effectiveness
2. To determine the effects on measures of disease-related damage
3. To determine the effects on long-term renal function

Exploratory Outcome Measures
1. Incremental cost-effectiveness ratio
2. Combined Damage Assessment Index (CDA)
3. Estimated glomerular filtration rate (eGFR)

Inclusion Criteria
1. New or previous relapsing clinical diagnosis of Wegener’s granulomatosis or microscopic polyangiitis consistent with the Chapel-Hill consensus definitions AND
2. Positive test for proteinase 3-ANCA or myeloperoxidase-ANCA AND
3. Severe vasculitis defined by at least one of the following:
   a. Renal involvement with both:
      i. Renal biopsy demonstrating focal necrotizing glomerulonephritis or active urine sediment characterized by glomerular haematuria or red cell casts and proteinuria AND
      ii. eGFR <50 ml/min/1.73 m²
   b. Pulmonary hemorrhage due to active vasculitis defined by:
      i. A compatible chest x-ray or CT scan (diffuse pulmonary infiltrates) AND
      ii. The absence of an alternative explanation for all pulmonary infiltrates (e.g. volume overload or pulmonary infection) AND
      iii. At least one of the following:
         1. Evidence of alveolar hemorrhage on
bronchoscopic examination or increasingly bloody returns with bronchoalveolar lavage
2. Observed hemoptysis
3. Unexplained anemia (<10 g/dL) or documented drop in hemoglobin (>1 g/dL)
4. Increased diffusing capacity of carbon dioxide

4. Provision of informed consent by patient or a surrogate decision maker. In some participating countries permission has also been granted to use deferred consent for enrolling a patient until a legal representative becomes available to consent on their behalf. Please check your national regulations for further guidance.

**Exclusion Criteria**

1. A diagnosis of vasculitis other than Wegener’s granulomatosis or microscopic polyangiitis
2. Positive anti-glomerular basement membrane antibody test or renal biopsy demonstrating linear glomerular immunoglobulin deposition
3. Receipt of dialysis for >21 days immediately prior to randomization or prior renal transplant
4. Age <15 years (age <18 years at centres that do not treat pediatric patients)
5. Pregnant at time of study entry
6. Treatment with >1 IV dose of cyclophosphamide and/or >14 days of oral cyclophosphamide and/or >14 days of prednisone/prednisolone (>30 mg/day) and/or >1 dose of rituximab within the 28 days immediately prior to randomization
7. A comorbidity that, in the opinion of the investigator, precludes the use of cyclophosphamide, glucocorticoids, or plasma exchange or absolutely mandates the use of plasma exchange

**Treatment Description**

**Plasma Exchange:**

- Seven (7) plasma exchanges of 60 mL/kg, will be performed within 14 days after randomization.
- Plasma exchange may be provided by centrifugation or filter separation according to local practice and availability.
- Anticoagulation may be provided by heparinization or citrate according to local practice.
- Replacement fluid will consist of human serum albumin (3-5% depending on local availability). Albumin may be combined with crystalloid (e.g. saline).
- Patients with active bleeding may receive supplemental plasma to replace clotting factors according to local practice.

*Immunosuppressive and glucocorticoid therapy will be determined by the protocol for the first 12 months after trial entry.*
Glucocorticoids:
- All patients will receive between 1 and 3 g of IV methylprednisolone over 1 to 3 days, then daily oral GC.
- Oral GC may consist of prednisone or prednisolone and administered through a weight-based protocol.
- All participants will receive either 50, 60 or 75 mg/day (based on weight) of oral GC for 7 days
  - Participants in the standard-dose group will continue at 50, 60 or 75 mg/day for 7 additional days and taper to between 12.5 and 20 mg/day at 3 months and 5 mg/day at 6 months.
  - Participants in the reduced-dose group will continue at 25, 30 or 40 mg/day for 7 days and taper to between 6 and 10 mg/day by 3 months and 5 mg/day by 6 months.
- All patients will receive 5 mg/day from 6 months to 12 months after randomization.

Immunosuppressive Remission-Induction Therapy:
To consist of either cyclophosphamide or rituximab, per preference of site investigators/patients.

Cyclophosphamide:
- Participants may be treated with either intravenous (15mg/kg/pulse) or oral (2mg/kg/day) CYC according to local preferences.
- CYC doses will be reduced for advanced age, poor baseline renal function, or cytopenias.

Rituximab:
- Participants who are prescribed rituximab will receive 4 intravenous doses of 375 mg/m² according to the following schedule:
  - Dose 1 within first 14 days of participation
  - Subsequent doses: should follow the prior dose by 7 days but this may range between 5 and 14 days due to practical considerations for arranging rituximab infusions locally.
  - All doses should be given within 42 days of enrollment in the study.
  - Note: Rituximab will not be given within the 48 hours prior to receiving a PLEX treatment.

Immunosuppressive Remission-Maintenance Therapy:

Azathioprine:
- Participants receiving cyclophosphamide will be transitioned to azathioprine as maintenance immunosuppression no earlier than 3 months and no later than 6 months after starting CYC provided a remission is induced.
- Azathioprine (2 mg/kg/day) will begin immediately after the last
dose of oral CYC or 7 days after the last dose of IV CYC with dose reduction for advanced age, cytopenias, or based on TPMT genetic/activity testing (if performed).

- Patients intolerant of azathioprine may use an alternative immunosuppressive agent at the discretion of the local investigator.

**Prophylactic Therapies:**
Infection prophylaxis such as with low-dose sulfamethoxazole-trimethoprim (i.e. one single strength tablet [480 mg total] daily or one double strength tablet [960 mg total] thrice weekly) and osteoporosis prophylaxis. The use of prophylactic therapies will be left to local practice and the discretion of local investigators. Other Therapies:
Treatments for AAV not included in the study protocol will not be allowed as adjunctive therapies (e.g. intravenous immunoglobulin, anti-TNF alpha therapy, high-dose sulfamethoxazole-trimethoprim or other immunomodulatory treatments).

**Sample Size**
500 patients

**Primary Analyses**

- The primary analysis will be of time to the composite endpoint of all-cause mortality or end-stage renal disease using log-rank test and Cox proportional hazards models, with survival curves generated using the Kaplan-Meier method.

**Secondary Analyses**
1. Sustained remission will be analyzed by comparing the difference in proportions (and associated 95% confidence intervals) of patients that achieve a sustained remission in each treatment group.
2. Death and ESRD will be analyzed separately in an identical manner to the composite primary endpoint.
3. Safety analyses will be performed by assessing the 95% confidence interval of the rate difference of serious adverse events between treatment groups.
4. The rate of serious infections will be assessing the 95% confidence interval of the rate difference between the treatment groups both for the first year and at trial end.
5. Health-related quality of life using the SF-36 Physical Composite, Mental Composite and EQ-5D Index Score will be assessed by constructing repeated measures models.

**Safety and Monitoring**
Adverse events will be assessed at each study visit.

Important expected adverse events will be actively surveyed (i.e. must be assessed to complete the case report form).
An independent Data Monitoring Committee (DMC)/Data Safety Monitoring Board (DSMB) will review adverse event data annually or more frequently if requested by the DMC/DSMB.
# Glossary of Terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Common Closing Date</td>
<td>24 months after the last patient is enrolled</td>
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<tr>
<td>End Stage Renal Disease</td>
<td>The requirement of a renal replacement therapy (hemodialysis or peritoneal dialysis) for at least 12 consecutive weeks or the receipt of a renal transplantation.</td>
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<tr>
<td>First Relapse</td>
<td>The first major or minor relapse.</td>
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<tr>
<td>Major Relapse</td>
<td>New or recurrent disease activity that occurs after remission has been initially induced and affects a major item of the BVAS/WG (gangrene, scleritis, retinal exudates/haemorrhage, sensorineural deafness, mesenteric ischemia, pulmonary haemorrhage, respiratory failure, red blood cell urinary casts, rise in creatinine &gt;30% or fall in creatinine clearance &gt;25%, meningitis, spinal cord lesion, stroke, cranial nerve palsy, sensory peripheral neuropathy, mononeuritis multiplex, or other manifestation deemed major by the investigator).</td>
</tr>
<tr>
<td>Minor Relapse</td>
<td>New or recurrent disease activity that occurs after remission has been initially induced but does not constitute a major relapse/does not affect a major item of the BVAS/WG.</td>
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<td>Remission</td>
<td>The absence of disease activity (BVAS/WG= 0)</td>
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<td>Resistant Disease</td>
<td>Active AAV that does not improve or worsens despite commencing the allocated induction of remission therapy.</td>
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<td>Sustained remission</td>
<td>Remission that is obtained within 6 months of randomization and lasts without a first relapse until at least 12 months after randomization.</td>
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</table>
3 Abbreviations

AAV       ANCA-associated vasculitis
ANCA      Anti-neutrophil cytoplasm antibody
AZA       Azathioprine
BCTU      Birmingham Clinical Trials Unit
BVAS/WG   Birmingham Vasculitis Activity Score/Wegener’s Granulomatosis version
CDA       Combined Damage Assessment Index
CYC       Cyclophosphamide
DMC       Data Monitoring Committee
DSMB      Data Safety Monitoring Board
eGFR      Estimated glomerular filtration rate
EQ5D      EuroQol 5D Quality of Life Questionnaire
ESRD      End-stage renal disease
FDA       Food and Drug Administration
GC        Glucocorticoids
MDRD      Modification of Diet in Renal Disease
MHRA      Medicines and Healthcare products Regulatory Agency
MPA       Microscopic Polyangiitis
NIAMS     National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIH       National Institutes of Health
NIHR      National Institutes of Health Research
PLEX      Plasma Exchange
TMC       Trial Management Committee
TPMT      Thiopurine Methyltransferase
TSC       Trial Steering Committee
SAE       Serious Adverse Event
SF-36     Medical Outcomes Survey Short Form 36 Questionnaire
SUSAR     Suspected unexpected Serious Adverse Reaction
WG        Wegener’s Granulomatosis
4 Table of Contents
1 Protocol Synopsis ................................................................. 3
2 Glossary of Terms .................................................................. 8
3 Abbreviations ........................................................................ 9
4 Table of Contents .................................................................... 10
5 Background and Rationale ....................................................... 13
  5.1 Target Population .................................................................. 13
  5.2 Plasma Exchange for Treatment of ANCA-Associated Vasculitis  15
  5.3 The treatment of ANCA-Associated Vasculitis with Glucocorticoids  17
6 Trial Objectives ........................................................................ 18
  6.1 Primary Objectives ............................................................... 18
  6.2 Secondary Objectives ............................................................ 18
  6.3 Exploratory Objectives ........................................................... 18
7 Trial Design ............................................................................... 18
  7.1 Overview ............................................................................... 18
  7.2 Number of Centres ............................................................... 19
  7.3 Number of Participants ........................................................ 19
  7.4 Methods to Protect Against Bias ........................................... 19
  7.5 Study Duration ...................................................................... 20
  7.6 Trial Endpoints ..................................................................... 20
   7.6.1 Primary Endpoint .............................................................. 20
   7.6.2 Secondary Endpoints ......................................................... 20
   7.6.3 Tertiary Endpoints ............................................................. 21
  7.7 Treatments ............................................................................ 21
   7.7.1 Adjunctive Plasma Exchange Induction Therapy .................. 21
   7.7.2 Glucocorticoids Therapy ..................................................... 22
   7.7.3 Cyclophosphamide Remission-Induction Immunosuppressive Therapy ............................................................. 23
   7.7.4 Rituximab Remission-Induction Therapy .............................. 25
   7.7.5 Remission-Maintenance Immunosuppressive Therapy .............. 25
  7.8 Guidelines for the Treatment of Resistant Disease .................... 26
  7.9 Guidelines for the Treatment of Major Relapses ....................... 26
  7.10 Guidelines for the Treatment of Minor Relapses ..................... 27
  7.11 Prophylactic Therapies ........................................................ 27
  7.12 Criteria for Discontinuation ................................................ 27
   7.12.1 Individual Subject ......................................................... 27
7.12.2 Trial .................................................................................................................27
7.13 Patient Selection ..................................................................................................28
7.13.1 Inclusion Criteria .............................................................................................28
7.13.2 Exclusion Criteria ...........................................................................................29
7.13.3 Randomization .................................................................................................29
7.13.4 Subject Withdrawal Criteria ...........................................................................30
7.13.5 Disease definitions ...........................................................................................30
7.14 Screening Evaluation and Informed Consent .......................................................32
7.15 Baseline Data .......................................................................................................32
7.16 Randomization .....................................................................................................32
7.17 Induction of Remission ........................................................................................33
7.18 Visits for Plasma Exchange ..................................................................................33
7.19 Maintenance of Remission ...................................................................................33
7.20 Unscheduled Visits ..............................................................................................33
7.21 Termination of Study ..........................................................................................33
8 Assessment of Safety ...............................................................................................33
8.1 Definitions .............................................................................................................33
8.1.1 Adverse event ....................................................................................................33
8.1.2 Adverse reaction of an investigational medicinal product (AR) .......................34
8.1.3 Unexpected adverse reaction ...........................................................................34
8.1.4 Serious adverse event or serious adverse reaction ...........................................34
8.2 Expected adverse drug reactions .........................................................................34
8.3 Recording and evaluation of adverse events .........................................................35
8.3.1 Assessment of seriousness ..............................................................................36
8.3.2 Assessment of causality ...................................................................................36
8.4 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) ........36
8.4.1 Who should report and whom to report? ..........................................................36
8.4.2 When to report? ...............................................................................................36
8.4.3 How to report? ..................................................................................................37
8.5 Reporting adverse events .....................................................................................38
8.6 Known Potential Risks .........................................................................................38
8.6.1 Plasma Exchange ..............................................................................................38
8.6.2 Glucocorticoids ................................................................................................39
8.6.3 Cyclophosphamide ............................................................................................40
8.6.4 Azathioprine ................................................................. 41
9 Study Risk Assessment........................................................... 44
9.1 Risks to the Subjects ................................................................ 44
9.2 Adequacy of Protection Against Risks ........................................... 45
9.3 Potential Benefits of the Proposed Research to the Subject and Others ........................................................................... 45
9.4 Importance of the Knowledge to be Gained .................................... 46
10 Study Monitoring.......................................................................... 46
11 Data and Safety Monitoring Plan...................................................... 46
12 Statistical Considerations ............................................................. 47
12.1 Sample Size Estimation ............................................................ 47
12.2 Planned Analyses ...................................................................... 47
12.2.1 Interim Analyses................................................................. 47
12.2.2 Primary Endpoint Analyses .................................................... 47
12.2.3 Secondary Endpoint Analyses ............................................... 48
12.2.4 Tertiary Endpoint Analyses ................................................. 49
13 Biomedical Substudies ................................................................. 49
14 Ethical Considerations ................................................................ 50
14.1 Evaluation of Risks to Patients ................................................... 50
14.2 Protection Against Risks ............................................................ 50
14.3 Potential Benefits to Participants ................................................ 51
14.4 Trial Ethical Approval .............................................................. 51
14.5 GCP Statement ...................................................................... 51
15 Trial Organization ...................................................................... 51
15.1 Principal Investigators ............................................................... 51
15.2 Trial Coordination and Data Management Centre ......................... 52
15.3 Trial Communications .............................................................. 52
16 Funding .................................................................................... 52
17 Appendices ............................................................................ 55
17.1 Birmingham Vasculitis Activity Score for WG Vasculitis (BVAS/WG) ... 55
17.2 CDA - Combined Damage Assessment Index ............................... 63
17.3 SF-36 ................................................................................. 65
17.4 EQ5D .............................................................................. 68
17.5 Modification of Diet in Renal Disease (MDRD) Estimated Glomerular Filtration Rate Calculation ............................................... 71
17.6 PEXIVAS Trial Centres ........................................................... 69
5 Background and Rationale

Wegener’s granulomatosis (WG) and microscopic polyangiitis (MPA) are syndromes of primary systemic vasculitis associated with anti-neutrophil cytoplasm antibodies (ANCA). Together, these syndromes are grouped as ANCA-associated systemic vasculitis (AAV). The prevalence of AAV is estimated at 14 - 30 patients per 100 000 in England (1). Left untreated, AAV has a universally poor prognosis with mortality approaching 100% within 5 years (2). The introduction of treatment regimens based on cyclophosphamide (CYC) and glucocorticoids (GC) have transformed AAV from a rapidly fatal disease to one of chronic morbidity and reduced survival often preceded by end-stage renal disease (ESRD).

Plasma exchange (PLEX), a method of rapidly removing potentially pathogenic ANCA and other mediators of inflammation and coagulation, has shown promise as an adjunctive therapy in AAV to improve early disease control and improve rates of renal recovery in severe disease. GC are a standard of care in the treatment of AAV. High doses of GC early in disease although undeniably reduce disease activity due to their anti-inflammatory and immunosuppressive properties also increase the risk of infection particularly in the elderly and in the presence of uremia. There is no randomized trial data to guide GC dosing.

There is a need for therapies with reduced toxicity while improving disease control. Defining the role of therapies that are already in use but that are invasive, expensive, but unproven is a priority in AAV research. PEXIVAS is a randomized control trial to test two interventions in a two-by-two factorial design (standard care and PLEX compared to standard care alone and a standard-dose GC compared to a low dose GC regimen) to address these issues.

5.1 Target Population

Current standard treatment regimens still have poor outcomes. Unselected cohorts now demonstrate 5 year renal survival (defined as the composite of ESRD or death) of 60 to 70% (3;4). In patients with vital organ threatening disease (e.g. kidneys or lungs), renal survival is worse. Long-term follow-up data from three recently completed RCTs by the European Vasculitis Study Group (EUVAS) with 285 patients with an estimated glomerular filtration rate (eGFR) of less than 50 ml/min/1.73 m² demonstrated 5 year ESRD-free survival was only 54% and the median time to renal failure or death was 6 years despite the exclusion of patients with lung hemorrhage (Figure 1). In the subgroup of patients with a creatinine of less than 500, a group traditionally thought to have a favorable prognosis, 33% died or developed ESRD by 5 years (Figure 2). Additionally, patients with lung hemorrhage, who were excluded from these studies, have a mortality of up to 50% in the first year.
**Figure 1** Differences in long-term renal survival (end-stage renal disease or death) on the basis of estimated glomerular filtration (eGFR) for patients with ANCA-associated vasculitis enrolled in three randomized trials. Blue line represents patients with an eGFR of $\leq 50$ ml/min/1.73 m$^2$; red line represents patients with an eGFR of $>50$ ml/min/1.73 m$^2$.

**Figure 2** Differences in long-term renal survival (end-stage renal disease or death) on the basis of estimated glomerular filtration (eGFR) for patients with ANCA-associated vasculitis enrolled in two randomized trials with baseline creatinines < 500 µmol/L. Blue line represents patients with an eGFR of $\leq 50$ ml/min/1.73 m$^2$; red line represents patients with an eGFR of $>50$ ml/min/1.73 m$^2$. 
Poor outcomes in AAV are attributed both to ineffective therapies and complications of standard treatments, CYC and GC. Approximately 20% of patients either do not have adequate disease control or are intolerant of their induction of remission treatment (5-7). An additional 50% of patients will have relapsing AAV over the subsequent five years. Inadequate disease control is associated with increased immunosuppressive medication and thus increased risk for treatment related toxicity and progressive organ scarring and death. Additionally, between 25 and 50% of patients with severe AAV experience a severe infection within the first 12 months of treatment and the most frequently cited causes of death are infection or uncontrolled vasculitis (8,9).

Treatment regimens that minimize toxicity and infections while providing adequate disease control are therefore needed.

5.2 Plasma Exchange for Treatment of ANCA-Associated Vasculitis

PLEX removes potentially pathogenic antibodies as well as mediators of coagulation and inflammation from the circulation and has been advocated as a method of rapidly controlling AAV. Early studies of PLEX in rapidly progressive glomerulonephritis due predominantly to AAV have had mixed results (10-12). These studies had heterogeneous treatment regimens, small sample sizes, and short follow-up periods.

MEPEX examined the effect of PLEX on renal recovery for patients with renal failure due to AAV (8). This trial compared PLEX to IV methylprednisolone as an addition to standard therapy in 137 incident patients with severe AAV manifested by a creatinine >500 µmol/L or dialysis dependency at presentation and demonstrated an absolute reduction in the development of ESRD by 24% (95% CI 6.5 – 41%) after 12 months for patients treated with PLEX. There was no demonstrable difference in mortality at 12 months between those treated with PLEX compared to IV methylprednisolone (mortality of 25% in both groups). Long-term results from MEPEX, however, did not demonstrate a statistically significant difference between the treatment groups in terms of ESRD or death (p=0.57) (Figure 3).

The role of PLEX in patients with less severe renal dysfunction at the time of presentation is even less clear. Exploratory work from Jayne et al found patients with a renal biopsy demonstrating active lesions were the most likely to have a benefit from PLEX. In patients who do not have advanced, chronic renal injuries, the rapid disease control afforded by PLEX may prevent renal (or other vital organ) scarring and thus the cascade of glomerulosclerosis and hyperfiltration that perpetuates renal injury.

PLEX is also widely used for patients with lung hemorrhage due to AAV. This practice comes from cohort data in AAV and experience with anti-glomerular basement membrane disease but has never been rigorously tested and in contemporary cohort data appears effective only in selected subgroups of patients with lung hemorrhage (13). However, PLEX has the potential to exacerbate haemorrhage through removal of clotting factors and increase the risk of infection through antibody removal. Its use in this indication demands critical appraisal.
Figure 3 Results of long-term follow-up of the MEPEX study. Renal survival is defined as the composite of end-stage renal disease or all-cause mortality.

A systematic review of PLEX in AAV identified nine randomized studies. The study populations were skewed towards severe renal dysfunction and often included diseases other than AAV. A meta-analysis of the nine trials that reported death and ESRD outcomes showed a benefit at reducing dialysis dependency (relative risk [RR] 0.64; 95% confidence interval [CI] 0.47 to 0.88) but no benefit at reducing mortality (RR 1.01; 95% CI 0.71 to 1.43). When considering the composite endpoint of death or dialysis the relative risk was 0.81 (95% CI 0.66 to 1.00) (Figure 4).
5.3 The treatment of ANCA-Associated Vasculitis with Glucocorticoids

High dose oral GC are the standard of care for the treatment of AAV on the basis of cohort data prior to the widespread use of cytotoxic medications and strategies for earlier diagnosis with ANCA testing. There is a complex relationship between GC dose and its effects on the immune system as an immunosuppressive versus an anti-inflammatory (14). There is also an increasing trend to reduce GC doses to mitigate their toxicity while maintaining efficacy, a trend supported by laboratory evidence of a ceiling effect of GC dosing with respect to anti-inflammatory properties (15). When combined with cytotoxic medications, high dose GC may significantly increase treatment related toxicity while adding little to therapeutic efficacy.

Infections in AAV are most common in the first two months of treatment when GC doses are highest. Although this relationship is confounded by disease activity and co-treatment with CYC, it is important to note that infection rates fall in parallel with decreasing GC dose despite the maintenance of constant immunosuppression. Dose dependent increases in infections are also observed in rheumatoid arthritis and lupus nephritis (16;17). Furthermore, high cumulative doses of GC are associated with osteoporosis, infections, cardiovascular disease and gastrointestinal bleeding (18). Despite the association between higher GC doses and adverse events and despite their widespread use, there is a paucity of literature to guide the optimal exploitation of GC in AAV.
6 Trial Objectives

6.1 Primary Objectives

1. To determine the efficacy of PLEX in addition to immunosuppressive therapy and glucocorticoids with respect to death and end-stage renal disease (ESRD)
2. To determine whether a reduced-dose glucocorticoids regimen is non-inferior to a standard-dose regimen with respect to death and ESRD

6.2 Secondary Objectives

Secondary objective are limited to those of direct relevance to the assessment of the efficacy and safety of the investigational treatments.
For both of PLEX in addition to immunosuppressive therapy and glucocorticoids compared to immunosuppressive therapy and glucocorticoids alone and for a reduced-dose of glucocorticoids compared to a standard-dose of glucocorticoids:
   1. To determine the effect on disease activity
   2. To determine the effect on death
   3. To determine the effect on ESRD
   4. To determine safety
   5. To determine effects on serious infections
   6. To determine effects on health related quality of life

6.3 Exploratory Objectives

For each of PLEX in addition to immunosuppressive therapy and glucocorticoids compared to immunosuppressive therapy and glucocorticoids alone and for a reduced-dose of glucocorticoids compared to a standard-dose of glucocorticoids:
   1. To determine the cost effectiveness
   2. To determine the effects on measures of disease related damage
   3. To determine the effects on long term renal function

7 Trial Design

7.1 Overview

This trial will randomize patients with AAV in a two-by-two factorial design. Randomization to each intervention will be in a one-to-one ratio stratified by the other intervention. Patients will be randomized to receive either adjunctive PLEX or no PLEX and randomized to receive either a standard GC dose or a low GC dose. All patients will receive standard immunosuppressive induction therapy. The primary outcome of the trial will be the composite endpoint of all-cause mortality or end-stage renal disease.
7.2 Number of Centres

PEXIVAS will occur in multiple centers internationally including Europe, North America and Australia/New Zealand. Over 90 centers are planned to recruit patients.

7.3 Number of Participants

This study will aim to recruit 500 patients with AAV over 5 years.

7.4 Methods to Protect Against Bias

Participants will be allocated to the interventions in a one-to-one ratio by a central randomization facility utilizing a computerized minimization algorithm. The algorithm will not be made available to investigators. 250 patients will receive PLEX and be compared to 250 patients that do not. 250 patients will receive reduced-dose GC and be compared to 250 patients that receive standard-dose GC. Allocation will follow a minimisation scheme (see 7.13.3) based on the following prognostic factors in AAV: severity of renal disease at presentation (requiring dialysis or creatinine ≥ 500 µmol/L vs. <500 µmol/L), age (<60, ≥ 60 years old), ANCA subtype (PR3-ANCA vs. MPO-ANCA), severity of lung hemorrhage (no hemorrhage, lung hemorrhage with an oxygen saturation of ≤85% on room air or ventilated, or lung hemorrhage with an oxygen saturation of >85% on room air), and type of induction therapy (oral CYC vs. intravenous CYC vs. rituximab).

PLEX is an invasive procedure requiring the placement of a large central venous catheter and the use of a large, complex device with additional monitoring and nursing care. As such, it is not feasible to blind either patients or treating physicians to this treatment allocation. There is the

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**Figure 5** General schema of randomization.
potential for treating physicians to alter their treatment on the basis of knowing whether the patient will receive PLEX. This will partially be controlled by randomly determining their GC regimen. Although CYC dosing will be protocol driven, the route of administration will not. The route of CYC administration, determined before randomization, will therefore be used as a stratification variable thus removing some potential for confounding (see 8.12.3 below).

7.5 Study Duration

Each patient will be followed until study close with a minimum duration of follow-up of 2 years. Patient recruitment is anticipated to require 5 years. Therefore, the maximum duration of follow-up is 7 years. Patients will be followed more frequently when they begin the trial when the interventions are most intense and treatment is designed to induce remission of disease (Induction of Remission Period) and follow-up will be less intense after this period (Maintenance of Remission Period). The patient follow-up schedule is provided below (Table 4).

7.6 Trial Endpoints

7.6.1 Primary Endpoint

The primary endpoint for this trial is a composite of all-cause mortality or end-stage renal disease. End-stage renal disease is defined as the requirement of a renal replacement therapy (hemodialysis or peritoneal dialysis) for at least 12 consecutive weeks or the receipt of a renal transplantation. Endpoints will be ascertained at study assessments. In the event a patient does not attend an assessment, investigators will attempt to contact any or all of the following: (in order) the patient, the patient’s family physician/general practitioner, the patient’s next of kin, and the patient’s listed contacts in order to ascertain their endpoint status. In countries with vital status registries, we will use the registry to ascertain missing patient’s endpoint status.

7.6.2 Secondary Endpoints

The secondary objectives will be assessed using the following outcome measures:

- Sustained remission (remission that occurs before 6 months after randomization and lasts without a first relapse until at least 12 months after randomization)
- All cause mortality (Section 7.6.1).
- End stage renal disease (ESRD) as described above (Section 7.6.1)
- Serious adverse events defined as any medical occurrence that results in permanent disability, hospitalization or the prolongation of a hospitalization, is life threatening or results in death (Section 8.4).
- Serious infections defined as an infectious syndrome that requires intravenous antibiotics or hospitalization for treatment.
- Medical Outcomes Survey Short Form 36 (SF-36) Physical Composite Score and Mental Composite Score.
- EuroQoL EQ5D Index score.
7.6.3 Tertiary Endpoints

The tertiary objectives will be assessed using the following outcome measures:

- Estimated glomerular filtration rate (Modification of Diet in Renal Disease four variable formula)
- Combined Damage Index
- Cost-Effectiveness Ratios

7.7 Treatments

7.7.1 Adjunctive Plasma Exchange Induction Therapy

PLEX therapy will only be prescribed in addition to standard induction therapy. PLEX will consist of 7 exchanges within 14 days of randomization, of at least 60 ml/kg (based on actual body weight) per session using albumin (3% to 5% depending on local availability, with or without crytalloid) as a replacement solution. The minimum replacement solution volume is 3000 mL. Intravenous immunoglobulin should not be used after PLEX.

The following parameters may be determined according to local practice: 1) PLEX may be performed by centrifugation or filter separation technique, 2) Anticoagulation may be provided by citrate or by heparin but it is suggested that in patients with active bleeding regional citrate anticoagulation be utilized, 3) PLEX may be performed via a central venous catheter if patient is deemed unsuitable for peripheral venous access, the latter is strongly recommended, and 4) monitoring of coagulation parameters or immunoglobulin levels.

7.7.1.1 Patients with Bleeding Risks

Renal biopsy the day of PLEX should be avoided, to minimize the risk of bleeding from dilutional coagulopathy.

Local practice should be followed for patients with active bleeding including patients with known pulmonary hemorrhage or a bleeding episode from any source within the 24 hours prior to PLEX treatment. This may include fresh frozen plasma at the end of the exchange. This information will be recorded in the case report form.

7.7.1.2 Additional Plasma Exchange Treatments

Patients will not receive additional PLEX treatments for ongoing signs or symptoms of AAV (unless they imminently threaten vital organ function – see Major Relapses section 7.9), serological markers of disease (e.g. elevated ANCA titres), elevated markers of inflammation, or histologic evidence of disease activity. Any PLEX treatments considered outside of the treatment protocol should be discussed with the trial medical monitor and the details must be recorded in the patient’s trial case report form.
7.7.2 Glucocorticoids Therapy

GC therapy shall commence with intravenous (IV) methylprednisolone irrespective of the GC group the patient is allocated to. IV methylprednisolone shall be given as three daily pulse doses (minimum 1g maximum 3g, total dose). Each pulse dose may be between 0.5 g and 1 g at the local investigators discretion. IV GC administered immediately (within three days) prior to randomization will contribute to the maximum allowable dose of 3g.

Oral GC therapy shall commence the day following the last bolus of IV methylprednisolone. Oral GC therapy will consist of non-enteric coated prednisone or prednisolone at equivalent mg to mg doses. Dosing will depend on patient weight with three possible weight categories. All oral GC will be given as a single daily dose. Patients intolerant of oral medications or for whom oral medications are contraindicated may be given an equivalent daily IV dose. Pre-printed prescriptions for oral GC therapy will be provided for each patient in the trial after randomization to ensure adherence to the allocated GC regimen. The standard-dose regimen and reduced-dose regimen are summarized in Table 1. The reduced-dose regimen will expose patients to approximately 50% of the standard oral dose over the first 3 months and 53% over the first 6 months of treatment. Oral GC therapy will continue at a dose of 5 mg/day until at least week 52 of the study after which GC therapy will revert to local practice. Alternate day dosing regimens (i.e. those that use two different doses on alternate days) may be used to achieve the appropriate average daily dose required by the protocol but differences in alternative day doses may not be >5 mg. For example, a dose of 12.5 mg/day may be achieved by alternating daily doses of 15 mg/day and 10 mg/day.

Table 1 Dosing for oral Glucocorticoids in the standard and reduced-dose limbs from trial start

<table>
<thead>
<tr>
<th>Week</th>
<th>Standard</th>
<th>Reduced-dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;50 kg</td>
<td>50-75 kg</td>
</tr>
<tr>
<td>1</td>
<td>pulse</td>
<td>pulse</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>3-4</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>5-6</td>
<td>40</td>
<td>50</td>
</tr>
<tr>
<td>7-8</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>9-10</td>
<td>25</td>
<td>30</td>
</tr>
<tr>
<td>11-12</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>13-14</td>
<td>15</td>
<td>20</td>
</tr>
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<td>15-16</td>
<td>12.5</td>
<td>15</td>
</tr>
<tr>
<td>17-18</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>19-20</td>
<td>10</td>
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</tr>
<tr>
<td>21-22</td>
<td>7.5</td>
<td>7.5</td>
</tr>
<tr>
<td>23-25</td>
<td>7.5</td>
<td>7.5</td>
</tr>
<tr>
<td>&gt;52</td>
<td>Investigators’ Local Practice</td>
<td>Investigators’ Local Practice</td>
</tr>
</tbody>
</table>
7.7.3 Cyclophosphamide Remission-Induction Immunosuppressive Therapy

Standard induction therapy with CYC will be prescribed for at least 13 weeks and no more than 26 weeks. As the experience of using either oral or intra-venous routes of administration varies between centres and there is no apparent difference in efficacy or safety, the study protocol will allow the use of either oral or IV CYC. The CYC regimens will be identical for all treatment groups.

A starting dose of 15 mg/kg/pulse will be used for pulse CYC (maximum 1.2 g/dose) or 2 mg/kg/day for oral CYC (maximum 200 mg/day) with reductions made for age and renal function in each group according to previous trials conducted in Europe. Oral CYC will be administered daily with the recommendation for morning administration of full dose, if tolerated. Pulse CYC will be administered IV at a frequency of every two weeks for the first 3 doses then every three weeks thereafter (Table 2). Modifications to dose and frequency will be made in the case of leucopenia.

For patients undergoing PLEX, PLEX will not occur for at least 24 hours following an IV dose of CYC.

Table 2. Pulse intravenous cyclophosphamide schedule. Doses may be modified for age and renal function. After week 13, patients in remission may be transitioned to remission-maintenance therapy.

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Pulse number</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>15 mg/kg</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>15 mg/kg</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>15 mg/kg</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>15 mg/kg</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>15 mg/kg</td>
</tr>
<tr>
<td>13</td>
<td>6</td>
<td>15 mg/kg</td>
</tr>
<tr>
<td>16</td>
<td>7</td>
<td>15 mg/kg</td>
</tr>
<tr>
<td>19</td>
<td>8</td>
<td>15 mg/kg</td>
</tr>
<tr>
<td>22</td>
<td>9</td>
<td>15 mg/kg</td>
</tr>
<tr>
<td>25</td>
<td>10</td>
<td>15 mg/kg</td>
</tr>
</tbody>
</table>

For patients receiving PLEX and daily CYC (oral or IV), on days when PLEX is performed, CYC will be given following PLEX. PLEX will not be performed for at least 12 hours following a dose of oral CYC.

Full (complete) blood counts will be performed according to local protocol but the following minimum is recommended: patients receiving oral CYC should have their blood count monitored weekly for the first four weeks and weekly for four weeks after any dose adjustment and every
other week thereafter. Patients receiving pulse CYC should have their blood count monitored 10 to 14 days after each dose and within 1 day prior to each dose.

Concomitant use of mesna is optional and left to the discretion of the investigator and local practice.

7.7.3.1 Dosage Modifications

7.7.3.1.1 Renal Function and Age

Starting doses of CYC should be adjusted for advanced age or reduced renal function. Renal function may change over the course of the trial and medication dosages may be adjusted to reflect these changes (Table 3.)

7.7.3.1.2 Leucopenia

Oral cyclophosphamide

Oral CYC should be held if the total WBC count is <4x10^9/L. Oral CYC may be restarted at a dose at 25 mg/day less than previous once the WBC count is >4x10^9 on two consecutive tests or >5x10^9 on at least 1 test. After an episode of leucopenia, WBC counts should be monitored at least weekly for at least four weeks.

In the case of severe (WBC < 1x10^9/L) or prolonged (< 4x10^9/L for >2 weeks) leucopenia, oral CYC should be restarted at a dose at least 50 mg/day lower than the previous dose once the weekly WBC count permits. In cases of severe leucopenia, consideration should also be given to granulocyte-colony stimulating factor (G-CSF), fungal prophylaxis, and other precautions for patients with severe leucopenia.

Patients with a declining WBC count but no overt leucopenia (i.e. WBC count <6x10^9 and at least 2x10^9/L lower than previous) should have their WBC count rechecked within 1 week and have their oral CYC reduced by at least 25 mg/day if the WBC count continues to fall.

Pulse cyclophosphamide

The WBC count should be determined within 1 day prior to an IV pulse CYC. If the WBC count is <4x10^9/L, the CYC dose should be postponed until the WBC count is >4x10^9/L and the dose should be reduced to 75% of the planned dose (planned dose x 0.75).

The WBC count nadir should also be determined 10 to 14 days after the pulse dose is given. If the nadir is <3x10^9/L, the next pulse should be reduced even if the next pre-dose WBC count is >4x10^9/L. For a nadir <2x10^9/L, the next dose should be 60% of the previous dose (previous dose x 0.6). For a nadir of 2-3x10^9/L, the next dose should be 80% of the previous dose (previous dose x 0.8).
7.7.3.1.3 Other Dose Modifications

Similar dose reductions to those made for leucopenia may be made for thrombocytopenia and anemia at the investigator’s discretion. Dose alterations should also be made in the event of infectious complications.

**Table 3.** Oral and intravenous cyclophosphamide dose adjustments (mg/kg) for age and renal impairment. NOTE: dose reductions for renal impairment should reflect renal function at the time the dose is given rather than baseline renal function.

<table>
<thead>
<tr>
<th>Oral Cyclophosphamide</th>
<th>IV Cyclophosphamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR (ml/min/1.73 m²)</td>
<td>eGFR (ml/min/1.73 m²)</td>
</tr>
<tr>
<td>Age</td>
<td>&gt;30</td>
</tr>
<tr>
<td>&lt;60</td>
<td>2</td>
</tr>
<tr>
<td>60-70</td>
<td>1.5</td>
</tr>
<tr>
<td>&gt;70</td>
<td>1.25</td>
</tr>
</tbody>
</table>

7.7.4 Rituximab Remission-Induction Therapy

Rituximab may be prescribed to patients as induction remission therapy. Rituximab will be prescribed as 4 intravenous doses of 375 mg/m² according to the following schedule:

1. Dose 1 within first 14 days of participation
2. Subsequent doses should occur 7 days after the previous dose. Doses may, however, occur 5 to 14 days to accommodate practical considerations of administering rituximab and to accommodate plasma exchange. All doses must be given within 42 days of the first dose. PLEX should not be given within the first 48 hours after administering rituximab.

Prophylaxis against infusion reactions must be given as 100 mg of intravenous hydrocortisone or equivalent with or without an anti-histamine agent immediately preceding the first rituximab infusion, and local guidelines should be followed before subsequent infusions of rituximab.

*The use of rituximab will not be allowed in Germany for this trial.*

7.7.5 Remission-Maintenance Immunosuppressive Therapy

Patients who have completed at least 13 weeks of CYC treatment and achieved a clinical remission of disease will be converted to maintenance therapy. A clinical remission is defined as the absence of disease activity that causes symptoms or signs of active vasculitis and has a BVAS/WG of 0. Symptoms or signs of disease that are due to the effects of scarring or damage caused by vasculitis or are a side-effect of therapy are not considered active disease (e.g. isolated
persistent proteinuria or some cases of isolated microscopic hematuria or healing lung cavitations). Patients will remain on CYC therapy for no longer than 26 weeks.

Azathioprine

Maintenance therapy consists of azathioprine at a target dose of 2 mg/kg/day (rounded to the nearest 25 mg/day) and will begin immediately after the last dose of oral CYC or 7 days after the last dose of IV CYC. Patients intolerant of azathioprine will be permitted to be maintained on either a lower dose or on an alternative agent such as methotrexate or mycophenolate mofetil at their physician’s discretion. TPMT activity or polymorphism assessments may be performed according to local availability and practice. Bone marrow and hepatotoxicity should be assessed according to local practice but as a minimum we suggest checking full blood counts and aminotransferases every two weeks for the first month of azathioprine therapy and then every two months for the first year of therapy and every three months thereafter.

7.7.5.1 Dosage Modifications

The starting dose of azathioprine may be reduced to 1.5 mg/kg/day in patients >60 years old and to 1 mg/kg/day in patients >75 years old.

Patients with a WBC count <4x10^9/L should have their azathioprine temporarily held and have their WBC count checked weekly. Once the WBC count is >4x10^9/L, azathioprine should be restarted at a dose of at least 25 mg/day less than the previous dose with continued weekly monitoring for at least one month.

Patients with a declining WBC count but no overt leucopenia (i.e. WBC count <6x10^9 and at least 2x10^9/L lower than previous) should have their WBC count rechecked within 1 week and have their oral azathioprine reduced by at least 25 mg/day if the WBC count continues to fall.

7.8 Guidelines for the Treatment of Resistant Disease

Resistant disease is active AAV that does not improve or worsens despite administration of the allocated induction of remission therapy.

For failure to improve or worsening of nephritis, lung hemorrhage, or other major organ threatening disease (neurological, gastrointestinal, cardiac, eye) within the first two weeks from entry, we recommend a repeated course of IV methyl prednisolone (1-3g total dose) or high dose oral prednisone/prednisolone (1 mg/kg for 1 week) according to local practice. Oral prednisone/prednisolone dosing should return to the allocated tapering regimen at that regimen’s starting dose (i.e. restart tapering regimen). Consideration of other therapies must be discussed with the medical monitor.

7.9 Guidelines for the Treatment of Major Relapses

A major relapse is new or worsened disease activity that occurs after remission has been initially induced and affects a major item of the BVAS/WG. New or worsening disease activity which occurs while the patient is on ≥20 mg/day of prednisone is considered resistant disease (Section 7.8).
For patients who received cyclophosphamide at the start of the study, major relapses may be treated with the reintroduction of cyclophosphamide (if it occurs during the maintenance of remission phase), an increase in the dose of cyclophosphamide if tolerated, rituximab, additional doses of IV methylprednisolone (up to 3 g), an increase in oral prednisone/ prednisolone to the same doses used during the initial induction of remission.

For patients who received rituximab at the start of the study, major relapses may be treated with the reintroduction of rituximab, introduction of cyclophosphamide, additional doses of IV methylprednisolone (up to 3 g), an increase in oral prednisone/ prednisolone to the same doses used during the initial induction of remission.

The use of plasma exchange to treat a major relapse must be discussed with the medical monitor.

7.10 Guidelines for the Treatment of Minor Relapses

A minor relapse is new or worsening disease activity that occurs after remission has been initially induced that does NOT affect a major item of the BVAS/WG. New or worsening disease activity which occurs while the patient is on ≥20 mg/day of prednisone is considered resistant disease.

Minor Relapses may be treated with up to 20 mg/day of prednisone or prednisolone for a maximum of 14 days. Following this, if disease activity is controlled, patients will resume their GC regimen starting at the next dose below 20 mg/day. If disease activity is not controlled within 14 days, patients will be regarded as having a major relapse.

7.11 Prophylactic Therapies

Consideration should be given to therapies to prevent the complications of treating AAV. This includes, but is not limited to, the use of prophylaxis against glucocorticoid induced osteoporosis, prophylaxis of Pneumocystis jiroveci (formerly P. carinii) pneumonia infections for at least 6 months. Appropriate prophylactic therapy includes sulfamethoxazole-trimethoprim as a single strength tablet daily (i.e. 480 mg daily) or a double strength tablet every other day thrice weekly (i.e. 960 mg Monday, Wednesday, and Friday). The use of prophylactic therapies will be left to local practice and the discretion of local investigators. Care should also be taken by the investigators to ensure the non-immunologic sequelae of AAV are also treated (e.g. hypertension, proteinuria).

7.12 Criteria for Discontinuation

7.12.1 Individual Subject

Patients will be withdrawn if they withdraw consent. All other patients will be followed until trial termination or death.

7.12.2 Trial

Either factor of the trial may be discontinued in the event of clear evidence of harm or benefit for one treatment regimen on the recommendation of the DMC/DSMB and in conjunction with the
Trial Management Committee. The Haybittle-Peto approach will be used whereby all interim analyses use a difference of 3 standard errors (approximately p=0.002) as a stopping guideline (19;20). Efficacy and safety data will be reviewed by the DMC/DSMB on an annual basis. The trial is planned to stop 24 months after the last patient is enrolled (common closing date).

7.13 Patient Selection

7.13.1 Inclusion Criteria

Patients must meet all of the following criteria:

1. New or previous relapsing clinical diagnosis of Wegener’s granulomatosis, or microscopic polyangiitis consistent with the Chapel-Hill consensus definitions (see 7.13.5) AND
2. Positive test for proteinase 3-ANCA or myeloperoxidase-ANCA AND
3. Severe vasculitis defined by at least one of the following manifestations:
   a. Renal involvement characterized by both of the following:
      i. Evidence of glomerulonephritis by either of the following:
         1. Renal biopsy demonstrating focal necrotizing glomerulonephritis or
         2. Active urine sediment characterized by glomerular haematuria/cellular casts and proteinuria
      AND
      ii. An estimated glomerular filtration (eGFR) rate of <50 ml/min/1.73 m².
      Patients known to have a stable eGFR <50 ml/min/1.73 m² for greater than three months prior to enrollment are NOT eligible.
   b. Pulmonary hemorrhage due to active vasculitis defined by the following:
      i. A compatible chest x-ray or CT scan (diffuse pulmonary infiltrates)
      AND
      ii. The absence of an alternative explanation for all pulmonary infiltrates (i.e. volume overload or pulmonary infection)
      AND
      iii. At least one of the following:
         1. Evidence of alveolar hemorrhage on bronchoscopic examination or increasingly bloody returns with bronchoalveolar lavage
         2. Observed hemoptysis
         3. Unexplained anemia (<10 g/dL) or documented drop in hemoglobin (>1 g/dL) from less than 10g/dl
         4. An increased diffusing capacity of carbon dioxide
4. Provision of informed consent by patient or a surrogate decision maker. In some participating countries permission has also been granted to use deferred consent for enrolling a patient until a legal representative becomes available to consent on their behalf. Please check your national regulations for further guidance.
7.13.2 Exclusion Criteria

Patients must have none of the following:
1. A diagnosis of vasculitis other than Wegener’s granulomatosis or microscopic polyangiitis
2. A positive serum test for anti-glomerular basement membrane or a renal biopsy demonstrating linear glomerular immunoglobulin deposition
3. Receipt of dialysis for greater than 21 days immediately prior to randomization or prior renal transplant
4. Age <15 years. In centres that do not routinely treat patients <18 years or if no local investigator routinely treats patients <18 years, enrollment may be restricted to patients 18 years or older*
5. Pregnant at time of study entry
6. Treatment with >1 IV dose of cyclophosphamide and/or >14 days of oral cyclophosphamide and/or >14 days of prednisone/prednisolone (>30 mg/day) and/or treatment with >1 dose of rituximab within the last 28 days
7. A comorbidity that, in the opinion of the investigator, precludes the use of cyclophosphamide, glucocorticoids, or plasma exchange or absolutely mandates the use of plasma exchange

* Patients < 18 years of age will be excluded in Germany

7.13.3 Randomization

Allocation will occur according to a minimization scheme. Minimization allows the allocation of treatments to be balanced for known prognostic risk factors and is particularly useful in small trials (<1000 participants) in diseases with many prognostic risk factors (>3).

The prognostic factors that will serve as minimization strata in PEXIVAS are:
- severity of renal disease at presentation (requiring dialysis or creatinine ≥ 500 µmol/L (5.6 mg/dL) vs. <500 µmol/L)
- age (<60, ≥ 60 years old)
- ANCA binding specificity (PR3 vs. MPO)
- severity of lung hemorrhage (no hemorrhage, hemorrhage with blood oxygen saturation >85% on room air, or hemorrhage with blood oxygen saturation ≤ 85% on room air or ventilated)
- induction immunosuppression therapy to be used (IV CYC vs. oral CYC vs. rituximab).

Participants will be minimized in a one-to-one ratio to each intervention or control group by a central facility utilizing a computerized randomization algorithm. Randomization will be performed using an internet/world wide web based secure program from the Birmingham Clinical Trials Unit. This program will provide the investigator with the patient’s unique trial identification number and the allocated interventions. The randomization program will also inform the responsible PLEX centre, the study pharmacy and the trial coordinator of the patient’s identification number and treatment allocation by email. The minimization sequence will not be shared with any investigator.
7.13.4 Subject Withdrawal Criteria

Subjects will be withdrawn from the trial at any time that they withdraw consent to participate. Patients will otherwise be followed to either the trial end or until death. In the event that consent to participate is withdrawn, we will request that we be allowed to collect vital status information from the patient and/or their family physician or general practitioner. Subjects who are withdrawn will not be replaced.

7.13.5 Disease definitions

Wegener’s granulomatosis is characterised by granulomatous inflammation of the respiratory tract, together with necrotizing vasculitis affecting small to medium-sized vessels (21). A C-ANCA pattern by IIF with ANCA specific for antibodies to PR3, is found in over 90% of untreated patients, a minority have MPO-ANCA. Diagnosis requires the presence of chronic inflammation, with a history of at least four weeks affecting the upper and/or lower respiratory tract and not attributable to another cause. The diagnosis may be supported by characteristic histology, such as a focal, necrotizing, pauci-immune glomerulonephritis; or non-renal biopsies with an inflammatory exudate dominated by polymorphonuclear leucocytes with at least one of (1) necrotizing vasculitis affecting small to medium-sized vessels; (2) epithelioid granulomata; or (3) giant cells; and the exclusion of other causes.

Microscopic polyangiitis is characterised by a chronic inflammatory process with non-granulomatous vasculitis of small vessels (i.e. capillaries, venules, arterioles or small arteries) (22). In contrast to Wegener’s granulomatosis, granulomatous vasculitis of the respiratory tract and/or lung nodules/cavities are absent. Renal involvement is usual and is reflected by a focal, necrotizing, pauci-immune glomerulonephritis. Arteritis of medium-sized vessels may also occur. Microscopic polyangiitis is associated with MPO-ANCA or PR3-ANCA; a minority are ANCA negative or recognise other ANCA autoantigens. Diagnosis of microscopic polyangiitis requires the exclusion of secondary causes of vasculitis, including drugs, infections and malignancy, and vasculitis mimics, such as, anti-phospholipid syndrome and atheroembolic disease.