HAVEN

Hydroxychloroquine in ANCA Vasculitis Evaluation - A Multicentre, Randomised, Double-blind, Placebo-controlled Trial

Protocol Short Title/Acronym: HAVEN

Trial Identifiers
EudraCT Number – 2018-001268-40
IRAS Number - 251987
REC Number - 20/LO/0028
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1. Study Synopsis

Title of clinical trial	HAVEN: Hydroxychloroquine in ANCA Vasculitis Evaluation - A Multicentre, Randomised, Double-blind, Placebo-controlled Trial
Protocol short title/acronym	HAVEN
Trial phase	Phase II *The trial uses phase II methodology but was submitted to regulatory bodies as a Phase IV study under the MHRA's definitions, as hydroxychloroquine is a licenced drug.
Sponsor name	Guy's and St. Thomas' NHS Foundation Trust
Chief Investigator	Professor David D'Cruz
EudraCT number	2018-001268-40
REC number	20/LO/0028
Medical condition or disease under investigation	ANCA associated Vasculitis (AAV)
Purpose of clinical trial	To investigate the addition of hydroxychloroquine (HCQ) as an adjunctive therapy to standard of care therapies to reduce disease activity in patients with AAV.
Primary objective	To investigate if adjunctive hydroxychloroquine is ranked superior to placebo in controlling active disease.
Secondary objective(s)	To investigate if adjunctive hydroxychloroquine reduces the cumulative prednisolone dosage, vasculitis related damage, adverse events, ANCA titres and improves quality of life.
Trial design	Patients will be randomised into 2 treatment arms: hydroxychloroquine or placebo with minimisation for: ANCA (positive vs negative), age (</≥ 60 years), rituximab treatment and current smoking status (smoking reduces hydroxychloroquine effectiveness by inducing cytochrome P450 enzyme) to ensure the groups are balanced.
Endpoints	Using the Birmingham Vasculitis Activity Score (BVAS) version 3, the primary endpoint will be the percentage of patients with: EITHER

	• uncontrolled AAV disease activity (defined as BVAS > 3) at any point during the final 12 weeks (±7 days) of the study OR • controlled AAV disease activity (BVAS≤3) but prednisolone dose for AAV >7.5mg daily at any point during the final 12 weeks (±7 days) of the study. OR • controlled AAV disease activity (BVAS ≤3) but any corticosteroid use > 7.5mg daily for any reason at any point during the final 12 weeks (±7 days) of the study. BVAS will be scored every 4 weeks during the final 12 (±7 days) weeks. Secondary outcomes will evaluate: • Cumulative number of visits where BVAS = 0 (excluding screening, baseline and week 56) • Proportion of patients with treatment failure at week 52 • Cumulative prednisolone dosage • Total number of adverse events • Total number of infections per patient • Total number of vasculitis flares (major and minor) per patient excluding screening, baseline and week 56 • Time to remission • Time to first severe flare • Time to first limited flare • Proportion of patients categorized as having a severe flare at each of the time points in the trial schedule (section 5.4) excluding screening, baseline and week 56 • Proportion of patients categorized as having a limited flare at each of the time points in the trial schedule (section 5.4) excluding screening, baseline and week 56 • Absolute values and relative change from baseline in the Vasculitis Damage Index (VDI) at each time point outlined in the trial schedule (section 5.4). Exploratory outcomes: • Incidence of new diabetes mellitus • Lipid profile and prevalence of dyslipidaemia • Fatigue (FACIT score) • Quality of life (SF-36, EQ5D, HAQ, AAV PRO (patient reported outcome) forms) • Glucocorticoid toxicity index • Physician's Global Assessment (PGA) as per trial schedule 5.4 • ANCA titres as per trial schedule 5.4

	• Proportion of patients with medicine compliance of ≤80% (see section 8.10) • Absolute values and relative change from baseline in the renal variables: serum creatinine, serum albumin, urine protein:creatinine ratio at each time point outlined in the trial schedule (section 5.4).
Sample Size	76 patients (38 patients in each treatment arm).
Summary of eligibility criteria	1. Active AAV (new or previous clinical diagnosis of granulomatosis with Polyangiitis (GPA) or microscopic Polyangiitis (MPA) or a diagnosis of Eosinophilic Granulomatosis with Polyangiitis (EGPA) consistent with the Chapel-Hill consensus definitions) AND 2. BVAS >3 with ***Minor*** Birmingham Vasculitis Activity Score (BVAS) Items only (No Major BVAS items) AND 3. Provision of informed consent by patient. See section 7 for full eligibility criteria.
IMP, dosage and route of administration	**Hydroxychloroquine sulfate 200mg tablet:** Patients will start taking a dose of 200mg OD and this will be up-titrated after the first week to a maximum daily dose of 400mg OD (provided eGFR>50 ml/min). Patients weighing < 50kg and/or those with an eGFR of 30-50 ml/min will receive a reduced dose of 200mg OD for the duration of the trial.
Comparator product(s)	Placebo will be a visual match to the IMP. Patients weighing ≥ 50kg will take 2 placebo tablets daily, provided eGFR > 50ml/min. Those weighing < 50kg and/or those with an eGFR of 30-50 ml/min will take 1 placebo tablet daily.
Maximum duration of treatment of a patient	52 weeks
Version and date of protocol amendments	REC Submission – v2.0 dated 18/11/2019 Substantial Amendment 1 – v3.0 18/12/2019 Substantial Amendment 2 – v4.0 21/08/2020

2. Glossary of Terms

AAV	ANCA-associated Vasculitis
ACR	American College of Rheumatology
AE	Adverse Event
ANCA	Anti-Neutrophil Cytoplasmic Antibodies
Anti-MPO	Anti- Myeloperoxidase Antibodies
Anti-PR3	Anti-Proteinase 3 Antibodies
ALT	Alanine Transaminase
AR	Adverse Reaction
AST	Aspartate Transaminase
AUC	Area under the curve
AZA	Azathioprine
BVAS	Birmingham Vasculitis Activity Score
C-ANCA	Cytoplasmic Antineutrophil Cytoplasmic Antibodies
CHCC	Chapel Hill Consensus Conference
Chem	Chemistry
CI	Chief Investigator
CrCl	Creatinine Clearance
CRA	Clinical Research Associate
CRF	Case Report Form
CRP	C-Reactive Protein
CTCAE	Common Terminology Criteria for Adverse Events
CYC	Cyclophosphamide
DMC	Data Monitoring Committee
DMID	Division of Microbiology and Infectious Diseases
DSUR	Development Safety Update Report
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EEA	European Economic Area
EGPA	Eosinophilic Granulomatosis With Polyangiitis
ELISA	Enzyme-Linked Immunosorbent Assay
ESR	Erythrocyte Sedimentation Rate
FACIT	Functional Assessment of Chronic Illness Therapy
G6PD	Glucose-6 Phosphate Dehydrogenase
GPA	Granulomatosis with Polyangiitis
GCP	Good Clinical Practice
GMPU	Guys and St Thomas' NHS Foundation Trust Pharmacy Manufacturing Unit
GTI	Glucocorticoid Toxicity Index
HAQ	Health Assessment Questionnaire
HbA1C	Haemoglobin A1C
HCQ	Hydroxychloroquine
HDPE	High-Density Polyethylene
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form

IME	Important Medical Event
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IUD	Intrauterine Device
IUS	Intrauterine System
KCTU	King's Clinical Trials Unit
KHP-CTO	King's Health Partners Clinical Trials Office
MHRA	Medicines and Healthcare products Regulatory Agency
MPA	Microscopic Polyangiitis
MPO	Myeloperoxidase
MRC	Medical Research Council
MTX	Methotrexate
OD	Once daily
P-ANCA	Perinuclear Antineutrophil Cytoplasmic Antibodies
PGA	Physician's Global Assessment
PI	Principal Investigator
PIN	Patient Identification Number
PR3	Proteinase 3
PRO	Patient Reported Outcome
QALY	Quality-Adjusted Life-Year
REC	Research Ethics Committee
RSI	Reference Safety Information
RTX	Rituximab
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SF-36	36 Item Short Form Survey
SmPC	Summary of Product Characteristics
SoC	Standard of Care
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
SLE	Systemic Lupus Erythematosus
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
USAR	Unexpected Serious Adverse Reaction
VDI	Vasculitis Damage Index
WG	Wegener's Granulomatosis

3. Definitions

Disease activity will be assessed using BVAS v3 and the following definitions will be used:

3.1 Remission

Remission is defined as a BVAS = 0 on two consecutive visits planned to be at least 4 weeks apart, regardless of prednisolone treatment or dosage. Remission could be achieved at any point before or at the week 52 time point.

3.2 Limited Flare

Patients will be categorized as having a limited flare if they have a new or worsening minor item on the BVAS with no new major items.

3.3 Severe Flare

Patients will be categorized as having a severe flare if they have a new or worsening major item on the BVAS.

3.4 Uncontrolled Disease

Patients will be categorized as having uncontrolled AAV disease activity if they have BVAS >3.

3.5 Persistent Disease

Persistent disease indicates the presence of one or more persistent items on the BVAS with no new or worsening items.

3.6 Treatment Failure

Treatment failure is defined as:

- Death due to vasculitis disease activity.
- A severe disease flare resulting in organ failure or critical care admission.

Contents

4 Background

The systemic vasculitides encompass a group of autoimmune inflammatory diseases affecting blood vessels of all sizes and in any organ or system. They are life threatening diseases where the body's defence system becomes overactive, causing inflammation of small blood vessels. The term ANCA-associated vasculitis (AAV) describes a subset of primary small vessel vasculitides characterized by the presence of anti-neutrophil cytoplasmic antibodies (ANCA): granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA).

AAV are serious multisystem autoimmune disorders that can affect any organ in the body and commonly involve the ear-nose-throat, lungs, kidneys, eyes and joints. Uncontrolled disease activity can lead to organ failure and death. There are approximately 20,000 AAV patients in the UK, with 1,300 diagnosed annually [1].

Although immunosuppressive treatments have improved outcomes, mortality is double that of the general population[2], 20% have persistent uncontrolled disease and 50% relapse by 5 years[3], costing >£23 million/year for hospitalizations and reducing patients' incomes by a quarter[4].

AAV patients have a 20X prothrombotic tendency [5], 3X cardiovascular risk [6] and are at higher risk of immunosuppression related infections and cancer [2]. However, early therapy withdrawal, especially of glucocorticoids, is associated with disease flares, lower quality of life and increased costs [7].

There is an unmet need for safe, effective therapies for non-severe AAV to reduce disease activity, prevent disease progression and damage and minimise drug toxicity. Safer medications are needed for non-life threatening ANCA vasculitis, where aggressive immune suppressive medications are not appropriate.

Hydroxychloroquine (HCQ) is an effective, safe and inexpensive therapy with an established track record of disease modifying effects in autoimmune rheumatic diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis and Sjögren's syndrome [8-13]. Hydroxychloroquine is safer than other immunosuppressive treatments (including in pregnancy) and reduces cumulative prednisolone doses and their harmful effects [10]. Hydroxychloroquine has been used to treat cutaneous vasculitis [14] and rheumatoid vasculitis [12] but has never been assessed in AAV [15]. The pleiotropic effects of hydroxychloroquine on cytokines, neutrophils, autoreactive T and B lymphocytes involved in the pathogenesis of AAV, provide a mechanistic rationale for its potential effectiveness [15]. Hydroxychloroquine has beneficial effects on lipids, glucose levels and arterial stiffness [16]. Hydroxychloroquine has antimicrobial [17,18], antithrombotic [19] and antineoplastic [20-21] effects that could be useful in immunosuppressed AAV patients. Early treatment with hydroxychloroquine could potentially reduce progression to severe disease and the need for escalation to biologic therapy such as rituximab which is administered for refractory or relapsing AAV [22-24].

The HAVEN trial has been impacted by the novel coronavirus COVID-19 that began in Wuhan, China in 2019. Research was paused to prioritise clinical care, and patients with AAV on immunosuppressive medication may have been considered high risk by the government, and advised to 'shield' accordingly. Those shielding were to remain in their homes having received a letter from NHS England. These restrictions have since been lifted but are constantly under review by the government. Early on in the pandemic, HCQ was explored as a potential treatment and received widespread media attention. HCQ was found to be ineffective as a potential COVID-19 treatment, but the media highlighted a paper that suggested that HCQ led to increased mortality. This paper has since been withdrawn, but the retraction did not receive as much publicity and thus may have an impact on recruitment. HCQ in standard doses

remains extremely safe. The protocol has been amended in light of the pandemic and will continue to be reviewed by the Trial Steering Committee (TSC) as the pandemic progresses. Please see section 6.15 for more details.

4.1 Summary of Proposed Research

Hydroxychloroquine in ANCA Vasculitis Evaluation (HAVEN) is a UK multicentre randomised double-blind placebo-controlled trial in active non-severe AAV, to investigate if hydroxychloroquine is ranked superior to placebo in controlling active non-severe disease, defined as a Birmingham Vasculitis Activity Score [25] (BVAS)>3 with minor BVAS items only. 76 AAV patients (38 in each treatment arm) will be recruited from up to 10 UK specialist vasculitis centres over 2 years. Patients will be randomised in a 1:1 ratio to adjunctive hydroxychloroquine daily or placebo in addition to maintenance therapy with prednisolone +azathioprine, methotrexate, mycophenolate or maintenance rituximab therapy. Both groups will receive a tapering regimen of oral prednisolone.

A sample size of 72 patients (36 in each arm) will be required to correctly rank hydroxychloroquine as superior to placebo with 90% probability, assuming 50% of patients in the standard treatment group have uncontrolled vasculitis (BVAS >3) and that the true reduction in this rate due to hydroxychloroquine is 15%. 76 patients will be recruited to allow for a 5% drop-out rate. Our trial will address an important gap in existing AAV research, with implications for patients worldwide.

5 Trial Objectives & Design

5.1 Trial Objectives

The study aim is to test the hypothesis that the addition of hydroxychloroquine to background therapy improves clinical response and quality of life in patients with AAV.

5.1.1 Primary Endpoints

The primary endpoint will be the percentage of patients with

- uncontrolled AAV disease activity (defined as BVAS>3)
  OR
- controlled AAV disease activity (BVAS ≤3) but prednisolone dose for AAV >7.5mg daily
  OR
- controlled AAV disease activity (BVAS ≤3) but any corticosteroid use >7.5mg daily for any reason

at any point during the final 12 weeks of the study (±7 days).

Inhaled corticosteroids will not contribute to the primary endpoint, nor will methylprednisolone given for rituximab maintenance therapy.

BVAS will be scored every 4 weeks during the final 12 weeks (±7 days). The assessment of BVAS in the final 12 weeks (±7 days) will come from the week 44, 48, and 52 visits, at each of which BVAS will be assessed for the previous 4 weeks.

5.1.2 Secondary Endpoints and Exploratory Outcomes

Secondary outcomes will evaluate:

- Cumulative number of visits where BVAS = 0 (excluding screening, baseline and week 56)
- Proportion of patients with treatment failure at week 52
- Cumulative prednisolone dosage
- Total number of adverse events
- Total number of infections per patient
- Total number of vasculitis flares (major and minor) per patient excluding screening, baseline and week 56
- Time to remission
- Time to first severe flare
- Time to first limited flare
- Proportion of patients categorized as having a severe flare at each of the time points in the trial schedule (section 5.4) excluding screening, baseline and week 56
- Proportion of patients categorized as having a limited flare at each of the time points in the trial schedule (section 5.4) excluding screening, baseline and week 56
- Absolute values and relative change from baseline in the Vasculitis Damage Index (VDI) at each time point outlined in the trial schedule (section 5.4).

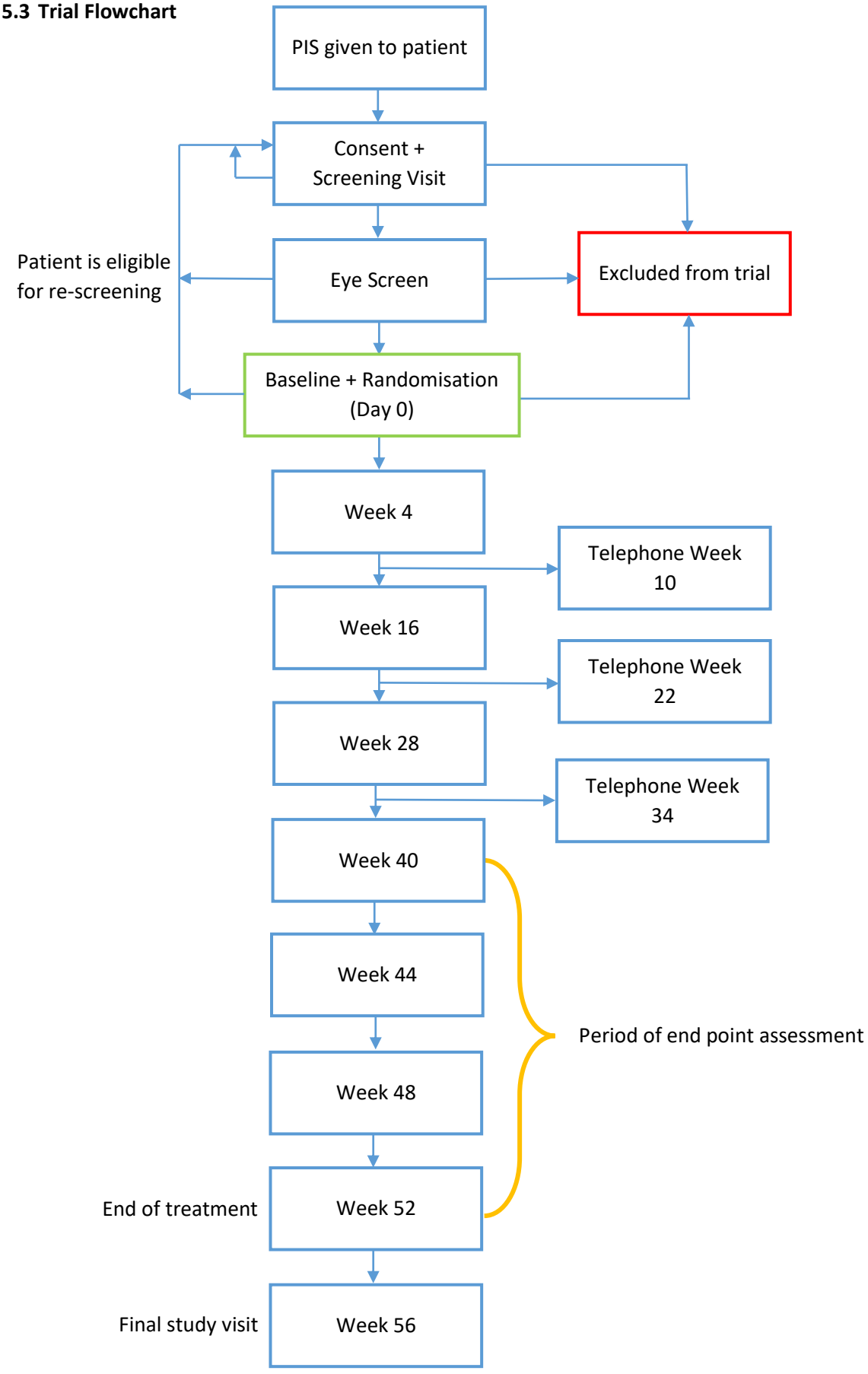
Exploratory outcomes will evaluate:

- Incidence of new diabetes mellitus
- Prevalence of dyslipidaemia
- Fatigue (FACIT score)
- Quality of life (SF-36, EQ5D, HAQ, AAV PRO (patient reported outcome) forms)
- Glucocorticoid toxicity index
- Physician's Global Assessment (PGA) as per trial schedule 5.4
- ANCA titres as per trial schedule 5.4
- Proportion of patients with medicine compliance of ≤80% (see section 8.10)
- Absolute values and relative change from baseline in the renal variables: serum creatinine, serum albumin, urine protein: creatinine ratio at each time point outlined in the trial schedule (section 5.4).

5.2 Trial Design

A double-blind, placebo-controlled multi-centre trial. Patients will be randomised to receive hydroxychloroquine or placebo in a 1:1 ratio, in addition to Standard of Care (SoC) maintenance therapy with prednisolone and stable doses of azathioprine, methotrexate, mycophenolate or maintenance therapy with B-cell depleting therapy (rituximab). Each patient will be treated with adjunctive hydroxychloroquine 400 mg daily (or placebo) with dose reduction according to actual body weight and renal function at baseline plus maintenance immunosuppressive treatment for 52 weeks.

5.3 Trial Flowchart



5.4 Trial Schedule

Study Visits[i]	Screen	Baseline	WK4	WK10 Telephone	WK16	WK 22 Telephone	WK28	WK 34 Telephone	WK40	WK44	WK48	WK52 End of study treatment	Follow up Wk56	Withdrawal [ii]
Visit Number	**1**	**2**	**3**	**-**	**4**	**-**	**5**	**-**	**6**	**7**	**8**	**9**	**10**	**-**
Day (Visit window)	**Up to 35 days**	**0**	**28** (± 7)	**70** (± 7)	**112** (± 7)	**154** (± 7)	**196** (± 7)	**238** (± 7)	**280** (± 7)	**308** (± 7)	**336** (± 7)	**364** (± 7)	**392** (± 7)	
Patient information and informed consent	X													
Study Drugs:														
IMP dispensing		X	X		X		X		X					
IMP dose recording / review of patient diary			X		X		X		X	X	X	X		X
Prednisolone dose recording	X	X	X		X		X		X	X	X	X	X	X
Data Forms:														
COVID symptom assessment	X	X	X		X		X		X	X	X	X	X	X
Eye screen by local optometrist	X													
Eligibility	X	X[iii]												
Randomisation		X												
Medical history including smoking history	X													
Demographics	X													
Physical exam	X	X	X		X		X		X	X	X	X	X	X
Weight	X	X	X		X		X		X	X	X	X	X	X
Vital signs[iv]	X	X	X		X		X		X	X	X	X	X	X
Urine dipstick	X	X	X		X		X		X	X	X	X	X	X
ECG	X				X									
Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BVAS[v]	X	X	X		X		X		X	X	X	X	X	X
VDI		X			X		X			X		X		
GTI		X					X					X		
Physician's Global Assessment	X	X	X		X		X		X	X	X	X	X	X
Urine drug screen	X													

Study Visits	Screen	Baseline	WK4	WK10 Telephone	WK16	WK 22 Telephone	WK28	WK 34 Telephone	WK40	WK44	WK48	WK52 End of study treatment	Follow up Wk56	Withdrawal [ii]
Visit Number	**1**	**2**	**3**	**-**	**4**	**-**	**5**	**-**	**6**	**7**	**8**	**9**	**10**	**-**
Day (Visit window)	**Up to 35 days**	**0**	**28** (± 7)	**70** (± 7)	**112** (± 7)	**154** (± 7)	**196** (± 7)	**238** (± 7)	**280** (± 7)	**308** (± 7)	**336** (± 7)	**364** (± 7)	**392** (± 7)	
SF-36, EQ5D, HAQ and AAV Pro		X		X[vi]	X	X[vi]	X	X[vi]		X		X	X	X
FACIT score		X			X		X			X		X	X	X
Adverse event reporting		X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Labs:														
ANCA	X				X		X		X			X	X	X
ESR, CRP		X			X		X		X			X	X	X
Glucose		X			X		X		X			X	X	X
HbA1C	X						X					X		
Lipids	X						X					X		
Renal profile including creatinine and eGFR	X	X	X		X		X		X			X	X	X
Full blood count	X	X	X		X		X		X			X	X	X
Liver function tests	X	X	X		X		X		X			X	X	X
Protein: creatinine ratio[vii]	X	X	X		X		X		X	X	X	X	X	X
Viral screen[viii]	X													
Pregnancy test[ix]	X	X												
Research Blood Specimens:														
Hydroxychloroquine levels		X			X		X					X		
Plasma, Serum and Cells[x]		X			X		X		X			X		X[xi]

i Patients will be followed up by telephone at weeks 10, 22 and 34 rather than visiting the study centre. The phone call will be structured using the AAV pro questionnaire. See section 6.13 for more details.

[ii] To be arranged if a patient withdraws from the trial but is willing to have a final study visit. This is only necessary in instances where the patient's last visit was more than 4 weeks ago.

[iii] The eligibility criteria require BVAS to be scored and for female patients to have a pregnancy test at baseline as well as screening. Other screening procedures do not need to be repeated.

[iv] Vital signs to include BP, pulse, respiration rate and temperature.

[v] BVAS and VDI to be scored locally following training. BVAS scores will be quality checked by a central adjudication panel to ensure consistency.

[vi] Telephone follow up interviews will only use the AAV Pro questionnaire to structure the conversation. The SF-36, EQ5D and HAQ questionnaires will not be included.

[vii] Protein:creatinine ratio should only be performed if urine dipstick for protein shows 1+ or more.

[viii] Patients who test positive for hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody or HIV-1 will be excluded.
[ix] Urine pregnancy test.
[x] Plasma and serum collected at all sites. Cells at Guy's Hospital only.
[xi] Samples only collected if the patient is identified as having a flare.

6 Trial Procedures

6.1 Screening

Patient information and informed consent

COVID symptom assessment

Patient eligibility

Medical history including smoking history

Medication history

Prednisolone dose recording

Demographics

Physical exam

Weight

Vital signs: BP, pulse, respiration, temperature

Eye screen

Urine dipstick (if protein shows 1+ or more then perform protein: creatinine ratio)

ECG

BVAS

Physician's global assessment (PGA) Urine pregnancy test

Urine drug test

Blood tests: HbA1c, Lipids, ANCA, Renal profile, Full blood count, Liver function test, Viral screen

6.2 Baseline

COVID symptom assessment

Physical exam

Weight, vital signs and urine dipstick (if protein shows 1+ or more then perform protein: creatinine ratio)

Patient eligibility

Medication history

Prednisolone dose recording

BVAS and VDI

Glucocorticoid Toxicity Index (GTI)

PGA

Patient questionnaires: SF36, EQ5D, HAQ and AAV Pro

FACIT score

Urine pregnancy test

Adverse event reporting

Clinical labs: ESR, CRP, Glucose, Renal profile, Full blood count, Liver function test

Research specific bloods collection

Randomisation

IMP dispensing

6.3 Week 4

COVID symptom assessment

Physical exam

Weight, vital signs and urine dipstick (if protein shows 1+ or more then perform protein: creatinine ratio)

Medication history

BVAS

PGA

IMP dispensing

IMP dose recording

Prednisolone dose recording

Adverse event reporting

Clinical Labs: Renal profile, Full blood count, Liver function test

6.4 Week 16

COVID symptom assessment

Physical exam

Weight, vital signs and urine dipstick (if protein shows 1+ or more then perform protein: creatinine ratio)

IMP dispensing

IMP dose recording

Prednisolone dose recording

BVAS and VDI

PGA

ECG

Medication history

Patient questionnaires: SF36, EQ5D, HAQ and AAV Pro

FACIT score

Adverse event reporting

Clinical labs: ANCA, ESR, CRP, Glucose, Renal Profile, Full blood count, Liver function test

Research specific bloods collection

6.5 Week 28

COVID symptom assessment

Physical exam

Weight, vital signs and urine dipstick (if protein shows 1+ or more then perform protein: creatinine ratio)

IMP dispensing

IMP dose recording

Prednisolone dose recording

BVAS and VDI

PGA

GTI

Medication history

Patient questionnaires: SF36, EQ5D, HAQ and AAV Pro

FACIT score

Adverse event reporting

Clinical labs: ANCA, ESR, CRP, Glucose, HbA1C, Lipids, Renal profile, Full blood count, Liver function test

Research specific bloods collection

6.6 Week 40

COVID symptom assessment

Physical exam

Weight, vital signs and urine dipstick (if protein shows 1+ or more then perform protein: creatinine ratio)

Medication history

BVAS

PGA

IMP dispensing

IMP dose recording

Prednisolone dose recording

Adverse event reporting

Clinical labs: ANCA, ESR, CRP, Glucose, Renal profile, Full blood count, Liver function test

Research specific bloods collection

6.7 Week 44

COVID symptom assessment

Physical exam

Weight, vital signs and urine dipstick (if protein shows 1+ or more then perform protein: creatinine ratio)

IMP dose recording

Prednisolone dose recording

BVAS and VDI

PGA

Medication history

Patient questionnaires: SF36, EQ5D, HAQ and AAV Pro

FACIT score

Adverse event reporting

6.8 Week 48

COVID symptom assessment

Physical exam

Weight, vital signs and urine dipstick (if protein shows 1+ or more then perform protein: creatinine ratio)

IMP dose recording

Prednisolone dose recording

BVAS

PGA

Medication history

Adverse event reporting

6.9 Week 52

COVID symptom assessment

Physical exam

Weight, vital signs and urine dipstick (if protein shows 1+ or more then perform protein: creatinine ratio)

IMP dose recording

Prednisolone dose recording

BVAS and VDI

PGA

GTI

Medication history

Patient questionnaires: SF36, EQ5D, HAQ and AAV Pro

FACIT score

Adverse event reporting

Clinical labs: ANCA, ESR, CRP, Glucose, HbA1C, Lipids, Renal profile, Full blood count, Liver function test

Research specific bloods collection

6.10 Follow-up Visit Week 56

COVID symptom assessment

Physical exam

Weight, vital signs and urine dipstick (if protein shows 1+ or more then perform protein: creatinine ratio)

Prednisolone dose recording

BVAS

PGA

Patient questionnaires: SF36, EQ5D, HAQ and AAV Pro

FACIT score

Medication history

Adverse event reporting

Clinical labs: ANCA, ESR, CRP, Glucose, Renal profile, Full blood count, Liver function test

6.11 Unscheduled Visits

To be arranged at the discretion of the treating physician to assess events related to disease or treatments. Data should be recorded in the disease flare log, and any changes to prednisolone dose and adverse events should be recorded.

6.12 Withdrawal Visit

In the instance that a patient withdraws from the trial, the patient should be asked whether they are happy to visit the hospital for a withdrawal visit. This is only required in instances where the patient withdraws more than 4 weeks since their last hospital trial visit, and should follow the schedule below. If the patient is unable to visit the hospital, but is happy to have a telephone interview, as much of the following should be completed as possible.

COVID symptom assessment

Physical exam and clinical data

Weight, vital signs and urine dipstick (if protein shows 1+ or more then perform protein: creatinine ratio)

Prednisolone dose recording

IMP dose recording

BVAS

PGA

Medication history

Patient questionnaires: SF36, EQ5D, HAQ and AAV Pro

FACIT score

Adverse event reporting

Clinical labs: ANCA, ESR, CRP, Glucose, Renal profile, Full blood count, Liver function test

Research specific bloods collection – these should only be taken if the patient is identified as having a flare.

6.13 Telephone Interviews

Between weeks 4 and 40, patients will be followed up by phone 6 weeks after each study visit. This phone call will be based on the AAV Pro questionnaire and patients will be asked for their list of current medications. Patients will also be encouraged to report any adverse events. Patients reporting new items or worsening previous symptoms will be invited to the hospital for unscheduled visits (as per 6.11). Patients will be encouraged to contact their research team if their symptoms get worse between visits.

6.14 Laboratory Tests

Additional blood samples will be taken for research purposes at the same time as routine blood tests, according to the schedule in the table below. Consent for blood samples taken for future research will be optional (i.e. the blood for serum, plasma and PBMCs), but all patients will need to provide consent for the collection of whole blood for the analysis of hydroxychloroquine levels. Patients who attend the hospital for a withdrawal will only have research bloods taken if they are identified as having a flare.

Sample Type	Baseline	Week 16	Week 28	Week 40	Week 52	Unscheduled
Blood for serum (6mls)	X	X	X	X	X	X
Whole blood for Hydroxychloroquine levels (4mls)	X	X	X		X	
Blood for plasma (6mls)	X	X	X	X	X	X
Blood for PBMCs for **Guy's patients only** (40mls)	X	X	X	X	X	X

Sample tubes will be labelled. The labels will be provided by the HAVEN coordinating centre, Guy's Hospital.

All blood samples will be centrifuged at 1100g for 20 minutes in the first instance. In addition, plasma will be separated from the supernatant and centrifuged at 1100gfor an extra 10 minutes.

Storage will take place at -80 degrees Celsius (the equivalent of -112 degrees Fahrenheit) in each local participation centre until the end of the study. On completion of the trial, all samples will be shipped via courier to the T-cell Signalling laboratory at King's College London within Guy's Hospital. In the instance that sites only have access to a -20°C freezer, samples will be shipped every 3 months to Guy's, where they will be stored at -80°C.

Blood samples for hydroxychloroquine levels will be analysed for the association between adherence with medication, hydroxychloroquine levels and vasculitis activity.

6.15 COVID-19 Adjustments

All participants should be contacted no more than 5 days prior to each appointment to confirm that they do not have any COVID symptoms. Patients who do have symptoms should be encouraged to stay at home and follow government advice for testing. Study visits may need to be rescheduled as a result.

In the instance that the patient tests positive at screening or baseline, they may be re-screened after three months.

If patients become COVID symptomatic at any point in the study, they should follow the routine NHS pathway for antigen swab testing and self-isolate as per government advice. If a patient tests positive, this should be recorded as an adverse event. These patients should be treated according to best practice, but may continue on the study treatment at the discretion of the treating physician. Patients admitted to hospital with COVID but who do not need critical care admission should suspend immunosuppressive therapy and study medication until the patient recovers and they can then resume treatment per protocol. Patients who are admitted to hospital with a critical care admission following COVID infection should be withdrawn from the IMP.

It is anticipated that patients may have to self-isolate despite not having symptoms (e.g. if a household member displays symptoms). If this occurs during screening, then the baseline visit may be postponed (but for no longer than two weeks), providing the patients remains symptomless. Screening procedures will not need to be repeated.

7 Selection and Withdrawal of Patients

7.1 Inclusion Criteria

Patients:

1. Are at least 18 years of age at screening.

2. Have a clinical diagnosis of Granulomatosis Polyangiitis (GPA) or a diagnosis of Microscopic Polyangiitis (MPA) or a diagnosis of Eosinophilic Granulomatosis with Polyangiitis (EGPA) according to the Chapel Hill criteria (Appendix 1).

3. Have a Birmingham Vasculitis Activity Score >3 BVAS v.3 (Appendix 2) with minor BVAS items only (no major BVAS items) and be receiving maintenance therapy at a stable dose for 4 weeks prior to randomisation. BVAS should be > 3 at screening and at randomisation.

4. Patients receiving corticosteroids for reasons other than vasculitis must be on a stable regimen for four weeks prior to randomisation.

5. A female patient is eligible to enter the study if she is:

- Not pregnant or nursing
- Of non-childbearing potential (i.e., women who have had a hysterectomy, are postmenopausal, defined as ≥1 year without menses, have both ovaries surgically removed or have documented tubal ligation or other permanent sterilization procedure); or
- Of childbearing potential. These women must have a negative urine pregnancy test at screening and at baseline and be using at least one effective method of contraception. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Consistent and correct use of one of the following acceptable methods of birth control for 1 month prior to the start of the study agent, during the study, and 16 weeks after the last dose of study agent:
  - Oral contraceptive, either combined or progestogen alone
  - Injectable progestogen
  - Implants of levonorgestrel or etonogestrel
  - Estrogenic vaginal ring
  - Percutaneous contraceptive patches

- Intrauterine device (IUD) or intrauterine system (IUS) with <1% failure rate as stated in the product label

6. No contraindications to hydroxychloroquine therapy and normal baseline visual fields at screening.

7. Willing and able to give written informed consent to participate in the trial.

8. Patients should have sufficient English in order to provide informed consent and complete the patient questionnaires.

7.2 Exclusion Criteria

1. Patients currently taking hydroxychloroquine or related antimalarial such as mepacrine or chloroquine.

2. Patients with eGFR <30 ml/min.

3. Patients weighing <40kg.

4. Sensitivity, anaphylaxis or allergy to hydroxychloroquine or any other 4-aminoquinoline compound.

5. Known glucose 6 phosphate dehydrogenase deficiency.

6. Known lactose intolerance.

7. Evidence of plaque psoriasis.

8. Concomitant use of the following medications:

- Tumour necrosis factor inhibitor treatment (e.g. etanercept)
- Cyclophosphamide
- Abatacept
- Alemtuzumab
- Any experimental or biological therapies
- Intravenous, intramuscular or sub-cutaneous immunoglobin
- Plasma exchange
- Antithymocyte globulin
- Tamoxifen
- Live vaccines

9. B cell depleting therapy (rituximab) for remission induction. Rituximab maintenance therapy is permitted.

10. Severe or rapidly progressive ANCA vasculitis with at least one major BVAS item.

11. Have clinical evidence of significant unstable or uncontrolled acute or chronic diseases not due to vasculitis (i.e., cardiovascular, pulmonary, hematologic, gastrointestinal, hepatic, renal, neurological, malignancy or infectious disease) which, in the opinion of the principal investigator, could confound the results of the study or put the patient at undue risk.

12. Have a history of malignant neoplasm within the last 5 years, except for adequately treated cancers of the skin (basal or squamous cell) or carcinoma in situ of the uterine cervix.

13. Have current drug or alcohol abuse or dependence, or a history of drug or alcohol abuse or dependence within 364 days prior to randomisation. A urine drug screen should be performed and confirmed negative prior to study entry.

14. Have a historically positive test or test positive at screening for hepatitis B surface antigen, hepatitis B core antibody or hepatitis C antibody or are known to be HIV-1 positive.

15. Have a Grade 3 or greater laboratory abnormality based on the CTCAE toxicity scale (version 5), unless considered by the investigator to be related to the underlying disease or induction therapy.

16. Screening 12-lead ECG that demonstrates clinically relevant abnormalities that may affect patient safety or interpretation of study results, including: – QT interval corrected using the same consistent formula at each visit (QTc) > 470 msec for female > 450 msec for male patients demonstrated by at least two ECGs.

17. Participation in any other interventional trial within the last 6 months.

18. Have a current symptomatic COVID-19 infection.

19. Have been admitted to the ICU in the past 6 months due to a COVID-19 infection.

7.3 Selection of Participants and Informed Consent

Participants will be recruited from the outpatient hospital clinics at study sites (specialist vasculitis centres based in the UK). Patients will be identified and approached by members of their direct care team (at some sites this may also be the research team). During the COVID-19 pandemic, routine appointments may instead take place through telephone consultations or virtual online clinics, and patients will be approached at these appointments. Sites will have posters advertising the study, directing potential participants to discuss with their local research team. Participants may be signposted to the study through social media or the study website, which will have details of the local participating sites.

Potential participants will be given as much time as they need to make a decision about participation and will be provided the opportunity to ask any questions they may have to the PI or delegated member of the research team. Participants will be encouraged to discuss with their friends, family or GP as needed. Patients will be asked to provide written informed consent to the Principal Investigator or a delegated sub-investigator, and the participant will be assured that they are under no obligation to participate, and that they can withdraw their consent at any time without providing a reason. The participant will be given a copy of the PIS and signed consent form to take home. A copy of the signed consent form will also be stored in the Investigator Site File and the participant's medical records.

Participants who satisfy the inclusion/exclusion criteria and provide consent will be randomised. All questions about eligibility criteria will be asked prior to randomisation.

7.3.1 Screen Failures

Re-screening refers to repeating the whole screening process. Re-screening is allowed if a patient has not met all of the eligibility criteria within the original screening period.

Patients are only allowed to be re-screened once. The interval time between initial screen fail and re-screening should be at least 4 weeks. Each patient must be re-consented before re-screening occurs. All screening procedures must be repeated.

Patients who are re-screened within a year do not need to repeat their eye screen. Patients who have not had their eye screen within 35 days of screening can have their screening period extended to 60 days, after discussion with trial management team. Patients who have had an eye screen within 6 months of screening and who have a report available do not need to repeat eye screen.

In the instance that the patient tests positive for COVID at screening or baseline, they may be re-screened after three months. Patients who do not test positive for COVID but are asked to self-isolate

(e.g. a household member has symptoms) can have their baseline visit delayed by up to 2 weeks to allow for those in quarantine. Screening procedures will not need to be repeated.

7.4 Randomisation Procedure/Code Break

7.4.1 Randomisation

Randomisation will be via a bespoke web-based randomisation system hosted by the KCTU. Authorised site staff will be allocated a username and password for the randomisation system via the Trial Manager. An authorised staff member will log into the randomisation system (www.ctu.co.uk), click 'randomisation' and select 'HAVEN', and enter the patient's details, including the unique PIN. Once a patient is randomised, the system will automatically generate emails to key staff within the study. Additional blinded emails may be generated from the randomisation system to key trial site staff depending on their role in the study.

Data will be exported upon request and passed to the trial statistician. Data may be exported in blinded, subgroup blinded, or unblinded formats.

Patients will be randomised with minimisation for: ANCA (positive vs negative), age (</≥ 60 years), rituximab treatment and current smoking status (smoking reduces hydroxychloroquine effectiveness by inducing cytochrome P450 enzyme) to ensure the groups are balanced. Current smoker status will be defined as anyone who has smoked tobacco or used nicotine replacement (e.g. vaping) in the past month.

7.4.2 Emergency Code Break

24hr Emergency Code Break and Medical Information will be provided by ESMS Global. The ESMS unblinding telephone number is 020 3282 0458.

Each randomised patient will be provided with a card detailing emergency contact details. Patients will be requested to carry this card with them at all times whilst participating in the trial.

7.5 Withdrawal of Participants

Participants have the right to withdraw from the study at any time and for any reason without affecting their routine medical care. The investigator also has the right to withdraw patients from the study drug in the event of inter-current illness, AEs, SAEs, and SUSARs, protocol violations, cure, administrative reasons or other reasons. Patients who become pregnant will be withdrawn from the study. It is understood by all concerned that an excessive rate of withdrawals can render the study un-interpretable. Therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible. A withdrawal visit should be arranged if agreed with the patient (see section 6.12). Should a patient withdraw from study drug only, efforts will be made to continue to obtain follow-up data, with the permission of the patient.

Participants who wish to withdraw from trial medication (IMP) will be asked to confirm whether they are still willing to provide trial specific data at study visits.

7.6 Expected Duration of Trial

The end of the trial will be defined as data lock. We will aim to recruit all 76 study patients over the course of 2 years. Each individual participant will remain in the trial for 52 weeks after randomisation. Therefore patient visits will take place over a period of 36 months. There will be one follow-up safety visit, 4 weeks after discontinuation of the study medication.

Study medication will not be provided after the end of the trial. If patients wish to take hydroxychloroquine, this will be at the discretion of the treating physician and local guidelines for the prescription and monitoring of hydroxychloroquine will be followed.

8 Trial Medications

8.1 Investigational Medicinal Products (IMPs)

The IMPs for this trial are:

- Hydroxychloroquine sulfate 200mg film-coated tablets. Hydroxychloroquine 200mg is presented as a white, round, film-coated tablet marked 'HCQ' on one side and '200' on the other side. Excipients: Lactose monohydrate, maize starch, magnesium stearate, polyvidone, Opadry OY-L-28900 (containing hypromellose, macrogol 4000, titanium dioxide (E171) and lactose).

- Placebo to match the hydroxychloroquine sulfate 200mg tablets. Excipients: Microcrystalline cellulose, lactose and magnesium stearate.

Guys and St Thomas' NHS Foundation Trust Pharmacy Manufacturing Unit (GPMU) are contracted to manufacture, package, label, QP release and distribute IMP to sites.

The Kings Clinical Trials Unit (KCTU) Intervention Management System will be used to allocate blinded supplies to patients. Each IMP pack will have a unique treatment pack number.

The (KCTU) trials pharmacist will maintain IMP stock levels, both centrally and at investigational sites, and will be responsible for ordering study drug for sites.

Trial specific stock will be distributed to each site once all regulatory and local approvals are in place.

The IMP will be dispensed by the pharmacy department against a trial specific prescription in accordance with the trial schedule (refer to section 5.4).

Refer to the Summary of Product Characteristics (SmPC) and the Simplified Investigational Medicinal Product Dossier (sIMPD) for more detail about the active and placebo IMPs.

Hydroxychloroquine has not been patented by any other individual or organisation for the treatment of individuals with AAV.

8.2 Dosing Regimen for IMPs

Patients will be randomised in a 1:1 ratio to adjunctive hydroxychloroquine or placebo daily in addition to maintenance therapy with prednisolone + azathioprine, methotrexate, mycophenolate or maintenance rituximab therapy. Both groups will receive a tapering schedule of oral prednisolone (refer to section 8.3 of the protocol).

Dosing table:

Patients weight and renal function	Dose
≥ 50kg and eGFR > 50ml/min	ONE tablet ONCE a day, increasing to TWO tablets ONCE a day after 7 days.
< 50kg and/or eGFR 30-50ml/min	ONE tablet ONCE a day for the duration of the trial.
If a patient's eGFR decreases to between 30-50ml/min during the trial	Reduce the dose to ONE tablet ONCE a day for the remainder of the trial

Patients weighing ≥ 50kg and with an eGFR of >50ml/min at baseline will receive either hydroxychloroquine 400mg (2 x 200mg) or two placebo tablets daily. The IMP will be started at a dose of 200mg OD and up-titrated after the first week to a maximum daily dose of 400mg, if permitted/required, taken orally for a total duration of 12 months.

Patients weighing < 50kg, and/or those patients with an eGFR of 30-50ml/min, will receive a reduced dose of either hydroxychloroquine 200mg (1 x 200mg) or one placebo tablet daily.

The IMP should be taken with or after food.

8.2.1 Permitted Dose Adjustment

If a patient's eGFR falls to between 30ml/min to 50ml/min at any point during the trial, the dose must be reduced to 200mg daily or one placebo tablet daily. The patient will remain on the reduced dose for the duration of the trial, even if the patient's renal function improves.

8.3 Dosing Regimen for Prednisolone

Standardised prednisolone will be administered to treat active AAV in all study patients. All study patients will be encouraged to take prednisolone as per tapering schedule below.

The recommended initial protocolised tapering schedule below will be followed:

Week	Maximum prednisolone dose (mg) / day
1 – 2	20 mg
3 – 4	15 mg
5 – 6	12.5 mg
7 – 8	10 mg
9 – 10	7.5 mg
11 – 12	7.5 mg
13 – 16	5 mg
17 – 26	5 mg (attempt to reduce prednisolone gradually below 5 mg, aiming to discontinue by 26 weeks)
26 – 52	Aim for prednisolone 0mg if clinical situation allows

8.3.1 Rescue Increases of Prednisolone

Patients experiencing increased disease activity will be permitted to have rescue doses of prednisolone as per clinical judgement, with a view to taper the prednisolone to the baseline dose preceding the flare.

Patients requiring prednisolone doses >7.5mg daily after 40 weeks, i.e. in the final 12 weeks of the study, will be permitted to continue in the study but will meet the end point category of uncontrolled disease activity/controlled but requiring prednisolone doses >7.5mg daily.

8.4 Packaging of IMP

All active and placebo tablets will be packed in labelled HDPE bottles with a child-security lid. Each HDPE bottle will contain 95 active or placebo tablets. Two bottles is sufficient for 12 weeks supply (at 2 tablets per day) and one bottle is sufficient for 12 weeks supply (at 1 tablet a day).

8.5 Storage of IMP

Do not store the IMP above 25^{o}C. Store in its original packaging.

If the IMP is exposed to temperatures above 25^{o}C, all affected supplies must be quarantined and the CRA and Trial Manager notified immediately.

8.6 Study Medication Labelling

All bottles will be labelled with an Annex 13 compliant clinical trial label. Each bottle will be assigned a unique pack number. The information presented on the labels for the IMP will comply with applicable national and local regulations.

8.7 Drug Accountability

The pharmacy clinical trials team must maintain accurate accountability records of the IMP, including, but not limited to, the number of bottles/tablets received, the number of bottles/tablets dispensed to which patient, batch number, expiry date, and the date of the transaction in addition to the quantity of investigational product returned by each patient.

Patients will be asked to return any unused IMP and/or empty packaging at each study visit and at the end of the active study period. The study drug returns will be returned to pharmacy by the research team for accountability. The returns will be verified by the pharmacy clinical trials team and the CRA prior to disposal at site. Destruction of IMP must be in accordance with the site IMP destruction SOP.

8.8 Management of Disease Flares

AAV is a relapsing remitting disease and flares may occur at any time during the disease course. Risk factors for disease flares include persistent or rising ANCA titres, upper airway disease, normal renal function, lower cumulative cyclophosphamide exposure and therapy withdrawal. Patients experiencing a disease flare should remain in the study and continue taking the study drug. Patients with a disease flare, or those reporting new or worsening symptoms, will be invited to the study centre for an unscheduled visit to assess and treat the flare (see section 6.11). Subsequent unscheduled visits should be arranged at the physician's discretion until the flare has been resolved. Current therapy doses may be increased at the discretion of treating physician. All medications should be recorded in the Case Record Form.

8.8.1 Life Threatening Flare

If a participant develops a severe life threatening flare, they could be continued in the study at the discretion of their treating physician. If a patient develops end stage renal failure or requires a critical care admission, they should be withdrawn from the IMP.

8.8.2 Discontinuation from the Study Drug

Clinicians are advised that the study drug should not be stopped in the instance of an adverse event (serious or otherwise) without prior discussion with the local PI. Patients who experience an adverse event leading to treatment discontinuation will be treated according to best medical judgment. For such patients, data will continue to be collected according to the study protocol where possible.

8.9 IMP Risks of Hydroxychloroquine

Cautions (as listed in the SmPC)

Acute porphyrias; diabetes; elderly; Glucose-6 phosphate dehydrogenase (G6PD) deficiency; may aggravate myasthenia gravis; may exacerbate psoriasis; neurological disorders (especially in those with a history of epilepsy); severe gastro-intestinal disorders. Patients will be assessed at screening and a clinical decision will be made on whether to include a patient with any of these conditions providing the inclusion and exclusion criteria are met.

8.9.1 Screening for Ocular Toxicity

A review group convened by the American Academy of Ophthalmology has updated guidelines for screening to prevent ocular toxicity on long-term treatment with chloroquine and hydroxychloroquine [26]. The risk of retinal toxicity is very low and is only 1% after 5 years and less than 2% after 10 years of use. In this study with a treatment duration of 12 months where half the patients will be on placebo, the risk of retinal toxicity is negligible.

The following recommendations relate to hydroxychloroquine in the HAVEN trial:

Before treatment:

- Assess renal function and patient weight (adjust dose of hydroxychloroquine or placebo if impaired or body weight ≤50kg as per section 8.2 Dosing Regimen for IMPs).
- All patients should undergo a screening visit by a local optometrist who should ask the patient about visual impairment (not corrected by glasses). Near visual acuity of each eye (with glasses where appropriate) should be recorded using a standard reading chart and assess visual fields using standard methods.
- The report from the optician should be recorded in the eCRF.
- If impairment or eye disease is present, but normal visual fields are recorded, referral to an ophthalmologist should be considered and the patient should continue to randomisation.
- Initiate study treatment if no relevant abnormality detected.
- The patient costs of the optometrist's assessment will be reimbursed upon provision of a valid receipt.

During treatment:

- Ask patient about visual symptoms.
- Refer to an ophthalmologist if visual acuity changes or if vision blurred and warn patient to seek prescribing doctor's advice about stopping treatment.

If long-term treatment is required after the end of the HAVEN trial, retinal screening assessments should be agreed with the local ophthalmologist in accordance with the current guidelines.

8.10 Patient Compliance

Patients will receive dosing instructions and be instructed to bring all tablet bottles (opened and unopened) to each study visit for assessment of compliance (based on the tablets remaining in the bottles). Patients will be asked to fill in the patient diary on a weekly basis and to record their IMP and prednisolone doses and any changes in symptoms. In the instance that the patient does not return the bottle, the diary may be used to estimate compliance.

Compliance will be documented on the source record by the research nurse. If compliance is ≤ 80% (based on number of tablets taken/returned), the investigator or designee is to counsel the patient and ensure steps are taken to improve compliance.

If compliance is ≥ 120%, it will be considered as an overdose and requires escalation to the Trial Steering Committee, as, additionally to counselling the patient, sites may need to take additional steps to ensure patient safety is not at risk.

8.10.1 Analysis of Study Medication Adherence, Disease Activity and Hydroxychloroquine Levels

Blood samples to measure hydroxychloroquine levels will be taken at four visits and analysed for the association between adherence with medication, hydroxychloroquine levels and vasculitis disease activity by BVAS.

8.11 Concomitant Medication

All patients will be on maintenance therapy with prednisolone + stable doses of azathioprine, methotrexate, mycophenolate mofetil, or rituximab maintenance and must be on a stable dose of maintenance therapy for 4 weeks prior to randomisation. Patients on rituximab maintenance should have the standard methylprednisolone 100mg dose. This standard dose will not contribute to the primary endpoint. Patients experiencing major flares requiring increased prednisolone/immunosuppressive treatment in addition to study protocol will receive rescue treatment according to best clinical care but study clinicians will continue to record their data as part of the study. See section 8.3.1 for rescue doses of prednisolone.

For management of concomitant therapies, please refer to the Summary of Product Characteristics. A complete listing of all concomitant medication received during the treatment phase must be recorded in the relevant CRF.

8.11.1 Prohibited Concomitant Medication

The following therapies are prohibited for all patients during the study:

- Tumour necrosis factor inhibitor treatment (e.g. etanercept)
- Cyclophosphamide
- Abatacept
- Alemtuzumab
- Any experimental or biological therapies
- Intravenous, intramuscular or sub-cutaneous immunoglobin
- Plasma exchange
- Antithymocyte globulin
- Tamoxifen
- Live vaccines

9 Assessment of Efficacy

9.1 Efficacy Endpoints

The primary endpoint will be the percentage of patients with uncontrolled AAV disease activity (defined as BVAS>3), or controlled AAV disease activity (BVAS ≤3) but prednisolone dose for AAV >7.5mg daily, or controlled AAV disease activity (BVAS ≤3) but any corticosteroid use > 7.5mg daily for any reason, at any point during the final 12 weeks of the study (±7 days). The assessment of BVAS in the final 12 weeks will come from the week 44, 48 and 52 week visits, at each of which BVAS will be assessed for the previous 28 days (±7 days).

Please see section 5.1.2 for the list of secondary endpoints and exploratory outcomes.

9.2 Procedures for Assessing Efficacy Outcomes

The Birmingham Vasculitis Activity Score (BVAS) Version 3 will be used to record the primary efficacy outcome. Secondary and exploratory efficacy outcomes will be determined using BVAS, Vasculitis Damage Index (VDI) [27], SF-36 [28], EQ5D [29], HAQ [30], AAV PROs [31] and FACIT [32] scores, as well as measurement of lipid profiles, serum glucose levels, HbA1c levels, ANCA titres by ELISA, calculation of the cumulative prednisolone dosage and assessment of adverse events.

The outcomes listed above and in trial schedule, section 5.4, will be recorded in the study CRFs.

10 Assessment of Safety

10.1 Specification, Timing and Recording of Safety Parameters

The investigator is responsible for the appropriate medical care of patients during the study. Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following Adverse Events (AEs) that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the patient to discontinue the investigational product before completing the study. The patient should be followed until the event resolves or stabilizes with appropriate diagnostic evaluation. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the Informed Consent Form (ICF) is signed, study site personnel will record via eCRF the occurrence and nature of each patient's pre-existing conditions, except AAV, as this is the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record the following via eCRF for each AE: start date, stop date (if applicable), severity, and their assessment of the potential relatedness of each AE to investigational product.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, or a study procedure, taking into account the disease, concomitant treatment or pathologies.

A "reasonable possibility" means that there is a cause and effect relationship between the investigational product and the AE.

10.2 Procedures for Recording and Reporting Adverse Events

The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 gives the following definitions:

10.2.1 Adverse Event (AE):

Any untoward medical occurrence in a patient to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.

Laboratory test abnormalities will be considered an AE if they represent a clinically significant finding, symptomatic or not, which was not present at study start or worsened during the course of the study or led to dose reduction, interruption or permanent discontinuation of study treatment.

In addition, all reports of intentional misuse and abuse of the study treatment are also considered an AE irrespective of whether a clinical event has occurred.

Given the safety profile of hydroxychloroquine, clinicians are advised that the study drug should not be stopped in the instance of an adverse event (serious or otherwise) without prior discussion with the local PI.

A positive COVID test should be recorded as an adverse event, regardless of whether the patients was symptomatic.

10.2.2 Adverse Reaction (AR):

Any untoward and unintended response in a patient to an investigational medicinal product which is related to any dose administered to that patient.

10.2.3 Unexpected Adverse Reaction (UAR):

An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in the summary of product characteristics (SmPC) for that product.

10.2.4 Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Unexpected Serious Adverse Reaction (USAR):

An SAE is defined by the ICH guidelines as any AE fulfilling at least 1 of the following criteria:

- Fatal;
- Life-threatening: refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death had it been more severe;
- Requiring in-patient hospitalization or prolongation of existing hospitalization;
- Resulting in persistent or significant disability or incapacity;
- Congenital anomaly or birth defect;
- Medically significant: refers to important medical events that may not immediately result in death, be life-threatening, or require hospitalization but may be considered medically significant based upon appropriate medical judgment, as they may jeopardize the patient, and/or may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

The following reasons for hospitalization are not considered as SAEs:

- Hospitalization for cosmetic elective surgery, or social and/or convenience reasons;
- Hospitalization for pre-planned (i.e., planned prior to signing ICF) surgery or standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a patient with stable angina pectoris.

However, complications that occur during hospitalization are AEs or SAEs (e.g., if a complication prolongs hospitalization).

The expectedness of an SAE is determined by the sponsor according to the reference safety information (RSI) section provided in the SmPC.

Any SAE that is assessed as related and unexpected against the RSI is known as a SUSAR.

10.2.5 Intensity of Adverse Events

The intensity of AEs is graded on a three-point scale — mild, moderate, severe — as follows:

- ❑ **Mild**

The event may be noticeable to the patient. It does not usually influence daily activities, and normally does not require intervention.

- ❑ **Moderate**

The event may make the patient uncomfortable. Performance of daily activities may be influenced, and intervention may be needed.

- ❑ **Severe**

The event may cause noticeable discomfort and usually interferes with daily activities. The patient may not be able to continue in the study, and treatment or intervention is usually needed.

A mild, moderate, or severe AE may or may not be serious. These terms are used to describe the intensity of a specific event. Medical judgment should be used on a case-by-case basis.

Seriousness, rather than intensity assessment, determines the regulatory reporting obligations.

10.2.6 Relationship to Study Treatment

Each AE/SAE must be assessed by the investigator, using the table below, as to whether or not there is a reasonable possibility of causal relationship to the study treatment, and reported as either related or unrelated.

Relationship to IMP	Description
Not related	There is no evidence of any causal relationship to study treatment.
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Likely	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

10.2.7 Time Period and Frequency for Adverse Event/Serious Adverse Event Assessment and Follow-up

The occurrence of an AE/SAE may come to the attention of study personnel during study visits, telephone calls or interviews of study participants presenting for medical care.

At each study visit (scheduled or unscheduled), the investigator will inquire about the occurrence of AE/SAEs since the last visit.

10.2.8 Follow-up of Adverse Events

AEs still ongoing at the End of Study visit will be recorded as ongoing. SAEs will need to be followed up until resolution.

10.2.9 Follow-up of Serious Adverse Events

SAEs still ongoing at the End of Study visit must be followed up until resolution, stabilization, or until the event outcome is provided.

10.3 Important Medical Events (IME) & Pregnancy

Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

Although not a serious adverse event, any unplanned pregnancy will also be reported via the SAE reporting system. Although hydroxychloroquine is safe and widely used in pregnancy, maintenance

immunosuppressive agents such as methotrexate and mycophenolate are teratogenic, so the patient will be withdrawn from the study and will have safety assessments as per local practice.

10.4 Reporting Responsibilities

The delivery of the Sponsor's responsibility for Pharmacovigilance (as defined in Regulation 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004) has been delegated to the King's Health Partners Clinical Trials Office (KHP-CTO).

All SAEs, SARs and SUSARs (excepting those specified in this protocol as not requiring reporting) will be reported immediately (and certainly no later than 24hrs) by the Investigator to the KHP-CTO and CI for review in accordance with the current Pharmacovigilance Policy. All data regarding the occurrence of adverse events will be made available to the IDMC for review.

Death as a result of disease progression and other events that are primary or secondary outcome measures are not considered to be SAEs and should be reported in the normal way, on the appropriate CRF.

The KHP-CTO will report SUSARs to the regulatory authorities (MHRA, competent authorities of other EEA (European Economic Area) states in which the trial is taking place if applicable.

The Chief Investigator will report to the relevant ethics committee. Reporting timelines are as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the sponsor first becoming aware of the reaction.
- The Chief Investigator and KHP-CTO (on behalf of the sponsor), will submit a Development Safety Update Report (DSUR) relating to this trial IMP, to the MHRA and REC annually.

10.4.1 Adverse Events That Do Not Require Reporting

The IMP (hydroxychloroquine) is licensed, therefore non-serious events or reactions listed in the SmPC for hydroxychloroquine do not need to be reported, but should be recorded. These include acute porphyrias; diabetes; Glucose-6 phosphate dehydrogenase (G6PD) deficiency; may aggravate myasthenia gravis; may exacerbate psoriasis; neurological disorders (especially in those with a history of epilepsy); gastro-intestinal disorders.

Events that are attributed to worsening vasculitis will not be reported as an AE or SAE but will instead be recorded in the BVAS and VDI. It is up to clinical judgement as to whether the event is attributed to vasculitis.

The period for AE reporting will be defined as first dose until 28 days post final IMP (hydroxychloroquine or placebo) administration.

10.5 Treatment Stopping Rules

The trial may be prematurely discontinued by the Sponsor, Chief Investigator or Regulatory Authority on the basis of new safety information or for other reasons given by the Data Monitoring Committee/Trial Steering Committee regulatory authority or ethics committee concerned.

If the trial is prematurely discontinued, active participants will be informed and no further participant data will be collected. The Competent Authority and Research Ethics Committee will be informed within 15 days of the early termination of the trial.

11 Statistics

11.1 Sample Size

As AAV is uncommon, the required sample size was optimised using a selection theory approach as proposed by Simon et al [65]. Software from the Centre for Clinical Research and Biostatistics, Hong Kong was used: (https://www2.ccrb.cuhk.edu.hk/stat/phase2/Randomized.htm).

The parameters for this calculation are p=0.35, D=0.15, and k=2, where p=the estimated percentage of hydroxychloroquine treated patients with uncontrolled AAV (BVAS>3) (or controlled but with >7.5mg prednisolone or other corticosteroid daily), D=Difference in response rate between hydroxychloroquine and placebo, and k= Number of treatment arms.

A sample size of 72 patients (36 in each arm) will be required to correctly rank hydroxychloroquine as superior to placebo with 90% probability, assuming 50% of patients in the standard treatment group have uncontrolled AAV (or controlled but with >7.5mg prednisolone or other corticosteroid daily) and that the true reduction in this rate due to hydroxychloroquine is 15%. 76 patients will be recruited to allow for a 5% drop-out rate. This drop-out rate is based on similar trials which had a <3% drop-out rate (www.vasculitis.org).

11.2 Randomisation

This is a randomised double-blind placebo controlled trial. Patients will be randomised into 2 blinded treatment arms (hydroxychloroquine vs placebo in a 1:1 ratio) with minimisation for ANCA (positive vs negative), age (</≥60 years), previous rituximab therapy (yes/no) and smoking (current smoker/non-smoker) in order to ensure balanced groups.

11.3 Analysis

The selection theory approach [33] assesses the ranking of results. The sample size of 72 patients will give a 90% probability of correctly ranking hydroxychloroquine and placebo. If the results show that hydroxychloroquine ranks better than placebo (i.e. the hydroxychloroquine treatment group has a smaller percentage of patients with uncontrolled BVAS, or controlled but with >7.5mg prednisolone or other corticosteroid daily), the study conclusion will be to take hydroxychloroquine forward into a larger definitive trial of effectiveness. If the observed hydroxychloroquine effect size is sufficiently larger than the estimated 15% (specifically, if ≥24%), then the difference will also be statistically significant and efficacy can be assumed. All analysis will be by intention to treat and appropriate imputation will be used for missing data. Patients experiencing major flares requiring increased prednisolone/immunosuppressive treatment in addition to study protocol in the final 12 weeks of the study (±7 days) will have met the primary endpoint and will be treated according to best clinical care but we will continue to record their data as part of the study. The primary endpoint is detailed in section 5.1.1.

12 Trial Steering Committee

The Trial Steering Committee (TSC) is the group responsible for oversight of the trial in order to safeguard the interests of trial participants. The TSC provides advice to the CI, KHP-CTO, the funder and sponsor on all aspects of the trial through its independent Chair.

13 BVAS and VDI Adjudication Committee

An independent Adjudication Committee blinded to treatment group will scrutinise all the BVAS and VDI scores and major and minor relapses. Details will be provided in the Terms of Reference.

14 Data Monitoring Committee

The Data Monitoring Committee (DMC) is the only oversight body that has access to unblinded accumulating comparative data, and is comprised of independent members. The DMC is responsible for safeguarding the interests of trial participants, monitoring the accumulating data and making recommendations to the TSC on whether the trial should continue as planned. The membership, frequency of meetings, activity (including review of trial conduct and data) and authority will be covered in the DMC terms of reference. DMC will consider data in accordance with the statistical analysis plan and will advise the TSC through its Chair.

The Data Monitoring Committee (DMC) will regularly review the accumulating data for the trial and provide advice to the Trial Steering Committee (TSC).

The DMC will inform the TSC if, in their view, the results are likely to convince a broad range of clinicians that, on balance, one trial arm is clearly indicated or contraindicated, and there is a reasonable expectation that this new evidence would materially influence patient management.

Possible recommendations from the DMC include:-

- No action needed, trial continues as planned
- Early stopping, due for example, to clear evidence of harm of a treatment or external evidence.

15 Direct Access to Source Data and Documents

The Investigator(s) will permit trial-related monitoring, audits, REC review, and regulatory inspections by providing the Sponsor(s), Regulators and REC direct access to source data and other documents (e.g. patients' case sheets, blood test reports, histology reports etc.).

16 Ethics and Regulatory Approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

This protocol and related documents will be submitted for review to the Health Research Authority, London - Riverside Research Ethics Committee (REC), and the Medicines and Healthcare products Regulatory Agency (MHRA) for Clinical Trial Authorisation.

The Chief Investigator will submit a final report at conclusion of the trial to the KHP-CTO (on behalf of the Sponsor), the REC and the MHRA within the timelines defined in the Regulations.

17 Quality Assurance

Monitoring of this trial will be to ensure compliance with Good Clinical Practice and scientific integrity will be managed and oversight retained, by the Kings Health Partners Clinical Trials Office (KHP-CTO) Quality Team.

18 Data Handling

The Chief Investigator will act as custodian for the trial data. The following guidelines will be strictly adhered to:

- Strict patient confidentiality will be observed throughout all aspects of the study. While medical records will be reviewed by members of the research team, no individually identifiable patient data will be distributed to non-research or care-giving team members. However, the onsite monitor could have access to identifiable patient info during inspections, as may authorised individuals on behalf of the Regulatory Authorities and the Sponsor in the instance of an audit or inspection.
- All anonymised data will be stored on a password protected computer.
- All trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006, the Data Protection Act 2018, and the General Data Protection Regulation and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the Kings Health Partners Clinical Trials Office Archiving SOP. Participating sites will archive their local study data in accordance with their site guidelines.

19 Data Management

A web based electronic data capture (EDC) system will be designed using the InferMed Macro 4 system. The EDC will be created in collaboration with the trial analyst/s and the CI and maintained by the King's Clinical Trials Unit for the duration of the project. It will be hosted on a dedicated secure server within KCL.

The CI or delegate will request usernames and passwords from the KCTU. Database access will be strictly restricted through user-specific passwords to the authorised research team members. It is a legal requirement that passwords to the EDC are not shared, and that only those authorised to access the system are allowed to do so. If new staff members join the study, a user-specific username and password must be requested via the CI or delegate (trial manager) from the KCTU team and a request for access to be revoked must be requested when staff members leave the project. Study site staff experiencing issues with system access or functionality should contact the CI or delegate (trial manager) in the first instance.

No identifiable data beyond participant initials, age at consent and year of birth will be entered on the EDC or transferred to the KCTU. No data will be entered onto the EDC system unless a participant has signed a consent form to participate in the trial. Source data will be entered by recruiting site staff by authorised staff onto the EDC by going to www.ctu.co.uk and clicking the link to access the MACRO 4 EDC system. A full audit trail of data entry and any subsequent changes to entered data will be automatically date and time stamped, alongside information about the user making the entry/changes within the system.

The CI team will undertake appropriate reviews of the entered data, for the purpose of data cleaning and will request amendments as required.

At the end of the trial, the site PI will review all the data for each participant and provide electronic sign-off to verify that all the data are complete and correct. At this point, all data can be formally locked for analysis.

Upon request, KCTU will provide a copy of the final exported dataset to the CI in .csv format and the CI will onward distribute as appropriate.

19.1 Screening and Enrolment Log

Screening and enrolment logs will be collected, linking participant identifiable data to pseudo anonymised participant identification number. Screening logs will capture number and characteristics of patients invited to participate and number who decline.

20 Publication Policy

It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals. The Chief Investigator will ensure that the results are analysed, written up, reported and disseminated upon completion of the trial.

21 Insurance/Indemnity

As the sponsor, Guy's and St Thomas' NHS Foundation Trust have clinical negligence cover as part of the NHS Clinical Negligence Scheme for Trusts.

22 Financial Aspects

Funding to conduct the trial is provided by the Medical Research Council via a DPFS grant MRC Reference: MR/R006253/1.

23 Signatures

30/10/2020

_____ _____

Professor David D'Cruz MD FRCP Date

Chief Investigator

28/10/2020

_____ _____

Ms Fiona Reid Date

Statistician

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25 Appendices

25.1 Chapel Hill Consensus Conference

CLASSIFICATION CRITERIA

Diagnostic criteria—as opposed to classification criteria or definitions—have not yet been developed. In 1994, the Chapel Hill International Consensus Conference developed definitions for the vasculitides which were revised in 2012 [34]. These definitions, along with the American College of Rheumatology (ACR) Criteria for the classification of vasculitides [35], are useful in formulating the criteria that will be applied to determine a participant's eligibility for this clinical trial.

Chapel Hill Consensus Conference Definitions for Microscopic Polyangiitis

1. Necrotizing vasculitis with few or no immune deposits affects small vessels (i.e., capillaries, venules, or arterioles).
2. Necrotizing arteritis involving small and medium-sized arteries may be present.
3. Necrotizing glomerulonephritis is very common.
4. Pulmonary capillaritis often occurs.

ACR Criteria for the Classification of Wegener's Granulomatosis

Among a group of patients with various forms of systemic vasculitis, the presence of at least two of these four criteria is associated with a sensitivity of 88.2% and a specificity of 92.0% for WG.

1. Nasal or oral inflammation: painful or painless oral ulcers or purulent or bloody nasal discharge
2. Abnormal chest radiograph: nodules, fixed infiltrates, or cavities
3. Urinary sediment: microhematuria or red cell casts
4. Granulomatous inflammation on biopsy: granulomatous inflammation within the wall of an artery or in the perivascular area

ACR Criteria for the Classification of Churg-Strauss Syndrome

Although we wish to exclude Churg-Strauss syndrome (CSS) from this trial, we will use the following ACR criteria for the classification of this disorder:
Among a group of patients with various forms of systemic vasculitis, the presence of at least four of these six criteria is associated with a sensitivity of 85.0% and a specificity of 99.7% for CSS.

1. Asthma: wheezing or high-pitched rales
2. Eosinophilia: >10% of white blood cell differential
3. Mononeuropathy or polyneuropathy: mononeuropathy, multiple mononeuropathies, or polyneuropathy attributable to vasculitis
4. Pulmonary infiltrates, nonfixed: migratory or transitory pulmonary infiltrates
5. Paranasal sinus abnormality: acute or chronic paranasal sinus pain, tenderness, or radiographic opacification
6. Extravascular eosinophils: biopsy, including artery, arteriole, or venule showing accumulations of eosinophils in extravascular areas.

25.2 Birmingham Vasculitis Activity Score (version 3.0)

Tick an item **only** if attributable to active vasculitis. If there are no abnormalities in a section, please tick 'None' for that organ-system.	If **all** abnormalities are due to persistent disease (active vasculitis which is not new/worse in the prior 4 weeks), tick the **PERSISTENT** box at the bottom right corner

Is this the patient's first assessment?						Yes	No
		None	Active Disease			None	Active disease
1.	**General**	☐		**6.**	**Cardiovascular**	☐	
	Myalgia		☐		Loss of pulses		☐
	Arthralgia / arthritis		☐		Valvular heart disease		☐
	Fever ≥38° C		☐		Pericarditis		☐
	Weight loss ≥2kg		☐		♦ **Ischaemic cardiac pain**		☐
2.	**Cutaneous**	☐			♦ **Cardiomyopathy**		☐
	Infarct		☐		♦ **Congestive cardiac failure**		☐
	Purpura		☐	**7.**	**Abdominal**		☐
	Ulcer		☐		Peritonitis		☐
	♦ **Gangrene**		☐		Bloody diarrhea		☐
	Other skin vasculitis		☐		♦ **Ischaemic abdominal pain**		☐
3.	**Mucous membrane / eyes**	☐		**8.**	**Renal**	☐	
	Mouth ulcers		☐		Hypertension		☐
	Genital ulcers		☐		Proteinuria >1+		☐
	Adnexal inflammation		☐		♦**Haematuria ≥10 RBCs/hpf**		☐
	Significant proptosis		☐		Creatinine 125-249µ/L(1.41-2.82mg/dl)*		☐
	Scleritis / Episcleritis		☐		Creatinine 250-499 µ/L(2.83-5.64mg/dl)*		☐
	Conjunctivitis / Blepharitis / Keratitis		☐		♦ **Creatinine ≥500 µ/L (≥5.66mg/dl)***		☐
	Blurred vision		☐		♦ **Rise in serum creatinine >30% or fall in creatinine clearance >25%**		☐
	Sudden visual loss		☐		***Can only be scored on the first assessment**		
	Uveitis		☐	**9.**	**Nervous system**	☐	
	♦ **Retinal changes (vasculitis / thrombosis/ exudate / haemorrhage)**		☐		Headache		☐
4.	**ENT**	☐			Meningitis		☐
	Bloody nasal discharge / crusts / ulcers / granulomata		☐		Organic confusion		☐
	Paranasal sinus involvement		☐		Seizures (not hypertensive)		☐
	Subglottic stenosis		☐		♦ **Cerebrovascular accident**		☐
	Conductive hearing loss		☐		♦ **Cranial nerve palsy**		☐
	♦ **Sensorineural hearing loss**		☐		Sensory peripheral neuropathy		☐
5.	**Chest**	☐			♦ **Mononeuritis multiplex**		☐
	Wheeze		☐	10.	Other	☐	
	Nodules or cavities		☐		a.		☐
	Pleural effusion/ pleurisy		☐		b.		☐
	Infiltrate		☐		c.		☐
	Endobronchial involvment		☐		d.		☐
	♦ **Massive haemoptysis / alveola haemorrhage**		☐		**PERSISTENT DISEASE ONLY:** (Tick here if **all** the abnormalities are due to persistent disease)		☐
	♦ **Respiratory failure**		☐				

◆ Major items highlighted

25.3 Features of Limited and Severe AAV

Severe (major) BVAS items [a]	**Limited (minor) BVAS items** [b]
Cutaneous gangrene	Arthralgias/arthritis
Scleritis	Fever (>38 °C)
Retinal exudates/hemorrhage	Purpura
Sensorineural hearing loss	Skin ulcer
Mesenteric ischemia	Mouth ulcers
Alveolar hemorrhage	Conjunctivitis/episcleritis
Red blood cell urinary casts	Orbital mass/proptosis
Rise in serum creatinine 30% over	Uveitis
baseline	Bloody nasal discharge/nasal crusting
Aseptic meningitis	Sinus involvement
Spinal cord lesions	Swollen salivary gland
Cerebrovascular accident caused by vasculitis	Subglottic inflammation Conductive deafness [3]
Cranial nerve palsy	Pericarditis
Sensory peripheral neuropathy	Pleurisy
Motor mononeuritis multiplex	Pulmonary nodules or cavities
Other pulmonary infiltrates secondary to Vasculitis	
Endobronchial lesions	
Hematuria	

25.4 Vasculitis Damage Index (VDI)

This is for recording organ damage that has occurred in patients since the onset of vasculitis.
Patients often have co-morbidity before they develop vasculitis, which must not be scored.
Record features of active disease using the Birmingham Vasculitis Activity Score (BVAS).
A new patient should usually have a VDI score of zero, unless:
(a) they have had vasculitis for more than three months of onset of disease and
(b) the damage has developed or become worse since the onset of vasculitis

		No	Yes			No	Yes
1.	**Musculoskeletal**			**7.**	**Peripheral vascular Disease**		
	None	☐			None	☐	
	Significant muscle atrophy or weakness		☐		Absent pulses in one limb		☐
	Deforming erosive arthritis		☐		2nd episode of absent pulses in one limb		☐
	Osteoporosis/vertebral collapse		☐		Major vessel stenosis		☐
	Avascular necrosis		☐		Claudication > 3mths		☐
	Osteomyelitis		☐		Minor tissue loss		☐
2.	**Skin/Mucous membranes**				Major tissue loss		☐
	None	☐			Subsequent major tissue loss		☐
	Alopecia		☐		Complicated venous thrombosis		☐
	Cutaneous ulcers		☐	**8.**	**Gastrointestinal**		
	Mouth ulcers		☐		None	☐	
3.	**Ocular**				Gut infarction/resection		☐
	None	☐			Mesenteric insufficiency/pancreatitis		☐
	Cataract		☐		Chronic peritonitis		☐
	Retinal change		☐		Oesophageal stricture/surgery		☐
	Optic atrophy		☐	**9.**	**Renal**		
	Visual Impairment/diplopia		☐		None	☐	
	Blindness in one eye		☐		Estimated/measured GFR≤ 50%		☐
	Blindness in second eye		☐		Proteinuria ≥ 0.5g/24hr		☐
	Orbital wall destruction		☐		End stage renal disease		☐
4.	**ENT**			**10.**	**Neuropsychiatric**		
	None	☐			None	☐	
	Hearing loss		☐		Cognitive Impairment		☐
	Nasal blockage/chronic discharge/crusting		☐		Major psychosis		☐
	Nasal bridge collapse/septal perforation		☐		Seizures		☐
	Chronic sinusitis/radiological damage		☐		Cerebrovascular accident		☐
	Subglottic stenosis (so surgery)		☐		2nd cerebrovascular accident		☐
	Subglottic stenosis (with surgery)		☐		Cranial nerve lesion		☐
5.	**Pulmonary**				Peripheral neuropathy		☐
	None	☐			Transverse myelitis		
	Pulmonary hypertension		☐	**11.**	**Other**		
	Pulmonary fibrosis		☐		None	☐	
	Pulmonary Infarction		☐		Gonadal failure		☐
	Pleural fibrosis		☐		Marrow failure		☐
	Chronic Asthma		☐		Diabetes		☐
	Chronic breathlessness		☐		Chemical cystitis		☐
	Impaired lung function		☐		Malignancy		☐
6.	**Cardiovascular**				Other		☐
	None	☐					
	Angina angioplasty		☐		**Total VDI score.**		
	Myocardial infarction		☐		Record the number of positive items		
	Subsequent myocardial infarction		☐		(1 point for each). The VDI score can		
	Cardiomyopathy		☐		either increase or remain the same over		
	Valvular disease		☐		time. Remember to carry forward any		
	Pericarditis ≥ 3mths or pericardectomy		☐		previous items of damage.		
	Diastolic BP ≥ 95 or requiring antihypertensives		☐				

VDI Modified from Exley AR, Bacon PA, Luqmani et al (1997) Development and initial validation of the VDI … Arthritis Rheum 40: 371-380

25.5 Summary of Protocol Changes

Amendment Number	Protocol Version & Date	Summary of Changes
REC Submission	2.0 18/11/2019	• Update to eligibility criteria • Rewording of IMP section and to IMP storage conditions • Clarification of unscheduled visits and addition of withdrawal visit • Minor clarifications
SA1	3.0 18/12/2019	• Update to IMP temperature storage conditions • Removal of week 52 ECG
SA2	4.0 21/08/2020	• Updates in light of COVID-19 pandemic, including update to eligibility criteria