5 Trial Synopsis

Title	An international, open label, randomised, controlled trial comparing rituximab with azathioprine as maintenance therapy in relapsing ANCA-associated vasculitis (AAV)
Sponsor name **North American Sponsor**	Cambridge University Hospitals NHS Foundation Trust University of Pennsylvania
Disease Under Investigation	Relapsing ANCA-associated vasculitis (AAV)
Purpose of Clinical Trial	To demonstrate the superiority of rituximab against azathioprine in the prevention of disease flare in AAV patients with relapsing disease
Clinical Phase	III (3)
Trial Design	Multi-centre, international, open-label, randomised controlled trial in relapsing AAV. 160 participants will be randomised 1:1 to receive fixed-interval repeat rituximab dosing or azathioprine maintenance therapy
Primary objective	To demonstrate the superiority of rituximab against azathioprine in the prevention of disease flare in AAV patients with relapsing disease
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
Trial Endpoints	Primary: Time to disease relapse (either minor or major relapse) from randomisation. Secondary: 1. Proportion of patients who maintain remission at 24 and 48 months 2. Time to a major or second minor relapse 3. Cumulative accrual of damage as measured by the combined damage assessment score (CDA) 4. Health-related quality of life as measured using SF-36 5. Cumulative glucocorticoid exposure 6. Severe adverse event rate 7. Infection (treated with either intravenous or oral antibiotics) rate Exploratory: 1. Health economic assessment based on

	EQ5D 2. Serum rituximab levels, and correlation with circulating B cell counts including key subsets and immunoglobulin levels 3. Changes in ANCA titres (both anti-MPO and anti-PR3 subsets) in relation to treatment, response, and relapse. 4. HACA rate and levels 5. Serum will be stored for future biomarker studies 6. mRNA will stored for disease and inflammatory gene activation studies 7. DNA will be stored for future genetic studies
Sample Size	Enrolment will be ongoing until 160 patients are randomised. We anticipate this will require 190 patients to be recruited.
Summary of Eligibility Criteria	Subjects must meet <u>all</u> of the following criteria to be eligible for enrolment: 1. Written informed consent (15 years and above) 2. A diagnosis of AAV (granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis), according to the definitions of the Chapel Hill Consensus Conference 3. Current or historical ANCA positivity either by ELISA or immunofluorescence. 3. Disease relapse defined by one major or three minor disease activity items on the Birmingham Vasculitis Activity Score for Wegener's (BVAS/WG), in patients that have previously achieved remission following induction therapy
Key Exclusion Criteria	1. Age < 15 years (age < 18 years at centres that do not treat paediatric patients) 2. Previous therapy with any biological B cell depleting agent (such as rituximab or belimumab) within the past 6 months
Investigational Medicinal Product and Dosage	**Rituximab** <u>*Induction Regimen*</u> Patients will be recruited at the time of relapse. All will receive rituximab 375 mg/m^2/week x 4 doses and glucocorticoids.

	Patients that achieve disease control (BVAS/WG ≤ 1 and daily prednisone dose ≤ 10mg) by month 4 will be randomised to the rituximab or control remission maintenance groups. *Rituximab maintenance group* Rituximab 1000 mg at months 4, 8, 12, 16 and 20 and glucocorticoids.
Active Comparator Products	**Azathioprine** *Induction Regimen* Patients will be recruited at the time of relapse. All will receive rituximab 375 mg/m^2/week x 4 and glucocorticoids. Those patients that achieve disease control (BVAS/WG ≤ 1 and daily prednisone dose ≤ 10 mg) by month 4 will be randomised to the rituximab or control remission maintenance groups. *Control maintenance group* Azathioprine 2 mg/kg/day from month 4 to 24. Methotrexate 25 mg/week, for patients with GFR > 50 ml/min and intolerant of azathioprine even at a reduced dose of 1 mg/kg/day, or mycophenolate mofetil 2 g/day, for patients intolerant of azathioprine and with GFR < 50 ml/min, and glucocorticoids. Dose reductions for intolerance, abnormal liver function, advanced age, cytopenias, or based on TPMT genetic/activity testing (if performed) will be made. Intolerance is defined as the occurrence of an adverse effect (see section 11.2.i) *NOT* lack of efficacy. At month 24, the azathioprine dose will be reduced by 50% and stopped at month 27 (dose = 0 mg/day at month 27).
Route of Administration	Rituximab will be administered intravenously. Azathioprine and mycophenolate mofetil will be administered orally. Methotrexate can be given orally, subcutaneously, or intramuscularly.
Concomitant Therapy	Glucocorticoids at induction For all glucocorticoid dosing, prednisone may be substituted for prednisolone. The investigator may choose one of two permitted GC regimens:

	Oral prednisone (prednisolone will be allowed), commencing at 1.0mg/kg/day, ***or*** 0.5mg/kg/day, both reducing to 10mg/day by month 3 (See schedule 1, pg. 26). Maximum daily dose of GC is 60 mg prednisolone in week 0. Round down to the nearest 5 mg above 20 mg. Round down to the nearest 2.5 mg below 20 mg. GC to be administered in a single daily dose. Intravenous (IV) GCs are not mandated by the protocol. At the investigator's discretion, patients may receive up to a maximum cumulative dose of 3000mg IV methylprednisolone, between 14 days prior to enrolment and 7 days after enrolment. Glucocorticoids in Maintenance Phase: A GC dose of prednisolone 10 mg/day or less is a requirement for randomisation. GC reduces to 5 mg/day by month 6, according to schedule 2 (pg. 26). At month 16, GC dose is reduced to 2.5mg/day and at month 20 GC are completely withdrawn.
Maximum Treatment Duration	Treatment is protocolised for the entire duration of the study, until the common close date, when the final patient recruited has completed 36 months within the study or until the patient has completed 48 months on study whichever the sooner. Patients in the rituximab arm will receive treatment until month 20, and those in the azathioprine arm until month 27.
Summary of Study Procedures Screening:	Procedures to establish inclusion/exclusion criteria.
Baseline:	Baseline data will include: 1. Date of birth, sex, limited medical history 2. Medications, including prior AAV treatments 3. Height/weight 4. Disease activity assessment (BVAS/WG) 5. Disease related damage assessment (CDA) 6. Patient self reported SF-36 questionnaire and EQ5D questionnaire.
Treatment period:	Evaluations will be performed at months 0, 1.5, 3, 4, 8, 12, 16, 20, 24, 27, 30, 36, and every 6 months until the last patient has

	completed 36 months in the study). The maximum duration in the study is 48 months. Assessments will also be performed at the time of relapse or study termination /withdrawal.
End of Trial:	The trial will end when the last patient has completed 36 months in the trial.
Safety and Monitoring	The NIH-sponsored VCRC Data and Safety Monitoring Board will provide independent oversight of this trial.