PROTOCOL

Protocol Amendment 4.0

TITLE PAGE

Study Title:	A Randomized, Double-Blind, Active-Controlled, Phase 3 Study to Evaluate the Safety and Efficacy of CCX168 (Avacopan) in Patients with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis Treated Concomitantly with Rituximab or Cyclophosphamide/Azathioprine
Protocol Number:	CL010_168
Investigational Product:	Complement 5a Receptor Antagonist CCX168 (INN/USAN avacopan)
Indication:	ANCA-Associated Vasculitis
Sponsor:	ChemoCentryx, Inc.
Development Phase:	3
IND number	120784
EudraCT number	2016-001121-14
Sponsor's Responsible Medical Officer:	[redacted] ChemoCentryx, Inc. [redacted]
Sponsor Signatory:	[redacted]
Approval Date:	**28 November 2016** **21 June 2017—Protocol Amendment 1.0** **15 June 2018 – Protocol Amendment 2.0** **18 Jan 2019 – Protocol Amendment 4.0**

Confidential

This study will be conducted according to the principles of Good Clinical Practice as described in International Council for Harmonisation guidelines, including the archiving of essential documents.

INVESTIGATOR SIGNATORY PAGE

Protocol Number: CL010_168

Protocol Title: A Randomized, Double-Blind, Active-Controlled, Phase 3 Study to Evaluate the Safety and Efficacy of CCX168 (Avacopan) in Patients with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis Treated Concomitantly with Rituximab or Cyclophosphamide/Azathioprine

I agree:

- to assume responsibility for the proper conduct of the study at this site.
- to conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by ChemoCentryx, Inc.
- not to implement any deviations from or changes to the protocol without agreement from the sponsor and prior review and written approval from the Institutional Review Board (IRB)/Ethics Committee (EC), except where necessary to eliminate an immediate hazard to the patients, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- that I am thoroughly familiar with the appropriate use of the investigational drug(s), as described in this protocol, and any other information provided by the sponsor including, but not limited to the following: the current version of the Investigator's Brochure prepared by ChemoCentryx, Inc. and approved product label, if applicable.
- that I am aware of and will comply with current ICH/FDA good clinical practices guidelines (GCP) and all regulatory requirements.
- to ensure that all persons assisting me with the study are adequately informed about the investigational drug(s) and their study-related duties and function as described in the protocol.

_____ _____
Principal Investigator Date

_____
Printed Name

Address*_____

_____

Phone Number* _____

* If the address or phone number needs to be changed during the course of the study, this will be done by the Investigator, with written notification to the Sponsor, and will not require (a) protocol amendment(s).

SPONSOR CONTACT INFORMATION

Protocol Number: CL010_168

Protocol Title: A Randomized, Double-Blind, Active-Controlled, Phase 3 Study to Evaluate the Safety and Efficacy of CCX168 (Avacopan) in Patients with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis Treated Concomitantly with Rituximab or Cyclophosphamide/Azathioprine

Medical Officer	[redacted]
Clinical Operations Manager	[redacted]

SPONSOR SIGNATURE FOR APPROVAL

Protocol Number: CL010_168

Protocol Title: A Randomized, Double-Blind, Active-Controlled, Phase 3 Study to Evaluate the Safety and Efficacy of CCX168 (Avacopan) in Patients with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis Treated Concomitantly with Rituximab or Cyclophosphamide/Azathioprine

[redacted] Date

PROTOCOL AMENDMENT 4.0: SUMMARY OF CHANGES

1. The protocol Title Page was updated with the new amendment number and date.
2. Study period in Synopsis has been updated to add details for clarity.
3. Efficacy Assessments no.4 has been updated to deleted “first morning” in First morning urinary albumin:creatinine ratio (UACR) in Study Synopsis to correct error in original, random void is acceptable and first morning void is not necessary.
4. To be consistent with section 6.1 Screening and Enrollment, record the Results from histology of renal biopsies performed within 4 weeks prior to Day 1 has been corrected to prior to Screening in Synopsis, Time and Events Table and Section 3.4.
5. The definition of ITT population and treatment failures were amended to align with definition in the Statistical Analysis Plan in the following sections: Synopsis, 8.1.1. Intent-to-Treat Population, 8.2.2. Secondary Endpoints, 8.6.5. Efficacy Analyses
6. The Time & Events Table was updated to add Hematology for study weeks 23, 29, 35, 42 and 48
7. Section 4.4 Removal of Patients from Therapy of Assessment was updated to
   a. Add language on pausing for Grade 2 neutropenia and also provided further details on transaminase elevations that were in the previously issued (June 2018) safety notification letter.
8. The blood samples will be collected for shipment to the central laboratory for hematology was added in the following Sections: 6.16 Study Week 23; 6.18 Study Week 29; 6.20 Study Week 35; 6.22 Study Week 42; 6.24 Study Week 48
9. Section 7.2.4.6 Laboratory Abnormalities was updated to incorporate recommendations of the DMC and rules for pausing administration of blinded study drug.
10. Based on DMC review of unblinded safety data from all completed and ongoing studies of CCX168, Section 12.14.2 Clinical Evaluation was updated.
11. Benefit/Risk reference to IB added.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

STUDY SYNOPSIS

Name of Sponsor	**Name of Active Ingredient**	**Study number:**
ChemoCentryx, Inc.	CCX168 (avacopan)	CL010_168
Title A Randomized, Double-Blind, Active-Controlled, Phase 3 Study to Evaluate the Safety and Efficacy of CCX168 (Avacopan) in Patients with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis Treated Concomitantly with Rituximab or Cyclophosphamide/Azathioprine		
Investigators Several		
Study centers Multi-center		
Study period Individuals participate for up to 60 weeks, 52 week treatment period and 8 week followup period	**Phase of development** Phase 3	
Objectives The primary objective is to evaluate the efficacy of CCX168 (avacopan) to induce and sustain remission in patients with active anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), when used in combination with cyclophosphamide followed by azathioprine, or in combination with rituximab. Disease remission is defined as achieving a Birmingham Vasculitis Activity Score (BVAS) of 0 and not taking glucocorticoids for treatment of AAV within 4 weeks prior to Week 26. Sustained remission is defined as remission at Week 26 without relapse to Week 52 (BVAS of 0 and not taking glucocorticoids for treatment of AAV within 4 weeks prior to Week 52). The secondary objectives of this study include:		

1. Evaluation of the glucocorticoid-induced toxicity in the CCX168 plus rituximab or cyclophosphamide/azathioprine group, compared to prednisone plus rituximab or cyclophosphamide/azathioprine, based on the Glucocorticoid Toxicity Index (GTI; Miloslavsky et al, 2016);
2. Evaluation of rapidity of response in the CCX168 plus rituximab or cyclophosphamide/azathioprine group, compared to prednisone plus rituximab or cyclophosphamide/azathioprine, based on remission (BVAS of 0) at Week 4;
3. Evaluation of the safety of CCX168 plus rituximab or cyclophosphamide/azathioprine, compared to prednisone plus rituximab or cyclophosphamide/azathioprine based on the incidence of adverse events and changes in vital signs, physical examinations, clinical laboratory tests, and electrocardiograms (ECGs) in these patients;
4. Assessment of health-related quality-of-life changes based on the Short Form-36 version 2 (SF-36 v2) and the EuroQOL-5D-5L (EQ-5D-5L) with CCX168 plus rituximab or cyclophosphamide/azathioprine, compared to prednisone plus rituximab or cyclophosphamide/azathioprine;
5. Assessment of changes in parameters of renal disease including estimated glomerular filtration rate (eGFR), albuminuria, and urinary excretion of monocyte chemoattractant protein-1 (MCP-1) in patients with active renal disease at baseline with CCX168 plus rituximab or cyclophosphamide/azathioprine, compared to prednisone plus rituximab or cyclophosphamide/azathioprine;
6. Assessment of changes in cumulative organ damage based on the Vasculitis Damage Index (VDI) with CCX168 plus rituximab or cyclophosphamide/azathioprine, compared to prednisone plus rituximab or cyclophosphamide/azathioprine;
7. Assessment of changes in markers of pharmacodynamics in plasma and urine with CCX168 plus rituximab or cyclophosphamide/azathioprine, compared to prednisone plus rituximab or cyclophosphamide/azathioprine;
8. Evaluation of the pharmacokinetic profile of CCX168 in patients with AAV.

Methodology

Standard therapy for patients with AAV, including granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), includes cyclophosphamide followed by azathioprine, or rituximab, plus a tapering schedule of oral glucocorticoids. Severe disease may warrant the addition of IV glucocorticoids and/or plasma exchange. Glucocorticoid use in these patients is associated with an increased risk of serious adverse events such as infections.

Based on compelling results from both preclinical studies in a mouse model of AAV and Phase 2 clinical trial results, CCX168 has the potential to be an effective therapy for this disease that will also allow for glucocorticoid sparing or elimination. Hence, the clinical hypothesis of the trial is to test whether CCX168 is effective in inducing and then sustaining remission in patients with AAV who are also treated with either cyclophosphamide/azathioprine or rituximab.

This hypothesis will be tested in a randomized, double-blind, double-dummy, active-controlled, Phase 3 clinical trial in approximately 300 patients with newly diagnosed or relapsing AAV.

To obtain balance across treatment groups, eligible patients will be stratified based on the following factors:

1. One of the following treatment regimens:
    a. IV rituximab
    b. IV cyclophosphamide followed by oral azathioprine
    c. Oral cyclophosphamide followed by oral azathioprine
2. Positive test for proteinase-3 (PR3) vs. myeloperoxidase (MPO) ANCA at diagnosis
3. Newly-diagnosed vs. relapsing disease

After stratification, patients will be randomized, using an interactive response technology (IRT) system and a minimization algorithm, in a 1:1 ratio to one of two treatment groups:

Group A: CCX168-matching placebo plus cyclophosphamide/azathioprine or rituximab plus full starting dose of prednisone;

Group B: CCX168 plus cyclophosphamide/azathioprine or rituximab plus placebo prednisone.

Treatments for each group are shown below:

Group	**CCX168 Active**	**CCX168-Matching Placebo**	**Prednisone Active**	**Prednisone-Matching Placebo**	**Cyclophosphamide (CYC)/azathioprine or Rituximab (RTX)**
A	None	3 Placebo capsules orally twice daily	60 mg starting dose (or 45 mg for patients <55 kg) with standard tapering schedule; Adolescents who weigh ≤37 kg will start at a prednisone dose of 30 mg per day.	None	CYC: 15 mg/kg IV up to 1.2 g maximum every 2 to 3 weeks for 13 weeks, followed by azathioprine 1 mg/kg/day starting at Week 15, with titration up to 2 mg/kg/day or CYC 2 mg/kg/day orally for 14 weeks, followed by azathioprine 1 mg/kg/day starting at Week 15, with titration up to 2 mg/kg/day or RTX: 375 mg/m^2 IV weekly x 4 infusions.

B	3 x 10 mg CCX168 capsules orally twice daily	None	None	Placebo capsules	CYC: 15 mg/kg IV up to 1.2 g maximum every 2 to 3 weeks for 13 weeks, followed by azathioprine 1 mg/kg/day starting at Week 15, with titration up to 2 mg/kg/day or CYC 2 mg/kg/day orally for 14 weeks, followed by azathioprine 1 mg/kg/day starting at Week 15, with titration up to 2 mg/kg/day or RTX: 375 mg/m^2 IV weekly x 4 infusions.

The selection of IV cyclophosphamide, oral cyclophosphamide, or IV rituximab is at the discretion of the Investigator. The treatment period is 52 weeks (364 days), followed by an 8-week (56 days) follow-up period.

Study drug and other medication for vasculitis will be taken as follows by study patients:

Group A (control group):

- Three CCX168-matching placebo capsules in the morning, preferably with food, and 3 in the evening, preferably with food, approximately 12 hours after the morning dose, daily for 52 weeks (364 days).
- Prednisone 60 mg orally per day if the patient's body weight is ≥55 kg, or 45 mg per day if the patient's body weight is <55 kg, starting on Day 1 with tapering according to the protocol-specified schedule. Adolescents who weigh ≤37 kg will start at a prednisone dose of 30 mg per day.
- If a patient is in the IV cyclophosphamide stratum, cyclophosphamide 15 mg/kg IV up to a maximum of 1.2 g will be given on Day 1 and also at the Week 2, 4, 7, 10, and 13 study visits. The IV cyclophosphamide dose will be adjusted based on the patient's age, eGFR, and WBC count according to protocol-specified criteria. Starting at Week 15, all patients will receive oral azathioprine at a starting dose of 1 mg/kg/day, with titration up to a target dose of 2 mg/kg/day at 2 weeks. If azathioprine is not tolerated, mycophenolate mofetil at a target dose of 2 g/day may be given. If mycophenolate mofetil is not tolerated or not available, enteric coated mycophenolate sodium may be given at a target dose of 1440 mg/day.
- If a patient is in the oral cyclophosphamide stratum, cyclophosphamide 2 mg/kg/day (maximum 200 mg/day) will be given orally starting on Day 1 and continuing up to the day before Week 15. The cyclophosphamide dose will be adjusted based on the patient's age, eGFR, and WBC count according to protocol-specified criteria. Starting at Week 15, all patients will receive oral azathioprine at a starting dose of 1 mg/kg/day, with titration up to a target dose of 2 mg/kg/day at 2 weeks. If azathioprine is not tolerated, mycophenolate mofetil at a target dose of 2 g/day may be given. If mycophenolate

mofetil is not tolerated or not available, enteric coated mycophenolate sodium may be given at a target dose of 1,440 mg/day.

- If in the rituximab stratum, rituximab IV will be given on Day 1, and then Weeks 1, 2, and 3 at a dose of 375 mg/m^2 at each visit for a total of 4 weekly infusions.

Group B (CCX168):

- Three 10 mg CCX168 capsules in the morning, preferably with food, and 3 capsules in the evening, preferably with food, approximately 12 hours after the morning dose, daily for 52 weeks (364 days).
- Prednisone-matching placebo capsules equivalent to 60 mg orally per day if the patient's body weight is ≥55 kg, or 45 mg per day if the patient's body weight is <55 kg, starting on Day 1 with tapering according to a protocol-specified schedule. Adolescents who weigh ≤37 kg will start at a prednisone-matching placebo dose of 30 mg per day.
- If a patient is in the IV cyclophosphamide stratum, cyclophosphamide 15 mg/kg IV up to a maximum of 1.2 g will be given on Day 1 and also at the Week 2, 4, 7, 10, and 13 study visits. The cyclophosphamide dose will be adjusted based on the patient's age, eGFR, and WBC count according to protocol-specified criteria. Starting at Week 15, all patients will receive oral azathioprine at a starting dose of 1 mg/kg/day, with titration up to a target dose of 2 mg/kg/day at 2 weeks. If azathioprine is not tolerated, mycophenolate mofetil at a target dose of 2 g/day may be given. If mycophenolate mofetil is not tolerated or not available, enteric coated mycophenolate sodium may be given at a target dose of 1,440 mg/day.
- If a patient is in the oral cyclophosphamide stratum, cyclophosphamide 2 mg/kg/day (maximum 200 mg/day) will be given orally starting on Day 1 and continuing up to the day before the Week 15 study visit. The cyclophosphamide dose will be adjusted based on the patient's age, eGFR, and WBC count according to protocol-specified criteria. Starting at Week 15, all patients will receive oral azathioprine at a starting dose of 1 mg/kg/day, with titration up to a target dose of 2 mg/kg/day at 2 weeks. If azathioprine is not tolerated, mycophenolate mofetil at a target dose of 2 g/day may be given. If mycophenolate mofetil is not tolerated or not available, enteric coated mycophenolate sodium may be given at a target dose of 1,440 mg/day.
- If in the rituximab stratum, rituximab IV will be given on Day 1, and then Weeks 1, 2, and 3 at a dose of 375 mg/m^2 at each visit for a total of 4 weekly infusions.

Patients with severe AAV will be allowed to receive up to 3 g IV methylprednisolone during the 4-week period prior to screening for the study. Patients with active AAV will also be allowed to receive oral glucocorticoids during the 6 weeks prior to screening for the study. Patients will not be considered for screening if they have received continuous treatment with moderate or high dose glucocorticoids, defined as more than 10 mg prednisone or equivalent, for more than 6 weeks prior to screening for the study.

For study centers where enrollment of adolescents (12 to 17 years old) is approved, CCX168 or placebo dosing will initially be given based on the body weight at screening and the dose will be adjusted based on CCX168 plasma levels as shown in the table below.

Only in 12 to 17 year old patients, blood samples will be taken pre-dosing and at Hours 0.5, 1, 2, 3, 4, and 6 after the first CCX168 dose on Day 1 and plasma samples will be sent for

expeditious measurement of CCX168 and CCX168-M1 in these patients. Dose adjustments will be made based on AUC_{0-6} as shown in the table. These AUC_{0-6} thresholds are based on the mean CCX168 plasma exposure (525 ng•hr/mL) and one standard deviation (174 ng•hr/mL) above or below the mean in adult patients from Phase 2 study CL002_168 in AAV. In order to maintain the blind, some patients on placebo will also be instructed to modify the number of placebo capsules taken.

Body weight	**Initial CCX168/placebo dose**	**CCX168 Plasma AUC_{0-6} (ng•hr/mL) on Day 1**	**CCX168 Dose Adjustment**
<40 kg (88 lb)	10 mg (1 capsule) twice daily	≥351	None
		<351	Increase dose to 20 mg (2 capsules) twice daily
40-55 kg (88-121 lb)	20 mg (2 capsules) twice daily	351 to 699	None
		<351	Increase dose to 30 mg (3 capsules) twice daily
		>699	Decrease dose to 10 mg (1 capsule) twice daily
>55 kg (121 lb)	30 mg (3 capsules) twice daily	≤699	None
		>699	Decrease dose to 20 mg (2 capsules) twice daily

Extra glucocorticoid treatment, i.e., that not provided as study medication, must be avoided as much as possible during the study. However, patients who experience a *relapse* of their AAV during the study may be treated with IV glucocorticoids (typically 0.5 to 1 g methylprednisolone per day for 3 days) and/or oral glucocorticoids, tapered according to the patient's condition. A *relapse* is defined as worsening of disease, after having previously achieved remission at Week 26 (BVAS = 0 and having received no glucocorticoids for treatment of vasculitis for 4 weeks), that involves:

- one or more major item in the BVAS, or
- three or more minor items in the BVAS, or
- one or two minor items in the BVAS recorded at two consecutive study visits.

These patients may continue study drug treatment and should continue in the study.

Patients who experience worsening of disease during the study that involves a major item in the BVAS may be treated with IV glucocorticoids (typically 0.5 to 1 g methylprednisolone per day for 3 days) and/or oral glucocorticoids, tapered according to the patient's condition. Worsening not involving a major item in the BVAS may be treated with a short burst (i.e., not more than 2 weeks) of oral glucocorticoids, at a maximum dose of 20 mg prednisone equivalent. Patients experiencing worsening of disease may continue study drug treatment and should continue in the study.

Patients who have one or more major items in the BVAS before study entry, and who do not show an improvement or stabilization of these items within the first 4 weeks of the study, may receive additional IV or oral glucocorticoids, tapered according to the patient's condition. If the Investigator considers giving other medications, such as additional rituximab or

cyclophosphamide treatment, these should be discussed with the Medical Monitor. These patients may continue study drug treatment and should continue in the study.

Patients need to receive prophylactic therapy according to local practice during the course of the study. This includes prophylaxis against *Pneumocystis jirovecii* (formerly *carinii*) infections (sulfamethoxazole 400 mg-trimethoprim 80 mg daily or sulfamethoxazole 800 mg-trimethoprim 160 mg every second day; if allergic, dapsone, atovaquone, or pentamidine may be used according to local practice), osteoporosis, nausea, and therapy for gastroprotection.

All patients will visit the study center during the screening period, and, if eligible, on Day 1 and Weeks 1, 2, 3, 4, 7, 10, 13, 16, 20, 23, 26, 29, 32, 35, 39, 42, 45, 48, 52, and 60. CCX168/placebo will be taken orally in the morning, preferably with food, and in the evening (approximately 12 hours after the morning dose), preferably with food.

The screening period will be kept as short as possible in order not to delay initiation of treatment. The screening period must not exceed 14 days. Screening procedures will include written informed consent, collecting demographic data, medical history, medication history, physical examination and vital signs, serum chemistry tests, hematology tests, serum pregnancy test (in women of childbearing potential: have experienced menarche and who is not permanently sterile or postmenopausal; postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause), urinalysis (including hematuria and albuminuria), 12-lead ECG, a test to exclude tuberculosis (interferon γ release assay [IGRA], tuberculin purified protein derivative [PPD] skin test, or chest radiography [X rays or CT scan]) if not done within 6 weeks prior to screening, viral screening (if not done within 6 weeks prior to screening), serology (anti-nuclear antibodies [ANA], anti-glomerular basement membrane [GBM] antibodies, IgG, IgM, and IgA) and complement (C3 and C4) measurements (if not done within the previous 12 months), estimated glomerular filtration rate (eGFR) based on serum creatinine, ANCA measurement (anti-PR3 and anti-MPO, if not done previously), and BVAS and VDI assessment. The BVAS version 3 will be used in this study (Mukhtyar et al, 2009; Suppiah et al, 2011).

To expedite the screening process, blood and urine tests may be done at the local laboratories for the Screening visit. Laboratory results from the local laboratories obtained within 72 hours of screening are acceptable in order to avoid unnecessary blood draws. Results from histology of renal biopsies (if performed within 4 weeks prior to Screening) will be recorded on standard histology forms.

Eligible patients must be ANCA-positive (having tested positive for antibodies to PR3 or MPO by ELISA or ALBIA, either at the time of enrollment or in the past) and must have at least one "major" item, or at least 3 minor items, or at least the two renal items of proteinuria and hematuria in the BVAS. Care must be taken to ensure that the renal items are due to vasculitis activity and not other factors such as menses or cyclophosphamide-related cystitis. If a patient has "other" items, not specified in the BVAS, these need to be discussed with the Medical Monitor before enrollment.

Eligible patients will visit the study center on Day 1, after an overnight fast of at least 9 hours, for physical examination and vital signs, serum chemistry tests (including HbA1c and LDL cholesterol), hematology tests, serum pregnancy test (in women of childbearing potential), urinalysis (including hematuria, urinary albumin:creatinine ratio [UACR], and MCP-

1:creatinine ratio assessment), eGFR, ANCA measurement (anti-PR3 and anti-MPO ELISA), SF-36 v2 and EQ-5D-5L assessment, Glucocorticoid Toxicity Index (GTI) baseline assessment, baseline pharmacokinetic (PK) and pharmacodynamic (PD) blood sample collection, saliva sample collection, stratification and randomization. Medication will be administered (IV) and dispensed (for oral medications). The patients will take the first dose of CCX168 or placebo, and prednisone or placebo while at the study center. A patient could be kept overnight in the hospital on Day 1, if necessary, based on the patient's clinical condition. This hospital stay may be extended, if the patient's condition demands it, and this hospital stay would not be considered a serious adverse event (SAE), unless other SAE criteria are met.

Twice daily dosing of CCX168 or placebo will continue for 364 days. At post-Day 1 study visits, study medication will be administered according to the protocol schedule, and blood and urine samples will be collected for safety and efficacy and PK/PD measurements. BVAS assessments will be made at Screening and Weeks 4, 10, 16, 26, 39, 52, and 60. VDI assessments will be made at Screening and Weeks 26, 52, and 60. SF-36 v2 and EQ-5D-5L will be completed on Day 1 and Weeks 4, 10, 16, 26, 39, 52, and 60. GTI assessments will be done on Day 1 and at Weeks 13 and 26. If a patient consents, renal biopsy for histology will be performed at Week 52. Physical examinations, vital sign assessments, and ECG measurements will be performed throughout the study. Concomitant medication and adverse event assessments will be made at every study visit.

Patients will be discharged from the study when all the Study Week 60 visit procedures have been completed. Each patient's condition will be evaluated by the Investigator at the end of the clinical trial (Week 60) and appropriate standard of care medical treatment will be provided to all patients as needed.

To the extent possible, any adverse events that are deemed study drug-related and are ongoing at discharge will be followed to resolution or until a determination is made that the unresolved event is stable.

Number of Patients

Approximately 300 patients with AAV will be randomized for this study. Patients who drop out of the study prematurely will not be replaced.

Main Criteria for Inclusion

1. Clinical diagnosis of granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis, consistent with Chapel-Hill Consensus Conference definitions (Jennette et al, 2013);
2. Aged at least 18 years, with newly-diagnosed or relapsed AAV where treatment with cyclophosphamide or rituximab is needed; where approved, adolescents (12 to 17 years old) may be enrolled; female patients of childbearing potential may participate if adequate contraception is used during the study, and for at least 6 months after the last cyclophosphamide dose (if receiving cyclophosphamide) and at least 12 months after the last rituximab dose (if receiving rituximab); male patients with partners of childbearing potential may participate in the study if they had a vasectomy at least 6 months prior to randomization or if adequate contraception is used during the study, and for at least 6 months after the last cyclophosphamide dose (if receiving cyclophosphamide) and at least

12 months after the last rituximab dose (if receiving rituximab); Adequate contraception is defined as resulting in a failure rate of less than 1% per year (combined estrogen and progestogen [oral, intravaginal, or transdermal], or progestogen-only hormonal contraception [oral, injectable, or implantable], intra-uterine device, intra-uterine hormone releasing system, bilateral tubal occlusion, vasectomized partner, or true [absolute] sexual abstinence, i.e., in line with the preferred and usual lifestyle of the patient); for patients who will be receiving mycophenolate instead of azathioprine, a second form of birth control must be used if the first form of birth control is hormonal contraception, such as progestogen-only hormonal contraception, because mycophenolate reduces blood levels of the hormones in the oral contraceptive pill and could theoretically reduce its effectiveness; sperm donation for at least 6 months after the last cyclophosphamide dose (if receiving cyclophosphamide), and at least 12 months after the last rituximab dose (if receiving rituximab), must not be performed.

3. Positive test for anti-PR3 or anti-MPO (current or historic) antibodies;
4. At least one major item, or at least 3 minor items, or at least the 2 renal items of proteinuria and hematuria in the BVAS; care must be taken to ensure that the renal items are due to vasculitis activity and not other factors such as menses or cyclophosphamide-related cystitis; if a patient has "other" items, not specified in the BVAS, these need to be discussed with the Medical Monitor before enrollment.
5. Estimated glomerular filtration rate ≥15 mL/minute/1.73 m^2 (using MDRD method for adults, and modified Schwartz equation for adolescents) at screening;
6. Willing and able to give written Informed Consent and to comply with the requirements of the study protocol; written Informed Consent should be obtained from the legal guardian in accordance with regional laws or regulations for patients 12 to 17 years of age, and
7. Judged by the investigator to be otherwise fit for the study, based on medical history, physical examination (including electrocardiogram [ECG]), and clinical laboratory assessments. Patients with clinical laboratory values that are outside of normal limits (other than those specified in the Exclusion Criteria) and/or with other abnormal clinical findings that are judged by the Investigator not to compromise patient participation in the study, may be entered into the study.

Main Criteria for Exclusion

1. Pregnant or breast-feeding;
2. Alveolar hemorrhage requiring invasive pulmonary ventilation support anticipated to last beyond the screening period of the study;
3. Any other known multi-system autoimmune disease including eosinophilic granulomatosis with polyangiitis (Churg-Strauss), systemic lupus erythematosus, IgA vasculitis (Henoch-Schönlein), rheumatoid vasculitis, Sjögren's syndrome, anti-glomerular basement membrane disease, or cryoglobulinemic vasculitis;
4. Required dialysis or plasma exchange within 12 weeks prior to screening;
5. Have had a kidney transplant;
6. Received cyclophosphamide within 12 weeks prior to screening; if on azathioprine, mycophenolate, or methotrexate at the time of screening, these drugs must be withdrawn prior to receiving the cyclophosphamide or rituximab dose on Day 1;

7. Received intravenous glucocorticoids, >3000 mg methylprednisolone equivalent, within 4 weeks prior to screening;
8. Have been taking an oral daily dose of a glucocorticoid of more than 10 mg prednisone-equivalent for more than 6 weeks continuously prior to the screening visit;
9. Received rituximab or other B-cell antibody within 52 weeks of screening or 26 weeks provided B cell reconstitution has occurred (i.e., CD19 count > $0.01x10^9$/L); received anti-TNF treatment, abatacept, alemtuzumab, IVIg, belimumab, tocilizumab, or eculizumab within 12 weeks prior to screening; immunosuppressive drugs not listed here must be discussed with the Medical Monitor;
10. Currently taking a strong inducer of the cytochrome P450 3A4 (CYP3A4) enzyme, such as carbamazepine, phenobarbital, phenytoin, rifampin, or St. John's wort;
11. Any of the following within 12 weeks prior to screening: symptomatic congestive heart failure requiring prescription medication, unstable angina (unless successfully treated with stent or bypass surgery), clinically significant cardiac arrhythmia, myocardial infarction or stroke;
12. History or presence of any form of cancer within the 5 years prior to screening, with the exception of excised basal cell or squamous cell carcinoma of the skin, or carcinoma in situ such as cervical or breast carcinoma in situ that has been excised or resected completely and is without evidence of local recurrence or metastasis;
13. Evidence of tuberculosis based on interferon γ release assay (IGRA), tuberculin purified protein derivative (PPD) skin test, or chest radiography done at screening or within 6 weeks prior to screening;
14. HBV, HCV, or HIV viral screening test showing evidence of active or chronic viral infection done at screening or within 6 weeks prior to screening;
15. Received a live vaccine within 4 weeks prior to screening;
16. WBC count less than 3500/μL, or neutrophil count less than 1500/μL, or lymphocyte count less than 500/μL before start of dosing;
17. Evidence of hepatic disease: AST, ALT, alkaline phosphatase, or bilirubin > 3 times the upper limit of normal before start of dosing;
18. Clinically significant abnormal ECG during screening, e.g., QTcF greater than 450 msec;
19. Known hypersensitivity to CCX168 or inactive ingredients of the CCX168 capsules [redacted], cyclophosphamide or its metabolites (for patients scheduled to receive cyclophosphamide), or known Type I hypersensitivity or anaphylactic reactions to murine proteins, Chinese Hamster Ovary cell proteins, or to any component of rituximab (for patients scheduled to receive rituximab), or any contraindications or hypersensitivity to the use of azathioprine, cyclophosphamide, mycophenolate, or prednisone, or excipients, where applicable, as per the local prescribing information; for patients who will receive azathioprine, concomitant use with allopurinol is contraindicated;
20. For patients scheduled to receive cyclophosphamide treatment, urinary outflow obstruction, active infection (especially varicella zoster infection), or platelet count <50,000/μL before start of dosing;

21. Participated in any clinical study of an investigational product within 30 days prior to screening or within 5 half-lives after taking the last dose;
22. Participated previously in a CCX168 study; and
23. History or presence of any medical condition or disease which, in the opinion of the Investigator, may place the patient at unacceptable risk for study participation.

Test Product

Group B will be the test group. Patients in this group will receive active CCX168 (avacopan) capsules. CCX168 will be administered orally via hard gelatin capsules containing 10 mg CCX168. The CCX168 capsules will be supplied to the study centers in plastic bottles containing 180 capsules.

Patients in Group B will receive one bottle of CCX168 capsules on Day 1 and Weeks 4, 7, 10, and 13, and two bottles at the Week 16, 20, 26, 32, 39, and 45 visits. Patients will be asked to take 3 CCX168 capsules orally every morning, preferably with food, and 3 capsules every evening, preferably with food, approximately 12 hours after the morning dose, as instructed. Study medication will be taken for 364 days continuously. Capsules will be taken orally with water. CCX168 and placebo bottles and capsules will be identical in appearance.

Patients in Group B will also take prednisone-matching placebo capsules orally according to the protocol-specified schedule.

Reference Therapy, Dose and Mode of Administration

Group A will be the control group. Patients in this group will receive CCX168-matching placebo capsules. Placebo will be administered orally via hard gelatin capsules containing only inactive ingredients. Placebo capsules will be supplied to the study centers in plastic bottles containing 180 capsules.

Patients in Group A will receive one bottle of CCX168-matching placebo capsules on Day 1 and Weeks 4, 7, 10, and 13, and two bottles at the Week 16, 20, 26, 32, 39, and 45 visits. Patients will be asked to take 3 CCX168-matching placebo capsules orally every morning, preferably with food, and 3 capsules every evening, preferably with food, approximately 12 hours after the morning dose, as instructed. Study medication will be taken for 364 days continuously. Capsules will be taken orally with water. Placebo and CCX168 bottles and capsules will be identical in appearance.

Patients in Group A will also take prednisone capsules according to the protocol-specified tapering schedule.

Prednisone or prednisone-matching placebo will be given as tablets, over-encapsulated with hard gelatin capsules in order to maintain the blind. Two dose strengths of prednisone capsules will be provided, 20 mg and 5 mg. Placebo for prednisone will be given as matching hard gelatin capsules with placebo tablets.

Oral or IV cyclophosphamide, azathioprine (or mycophenolate, if needed), and rituximab will be prescribed and provided by the study centers.

Duration of Treatment and Observation

Patients will be screened within a period not to exceed 14 days prior to Study Day 1 (the first day of dosing). The treatment period is 364 days and all patients will be followed for 56 days after the treatment period.

To the extent possible, any adverse events that are deemed study drug-related and are ongoing at discharge will be followed to resolution or until a determination is made that the unresolved event is stable. The patient's condition will be evaluated by the Investigator at the end of the clinical trial and appropriate standard of care medical treatment will be provided to all patients as needed.

Safety and Other Assessments

Safety assessments include adverse events, physical examination abnormalities, vital signs, and clinical laboratory tests (including blood chemistry, hematology, and urinalysis), the glucocorticoid toxicity index, and ECGs. Anti-MPO and anti-PR3 antibody levels will be measured over the course of the study.

Efficacy Assessments

Efficacy assessments include:

1. BVAS;
2. SF-36 v2 and EQ-5D-5L measurements;
3. Disease relapse events;
4. Urinary albumin:creatinine ratio (UACR);
5. eGFR by MDRD serum creatinine-based formula for adults, and modified Schwartz equation for adolescents;
6. Urinary MCP-1:creatinine ratio, and
7. VDI.

Pharmacokinetic Assessments

Concentrations of CCX168 and significant metabolites will be determined in plasma from blood collected on Day 1 (pre-dose baseline), Weeks 1, 2, 4, 7, 13, 26, 39, and 52 in all patients. Only for patients 12 to 17 years of age, CCX168 and metabolites will also be measured at Hours 0.5, 1, 2, 3, 4, and 6 after the first dose on Day 1. Samples from adolescent patients will be assayed expeditiously and CCX168 dose adjustments will be made, if necessary.

Pharmacodynamic Assessments

Plasma samples will be collected on Day 1 (pre-dose baseline), and Weeks 1, 2, 4, 13, 26, 39, 52, and 60 for pharmacodynamic marker measurements, including, for example, cystatin C, complement fragments, and inflammatory cytokine and chemokine levels. The PK plasma samples may also be used for these pharmacodynamic marker measurements.

Blood samples collected may be used for lymphocyte subtype counts, as well as for DNA and other biomarker assessments by RNA analysis.

Urine samples will be collected on Day 1 (pre-dose baseline), and Weeks 1, 2, 4, 13, 26, 39, 52, and 60 for biomarker assessments including, for example, complement fragments, inflammatory chemokine and cytokine levels.

A saliva sample will be collected on Day 1 from patients who have provided Informed Consent for assessment of genetic markers of ANCA disease as well as the complement pathway.

Statistical Methods

Demographics and Baseline Characteristics

All patient baseline characteristics and demographic data, i.e., age, sex, race, ethnicity, weight, height, body mass index, anti-PR3 and anti-MPO status, GPA vs. MPA disease type, newly-diagnosed vs. relapsing disease, IV cyclophosphamide vs. oral cyclophosphamide vs. IV rituximab use, vasculitis disease duration (from time of diagnosis), BVAS, VDI, SF-36 v2, EQ-5D-5L, GTI, eGFR, hematuria status, UACR, and urinary MCP-1:creatinine ratio will be listed and summarized by treatment group.

Glomerular histopathology (if biopsy was taken), physical examination abnormalities, medical history, previous and concomitant medications (including vasculitis medication use) at study entry will be listed and summarized by treatment group.

Efficacy Analysis

The primary efficacy endpoints are:

1. The proportion of patients achieving disease remission at Week 26, defined as a BVAS score of 0 and not taking glucocorticoids for treatment of AAV within 4 weeks prior to Week 26.
2. The proportion of patients achieving sustained disease remission, defined as remission at Week 26 without relapse to Week 52 (BVAS of 0 and not taking glucocorticoids for treatment of AAV within 4 weeks prior to Week 52).

Secondary endpoints include:

1. Glucocorticoid-induced toxicity as measured by change from baseline over the first 26 weeks in the glucocorticoid toxicity index;
2. Early remission, defined as BVAS of 0 at Week 4;
3. Change from baseline over 52 weeks in health-related quality-of-life as measured by the domains and component scores of the SF-36 v2 and EQ-5D-5L visual analogue scale (VAS) and index;
4. Proportion of patients and time to experiencing a relapse; relapse is defined as occurrence of at least one major item in the BVAS, or three or more minor items in the BVAS, or one or two minor items in the BVAS at two consecutive visits, after having previously achieved remission at Week 26 (BVAS = 0 and having received no glucocorticoids for treatment of vasculitis for 4 weeks);
5. In patients with renal disease at baseline (based in the BVAS renal component), the change in eGFR from baseline over 52 weeks;

6. In patients with renal disease at baseline (based in the BVAS renal component), the percent change in UACR from baseline over 52 weeks;
7. In patients with renal disease at baseline (based in the BVAS renal component), the percent change in urinary MCP-1:creatinine ratio from baseline over 52 weeks;
8. Change in the VDI from baseline over 52 weeks.

Summary statistics will be calculated for each of the endpoints. For categorical endpoints, numbers and percentages will be calculated. For continuous variables, numbers, means, medians, ranges, standard deviations, and standard error of means will be calculated. Geometric means will be calculated for data that are typically not normally distributed, e.g., UACR and urinary MCP-1:creatinine ratio.

Results will be presented by treatment group. Results will be presented by stratum for each of the three stratification factors, IV rituximab vs. IV cyclophosphamide vs. oral cyclophosphamide use, anti-PR3 vs. anti-MPO positive ANCA, and newly-diagnosed vs. relapsing patients, as well as GPA vs. MPA. Results will be presented for patients with renal AAV and those without renal AAV at baseline, as well as those who received IV glucocorticoids upfront compared to those who did not. Data will also be presented by geographic distribution, sex, age group, race, and ethnicity for at least the primary endpoints.

The overall efficacy hypothesis in this study is that CCX168 treatment will be effective in treatment of patients with AAV based on inducing and then sustaining remission without requiring chronic oral prednisone treatment.

For the two primary efficacy endpoints, the proportion of patients achieving disease remission at Week 26 and sustained disease remission at Week 52, and the two-sided 95% confidence intervals for the difference in proportions (CCX168 minus control) will be estimated for the comparison between the CCX168 group and the control group.

The proportion of patients achieving disease remission at Week 26 will be calculated as the number of patients with a BVAS of 0 during the 4-week period preceding the Week 26 visit, and having not received any glucocorticoid treatment for AAV during the 4-week period preceding and including the Week 26 visit, divided by the total number of patients randomized to the particular treatment group and who received at least 1 dose of blinded study drug.

The proportion of patients achieving sustained disease remission at Week 52 will be calculated as the number of patients who achieved remission at Week 26 (with a BVAS of 0 during the 4-week period preceding the Week 26 visit, and having not received any glucocorticoid treatment for AAV during the 4-week period preceding and including the Week 26 visit) AND who have also achieved remission at Week 52 (with a BVAS of 0 during the 4 week-period preceding the Week 52 visit, and having not received any glucocorticoid treatment for treatment of AAV during the 4-week period preceding and including the Week 52 visit), divided by the total number of patients randomized to the particular treatment group and who received at least 1 dose of blinded study drug. Patients who relapse after Week 26 and before Week 52 will be considered treatment failures for the sustained remission analysis at Week 52.

The following hypotheses will be tested for the first primary efficacy endpoint:

- The non-inferiority null hypothesis ($H1_0$) is that the CCX168 group is inferior to the control group when comparing the remission rate based on BVAS at Week 26.
- The non-inferiority alternative hypothesis ($H1_1$) is that the CCX168 group is not inferior to the control group when comparing the remission rate at Week 26.
- The superiority null hypothesis ($H2_0$) is that the CCX168 group is not different from the control group when comparing the remission rate at Week 26.
- The superiority alternative hypothesis ($H2_1$) is that the CCX168 group is superior to the control group when comparing the remission rate at Week 26.

The following hypotheses will be tested for the second primary efficacy endpoint:

- The non-inferiority null hypothesis ($H3_0$) is that the CCX168 group is inferior to the control group when comparing the sustained remission rate based on remission at Week 26 without relapse to Week 52.
- The non-inferiority alternative hypothesis ($H3_1$) is that the CCX168 group is not inferior to the control group when comparing the sustained remission rate based on remission at Week 26 without relapse to Week 52.
- The superiority null hypothesis ($H4_0$) is that the CCX168 group is not different from the control group when comparing the sustained remission rate based on remission at Week 26 without relapse to Week 52.
- The superiority alternative hypothesis ($H4_1$) is that the CCX168 group is superior to the control group when comparing the sustained remission rate at Week 26 without relapse to Week 52.

The two primary endpoints will be tested sequentially using a gatekeeping procedure to preserve the Type I error rate at 0.05. The sequence of testing will be as follows:

1. Test for non-inferiority ($H1_0$) of the CCX168 group compared to the control group regarding remission at Week 26; if the p-value for non-inferiority is < 0.05, proceed to step 2;
2. Test for non-inferiority ($H3_0$) of the CCX168 group compared to the control group regarding sustained remission at Week 52; if the p-value for non-inferiority is <0.05, proceed to the step 3;
3. Test for superiority ($H4_0$) of the CCX168 group compared to the control group regarding sustained remission at Week 52; if the p-value for superiority is <0.05, proceed to step 4;
4. Test for superiority ($H2_0$) of the CCX168 group compared to the control group regarding remission at Week 26.

For the non-inferiority test of the first primary efficacy endpoint, if the lower bound of the 95% confidence interval is greater than -0.20 (i.e., $P <0.05$ for the non-inferiority test) and the control group disease remission rate is at least 40% at Week 26, the CCX168 group will be considered not inferior to the control group. For the superiority test, if the lower bound of the 95% confidence interval is greater than 0.0 (i.e., $P <0.05$ for the superiority test), the CCX168 group will be considered superior to the control group in achieving the disease remission at Week 26.

For the second primary endpoint, the proportion of patients in disease remission at Week 26 without relapse to Week 52, and the two-sided 95% confidence interval for the difference in proportion (CCX168 minus control) will be estimated for the comparison between the CCX168 group and the control group. For the non-inferiority test of the second primary endpoint, if the lower bound of the 95% confidence interval is greater than -0.20 (i.e., P <0.05 for the non-inferiority test), the CCX168 group will be considered not inferior to the control group. For the superiority test, if the lower bound of the 95% confidence interval is greater than 0.0 (i.e., P <0.05 for the superiority test), the CCX168 group will be considered superior to the control group in achieving the disease remission at Week 26 without relapse to Week 52.

5. Patients who relapse after Week 26 and before Week 52 will be considered treatment failures for the sustained remission analysis at Week 52. A relapse is defined as worsening of disease that involves one or more major items, or three or more minor items in the BVAS, or one or two minor items in the BVAS recorded at two consecutive visits, after having previously achieved remission at Week 26 (BVAS = 0 and having received no glucocorticoids for treatment of vasculitis for 4 weeks).

The stratified Newcombe hybrid-score method will be used to calculate the confidence intervals for the common difference in proportions.

Binary variables of the secondary efficacy endpoints, the proportion of patients with early remission (Week 4) and the proportion of patients with relapse events, will be analyzed similarly to the primary efficacy endpoints.

If there are a sufficient number of relapse events, time from remission to relapse will be analyzed by Kaplan Meier methodology and log rank testing of the differences between treatment groups.

Continuous variables of the secondary efficacy endpoints will be analyzed using a mixed effects model for repeated measures (MMRM) with treatment group, visit, treatment-by-visit interaction, and randomization strata (IV rituximab, IV or oral cyclophosphamide, anti-PR3 or anti-MPO ANCA, and newly-diagnosed AAV or relapsed AAV) as factors, and baseline as covariate. Patients will be considered as repeated measure units over visits. Point estimates and corresponding 95% confidence intervals will be estimated for the difference between the CCX168 group and the control group across 52 weeks using simple contrast from the model. Continuous variables include change and/or percent change from baseline in GTI, eGFR, UACR, urinary MCP-1:creatinine ratio, SF-36 v2 (domains and component scores) and EQ-5D-5L VAS and index, VDI, and pharmacodynamics markers. Data that are not normally distributed, e.g., UACR will be log-transformed before analysis.

The Week 60 follow-up data will be summarized with no formal statistical testing.

All statistical testing will be two-sided, with the type I error rate at α=0.05.

The efficacy analyses will be performed in the intent-to-treat (ITT) and per protocol (PP) populations. All patients who are randomized and who received at least 1 dose of study drug will be included in the ITT population. Efficacy analysis in the ITT population will be considered the primary analysis. The PP population will consist of all randomized patients who receive at least one dose of study drug and do not have protocol deviations that could significantly affect the interpretation of the results for the primary endpoints. Patients'

inclusion/exclusion from the PP population will be determined and documented prior to the database lock and unblinding.

Baseline is defined as the last value prior to start of dosing with study medication (typically the Day 1 pre-dose value). For BVAS and VDI, baseline will be taken from the Screening visit.

Safety Analysis

Safety endpoints, other than glucocorticoid-induced toxicity, include:

1. Patient incidence of treatment-emergent serious adverse events, adverse events, and withdrawals due to adverse events;
2. Change from baseline and shifts from baseline in all safety laboratory parameters;
3. Change from baseline in vital signs, and
4. Incidence of clinically significant ECG changes from baseline.

All patients who are randomized and received at least one dose of study medication will be included in the safety population.

All clinical safety and tolerability data will be listed by treatment group and by patient, and will be summarized by treatment group.

All reported adverse events will be coded using MedDRA and listed by System Organ Class, Preferred Term, and verbatim term.

Treatment-emergent adverse events will be listed and will be summarized by treatment group by System Organ Class and Preferred Term, by relatedness and by maximum severity.

Treatment-emergent serious adverse events and adverse events leading to withdrawal will be summarized by treatment group.

Individual vital signs and change from baseline in vital signs will be listed by treatment group, patient, and study visit, and summarized by treatment group.

Laboratory data (actual values and change from baseline) will be listed by treatment group, patient, and study visit. Abnormal laboratory values will be flagged. Laboratory data will also be summarized by treatment group and study visit. Shift tables will be generated for shifts in laboratory parameters by study visit.

Abnormal ECG findings will be listed by treatment group and study visit, and clinical significance of abnormalities indicated.

Sample Size Assumptions

The proportion of patients in the control group achieving clinical remission at Week 26 is estimated to be ~60%, a blended proportion of 64% and 53% observed in the rituximab and cyclophosphamide/azathioprine groups, respectively, in the largest prior registration study in AAV (Stone et al, 2010).

A non-inferiority margin of -20 percentage points has been derived for the difference between CCX168 and control groups, and a one-sided alpha level of 0.025. This non-inferiority margin is based on a thorough review and meta-analysis of all previous clinical trials conducted in patients with AAV, as well as precedent (Stone et al, 2010).

A sample size of 150 patients per group (300 in total) is estimated to provide more than 90% power for the non-inferiority test. This sample size provides 90% power to detect approximately 18% superiority in the proportion of patients achieving clinical remission at Week 26 if the control group remission rate is 60%.

The proportion of patients in the control group with sustained remission at Week 52 is estimated to be ~45%, a blended proportion observed in a prior study comparing rituximab and cyclophosphamide/azathioprine in AAV (Specks et al, 2013).

A sample size of 150 patients per group (300 in total) is estimated to provide 85% power to detect approximately 18% superiority if the control group sustained remission rate at Week 52 is 45%.

Pharmacokinetic and pharmacodynamic marker analysis

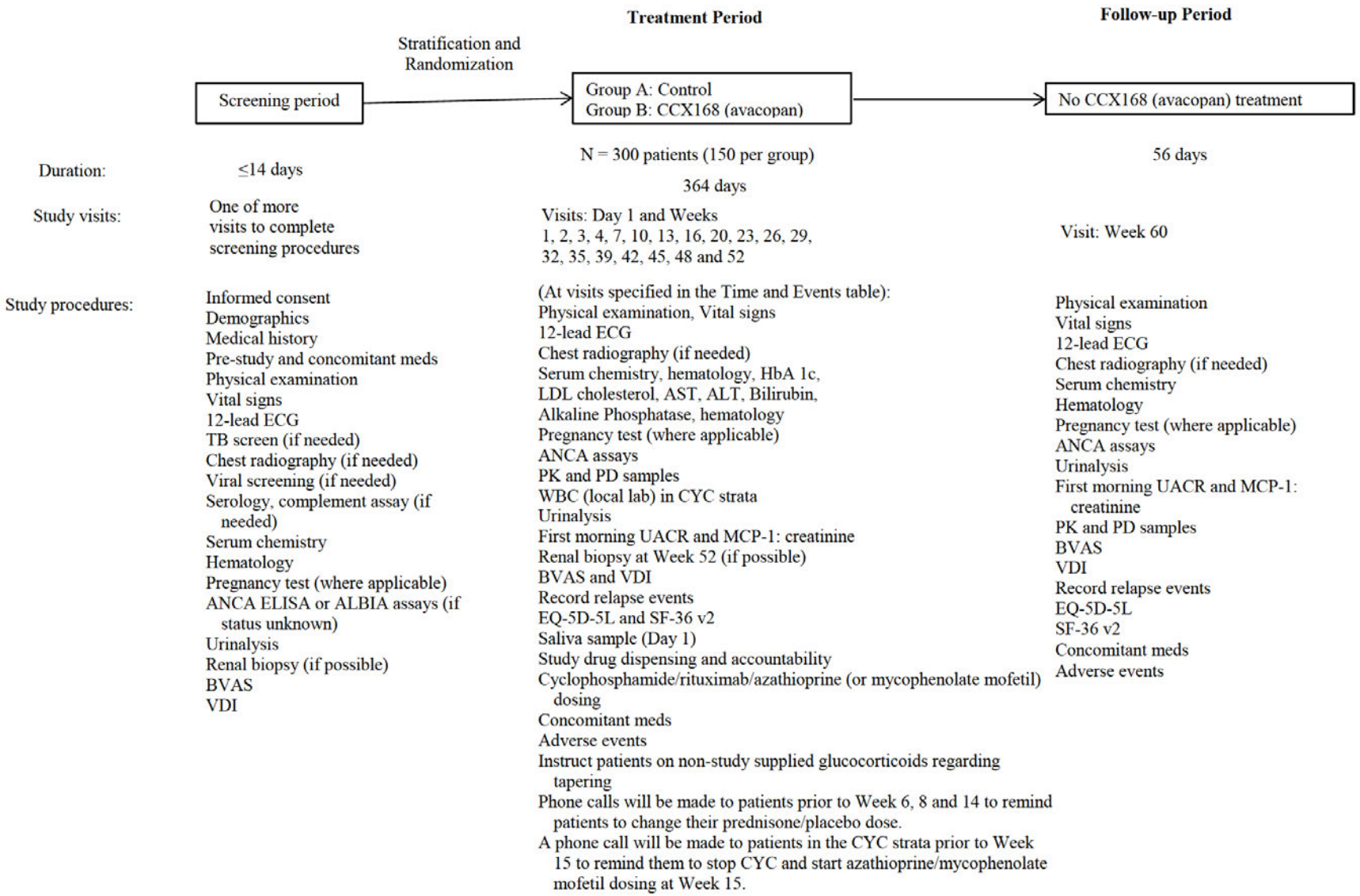
Individual plasma concentrations of CCX168 and significant metabolites at all study visits where these are measured will be listed, plotted, and summarized descriptively and graphically. Population PK analysis will be conducted based on the CCX168 and metabolite plasma concentration measurements.

For data collected in adolescents, PK parameters such as C_{max}, T_{max}, and $AUC_{0\text{-}6hr}$ will be calculated on Day 1 for CCX168 and significant metabolites.

Plasma and urinary PD markers will be summarized and may be analyzed using methods analogous to the efficacy parameters.

The relationship between PK parameters and renal function based on eGFR will be evaluated. The data may also be used to evaluate the PK/PD relationship of CCX168 treatment. To this end, the change and/or percent change from baseline in eGFR, UACR, urinary MCP-1:creatinine ratio, or other biomarkers may be used as PD markers.

Figure 1: Study Schema



TIME AND EVENTS TABLE: Please refer to bottom of this table for table footnotes.

	SCR[1]	Treatment Period																								ET	F/U
Study Day	**-14 to -1**	**1[2]**	**8**	**15**	**22**	**29**	**43**	**50**	**57**	**71**	**92**	**99**	**106**	**113**	**141**	**162**	**183**	**204**	**225**	**246**	**274**	**295**	**316**	**337**	**365**		**421**
Study Week[3]			**1**	**2**	**3**	**4**	**6**	**7**	**8**	**10**	**13**	**14**	**15**	**16**	**20**	**23**	**26**	**29**	**32**	**35**	**39**	**42**	**45**	**48**	**52**		**60**
Visit to study center	X	X	X	X	X	X		X		X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Phone call to patients as reminder to change prednisone/ placebo dose							X		X			X															
Phone call to patients in CYC strata as reminder to start azathioprine													X														
Informed Consent	X																										
Demographics Medical History, Prior Medications	X																										
Physical Examination[4]	X	X[5]	X	X		X				X	X			X			X				X				X	X	X
Vital Signs[6]	X	X[5]	X	X	X	X		X		X	X			X	X		X		X		X		X		X	X	X
12-lead ECG	X			X				X			X						X				X				X	X	X
Chest Radiography[7]	(X)					(X)				(X)				(X)			(X)				(X)				(X)	(X)	(X)
Tuberculosis Screening[8]	X																										
HIV, HBV, HCV Screening (if not done within 6 weeks)	X																										
ANA, anti-GBM antibodies, C3, C4, IgG, IgM, and IgA[9]	X																										

	SCR[1]	Treatment Period																								ET	F/U
Study Day	**-14 to -1**	**1[2]**	**8**	**15**	**22**	**29**	**43**	**50**	**57**	**71**	**92**	**99**	**106**	**113**	**141**	**162**	**183**	**204**	**225**	**246**	**274**	**295**	**316**	**337**	**365**		**421**
Study Week[3]			**1**	**2**	**3**	**4**	**6**	**7**	**8**	**10**	**13**	**14**	**15**	**16**	**20**	**23**	**26**	**29**	**32**	**35**	**39**	**42**	**45**	**48**	**52**		**60**
Serum Chemistry, Hematology	X	X[5]	X	X	X	X		X		X	X			X	X		X		X		X		X		X	X	X
ALT, AST, Bilirubin, Alkaline Phosphatase Hematology																X		X		X		X		X			
HbA1c, LDL cholesterol		X[5]									X						X									X	
Serum pregnancy test in women of childbearing potential	X	X				X				X				X			X				X				X	X	X
Urine pregnancy test															X				X				X				
ANCA Measurement[10]	X	X[5]									X						X				X				X	X	X
PK Plasma Sample Collection		X[5,11]	X	X		X		X			X						X				X				X		
Record date and time of last dose of CCX168/ placebo prior to PK blood sample collection			X	X		X		X			X						X				X				X		
Blood Sample Collection for PD markers and cells		X[5]	X	X		X					X						X				X				X		X
WBC count (local lab)[12]		X[5]		X		X		X		X	X																
Urine sample for Urinalysis[13]	X	X[5]	X	X	X	X		X		X	X			X	X		X		X		X		X		X	X	X

	SCR[1]	Treatment Period																								ET	F/U
Study Day	**-14 to -1**	**1[2]**	**8**	**15**	**22**	**29**	**43**	**50**	**57**	**71**	**92**	**99**	**106**	**113**	**141**	**162**	**183**	**204**	**225**	**246**	**274**	**295**	**316**	**337**	**365**		**421**
Study Week[3]			**1**	**2**	**3**	**4**	**6**	**7**	**8**	**10**	**13**	**14**	**15**	**16**	**20**	**23**	**26**	**29**	**32**	**35**	**39**	**42**	**45**	**48**	**52**		**60**
Urine samples for albumin, MCP-1 and creatinine Assays		X[5]	X	X		X					X						X				X				X		X
Urine sample for PD markers		X[5]	X	X		X					X						X				X				X		X
Renal Biopsy[14]	X																								X		
BVAS	X					X				X				X			X				X				X	X	X
Record relapse events[15]								X		X	X			X	X		X		X		X		X		X	X	X
VDI	X																X								X	X	X
SF-36 v2 and EQ-5D-5L		X[5]				X				X				X			X				X				X	X	X
Glucocorticoid Toxicity Index		X									X						X									X	
Saliva sample collection		X																									
Stratification and randomization		X[5]																									
CCX168 or Placebo Dispensing[16]		X[5]				X		X		X	X			X	X		X		X		X		X				
Inspection of CCX168 or Placebo bottles to ensure patient compliance			X	X	X																						
CCX168 or Placebo Accountability						X		X		X	X			X	X		X		X		X		X		X	X	
Prednisone or Placebo Dispensing		X[5]	X	X	X	X		X		X	X			X													
Prednisone or Placebo Accountability			X	X	X	X		X		X	X			X	X											X	

	SCR[1]	Treatment Period																								ET	F/U
Study Day	**-14 to -1**	**1[2]**	**8**	**15**	**22**	**29**	**43**	**50**	**57**	**71**	**92**	**99**	**106**	**113**	**141**	**162**	**183**	**204**	**225**	**246**	**274**	**295**	**316**	**337**	**365**		**421**
Study Week[3]			**1**	**2**	**3**	**4**	**6**	**7**	**8**	**10**	**13**	**14**	**15**	**16**	**20**	**23**	**26**	**29**	**32**	**35**	**39**	**42**	**45**	**48**	**52**		**60**
Cyclo-phosphamide IV dose[17]		X		X		X		X		X	X																
Cyclo-phosphamide oral dosing[18]		X→	→	→	→	→	→	→	→	→	→	→	X														
Azathioprine dosing[19]													X→	→	→		→		→		→		→		→		→X
Rituximab IV dose[20]		X	X	X	X																						
Concomitant Medications	X	X	X	X	X	X		X		X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
If receiving non-study supplied glucocorticoids on Day 1, instruct patients regarding tapering[21]		X	X	X	X																						
Adverse Event Assessment		X	X	X	X	X		X		X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X

ET = Early Termination; F/U = Follow-up; SCR = Screening.

[1] Screening must occur expeditiously (not to exceed 14 days) in order not to delay start of treatment; screening labs may be done at the local laboratory to expedite eligibility assessment; results from a renal biopsy, if performed within 4 weeks prior to Day 1 will be collected on the Histology Form provided. Laboratory and urinalysis results from the local laboratories obtained within 72 hours of screening are acceptable in order to avoid unnecessary blood draws.

[2] A patient could be kept overnight in the hospital on Day 1, if necessary based on the patient's condition. This hospital stay could be extended if deemed clinically necessary and would not be considered a serious adverse event, unless other SAE criteria are met.

[3] Visits for Weeks 1, 2, 3, and 4 may occur within a ± 2-day window. Visits for the rest of the study may occur within a ± 3-day window of the scheduled visit.

[4] Physical examination will include body weight measurement; Height will only be measured at Screening, except in adolescents (12-17 years old), in whom height will be measured as part of all physical examinations.

[5] These procedures must be done BEFORE taking the first dose of study medication.

[6] Assessment of heart rate, body temperature, and blood pressure (after at least 3 minutes of rest)

[7] Chest radiography (X rays or CT scan) done only if needed for TB screening or if in the clinical opinion of the Investigator there is pulmonary disease involvement that needs to be assessed for safety, BVAS, VDI, or GTI.

[8] Screening for TB could be done by one of the following: Interferon γ release assay (IGRA), tuberculin purified protein derivative (PPD) skin test, or chest radiography (done within 6 weeks prior to Screening or done during Screening).

[9] These tests do not need to be performed if results are available from tests done within the past 12 months prior to the Screening visit.

[10] At screening, tests for anti-proteinase-3 (PR3) and anti-myeloperoxidase (MPO) will be performed for study eligibility, if no historical data are available; for the rest of the study visits, ELISA tests for anti- PR3 and anti-MPO antibodies will be performed at the central laboratory.

[11] Only for patients who are 12 to 17 years old, blood samples will be taken at Hours 0 (pre-dose), 0.5, 1, 2, 3, 4, and 6 after the first dose of CCX168/placebo and plasma samples will be frozen and sent for expeditious measurements of CCX168 and metabolite plasma concentrations.

[12] For patients receiving cyclophosphamide, a blood sample must be taken early during the visit for WBC count at the local laboratory; the WBC count is necessary for cyclophosphamide dose decisions on these days. For patients receiving azathioprine, local WBC count will be done at the Week 13 visit.

[13] A clean catch, midstream urine sample will be collected. During screening, the local laboratory may perform a urinalysis for hematuria and proteinuria for eligibility assessment. For the rest of the visits, a urine sample will be sent to the central laboratory for urinalysis including protein, blood, and nitrites; if positive for blood, protein, or nitrites, a microscopic RBC count will be done.

[14] Renal biopsies are optional. In patients with renal involvement of AAV, renal histology results from biopsies performed within 4 weeks prior to Screening should be recorded on the provided standard Histology Form; follow-up biopsies should be performed within a 14-day window before or after the Week 52 visit, if a patient consents.

[15] Relapse assessment; relapse is defined as return of at least one major item, or three or more minor items, or one or two minor items in the BVAS recorded at two consecutive visits, after disease remission has been achieved previously (BVAS = 0).

[16] One bottle of CCX168/placebo will be dispensed at the Day 1 and Week 4, 7, 10, and 13 visits, and two bottles will be dispensed at the Week 16, 20, 26, 32, 39, and 45 visits.

[17] Applicable only to the IV cyclophosphamide stratum. Cyclophosphamide doses given from Day 1 through Week 13 must be given according to directions provided in the protocol. The date, and start and end time of the cyclophosphamide infusion will be recorded.

[18] Applicable only to the oral cyclophosphamide stratum. Cyclophosphamide must be taken daily from Day 1 through the day before Week 15 according to the protocol.

[19] Azathioprine must be taken daily from Week 15 (for those who received IV or oral cyclophosphamide) through the end of the study, but not for those patients receiving rituximab. Mycophenolate will be given instead of azathioprine to patients for whom azathioprine is not suitable.

[20] Applicable only to the rituximab stratum. A rituximab dose of 375 mg/m^2 IV must be given on Day 1 and Weeks 1, 2, and 3.

[21] If the patient has received glucocorticoids during the screening period, the glucocorticoid dose must be reduced to a dose not higher than 20 mg prednisone equivalent on Day 1, and the patient must be instructed on tapering the dose to zero within a period of 4 weeks after the Day 1 visit.

LIST OF ABBREVIATIONS AND ACRONYMS

AAV	anti-neutrophil cytoplasmic antibody associated vasculitis
AE	adverse event
ALBIA	Addressable Laser Bead ImmunoAssay
ALT	alanine aminotransferase
ANA	anti-nuclear antibodies
ANC	absolute neutrophil count
ANCA	anti-neutrophil cytoplasmic antibody
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
BID	twice daily
BLQ	below limit of quantification
BSA	body surface area
BUN	blood urea nitrogen
BVAS	Birmingham Vasculitis Activity Score
C3	complement 3
C4	complement 4
C3a	complement 3a
C4a	complement 4a
C5a	complement 5a
C5aR	complement 5a receptor
C5b-9	complement 5b-9 (also called membrane attack complex)
CA	competent authority
CBC	complete blood cell
C_{max}	maximum (plasma) concentration
CPK	creatinine phosphokinase
CRA	Clinical Research Associate (also known as the Study Monitor)
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CYC	cyclophosphamide
DMC	Data Monitoring Committee
EC	ethics committee
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EQ-5D-5L	EuroQOL-5D-5L
ELISA	enzyme linked immunosorbent assay
FDA	Food and Drug Administration
g	gram
GBM	glomerular basement membrane
GCP	good clinical practice
GPA	granulomatosis with polyangiitis (Wegener's)
GTI	Glucocorticoid Toxicity Index
HEENT	head, eyes, ears, nose, throat

HIV	human immunodeficiency virus
hpf	high power field
HRQOL	health-related quality-of-life
IC_{50}	concentration to inhibit 50%
ICH	International Council for Harmonisation
IGRA	interferon γ release assay
INN	International Nonproprietary Name
IRB	Institutional Review Board
IRT	interactive response technology
ITT	Intent-to-Treat
IVIg	intravenous immunoglobulin
kg	kilogram
KIM-1	kidney injury molecule-1
LDH	lactate dehydrogenase
MAC	membrane attack complex
MCP-1	monocyte chemoattractant protein-1
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Drug Regulatory Affairs
mg	milligram
mL	milliliter
MPA	microscopic polyangiitis
MPO	myeloperoxidase
N	number
NGAL	neutrophil gelatinase-associated lipocalin
NIM	non-inferiority margin
NOAEL	No observed adverse effect level
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PP	Per Protocol
PPD	purified protein derivative
PR3	proteinase 3
RBC	red blood cell
RTX	rituximab
SAE	serious adverse event
SAR	serious adverse reaction
SF-36 v2	Short Form-36 version 2
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TCC	terminal complement complex
T_{max}	time of maximum (plasma) concentration
TPMT	thiopurine S-methyltransferase
UACR	urinary albumin:creatinine ratio
USAN	United States Adopted Name
VDI	vasculitis damage index
WBC	white blood cell

1. INTRODUCTION

1.1. Background Information

The activation of the complement pathway generates biologically active fragments of complement proteins, e.g. C3a, C4a and C5a anaphylatoxins, and the C5b-9 membrane attack complex (MAC) or terminal complement complex (TCC), all of which mediate inflammatory responses by inducing leukocyte chemotaxis, activating macrophages, neutrophils, platelets, mast cells and endothelial cells and by increasing vascular permeability, cytolysis, and tissue injury.

C5a is one of the most potent pro-inflammatory mediators of the complement system, being at least 100 times more potent than C3a. This 12 to 14.5 kD polypeptide, along with a C5b fragment, is produced by enzymatic cleavage of a C5 precursor during activation of any of the 3 complement pathways. C5a induces expression of adhesion molecules and chemotactic migration of neutrophils, eosinophils, basophils, and monocytes. It also mediates inflammatory reactions by causing smooth muscle contraction, increasing vascular permeability, inducing basophil and mast cell degranulation, and inducing release of lysosomal proteases and oxidative free radicals. The anaphylactic and chemotactic effects of C5a are mediated through its interaction with the C5aR, a G protein-coupled receptor expressed on human neutrophils, monocytes, basophils, eosinophils, renal glomerular tissues, and lung smooth muscle and endothelial cells.

CCX168 (INN/USAN avacopan as of August 2016) is an orally administered, small molecule, selective complement 5a receptor (C5aR) antagonist.

As measured in vitro, CCX168 functionally inhibits C5a-mediated chemotaxis, displaces [^{125}I]-C5a from human C5aR, and inhibits C5a-mediated increase in cytoplasmic calcium levels with a potency (IC_{50}) of 0.2 to 0.9 nM.

CCX168 was evaluated for its ability to inhibit the C5a-mediated chemotaxis of neutrophils in freshly isolated human whole blood. CCX168 produced 50% inhibition (IC_{50}) of C5a-mediation neutrophil migration in this assay at a concentration of 1.7 nM; 90% inhibition (A_{10} value) occurred at a CCX168 concentration of 15.4 nM. CCX168 also inhibits C5aR in cynomolgus monkeys and hamsters with potencies similar to that observed with human whole blood. However, CCX168 possesses moderate potency for rabbit C5aR (IC_{50} ~ 1.4 µM) and lacks affinity for mouse, rat, or dog C5aR (IC_{50} >10 µM).

The efficacy of CCX168 was assessed using genetically-modified mice where the mouse C5aR coding region was substituted for the human C5aR coding region. In these studies, intravenous injection of mouse anti-myeloperoxidase (anti-MPO) IgG into the human C5aR knock-in mice caused glomerulonephritis in a manner mimicking ANCA disease in humans. At daily oral doses of 30 mg/kg CCX168, a marked inhibition of anti-MPO induced glomerulonephritis was documented histologically, as assessed by the number of necrotic and crescent-containing glomeruli. These results were consistent with reduced protein, leukocytes, and red blood cells in the urine, and reduced serum blood urea nitrogen and creatinine in mice receiving CCX168 (Xiao et al, 2014).

CCX168 has been evaluated in a series of safety pharmacology and toxicology studies. Results from these studies support chronic oral dosing of 30 mg CCX168 twice daily to humans. Refer to the Investigator's Brochure for details of these studies.

A randomized, double-blind, placebo-controlled Phase 1 study in 48 healthy volunteers was performed (CL001_168). This is a study in which subjects received either CCX168 or placebo (3:1 ratio) as a single oral dose in Period 1 and as multiple once daily or twice daily oral doses in Period 2. Single doses of 1, 3, 10, 30, and 100 mg CCX168 were studied. In Period 2, CCX168 doses of 1, 3, and 10 mg once daily for 7 days, and 30 and 50 mg twice daily for 7 days, were studied.

CCX168 appeared to be well tolerated by study subjects. No serious adverse events or withdrawals due to adverse events were observed.

A randomized, double-blind, placebo-controlled Phase 2 clinical trial in 67 patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) was performed (CL002_168). In this clinical trial, eligible patients were randomized to one of three treatment groups:

1. Placebo twice daily orally plus cyclophosphamide/azathioprine or rituximab plus full dose prednisone (60 mg),
2. 30 mg CCX168 twice daily orally plus cyclophosphamide/azathioprine or rituximab plus one-third dose prednisone (20 mg), or
3. 30 mg CCX168 twice daily orally plus cyclophosphamide/azathioprine or rituximab plus no oral prednisone.

The treatment period was 12 weeks, with a 12-week follow-up period.

The aim of the trial was to determine if CCX168 could provide an effective treatment for AAV while also allowing for the reduction or elimination of glucocorticoids without compromising safety or efficacy. The primary efficacy objective was to evaluate the efficacy of CCX168 based on the Birmingham Vasculitis Activity Score (BVAS).

Results showed that CCX168 plus cyclophosphamide/azathioprine or rituximab was at least as effective as high dose glucocorticoids plus cyclophosphamide/azathioprine or rituximab in treatment of patients with AAV. The BVAS response rate, defined as the proportion of patients with a BVAS percent change from baseline of at least 50%, with no worsening in any body system, at Week 12 was numerically higher and statistically non-inferior in patients receiving CCX168 compared to control. CCX168 treatment was effective across all specified subgroups, including patients with granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA), and patients with proteinase-3 (PR3) or MPO ANCA disease. Remission (defined as BVAS of 0) was similar across treatment groups at Week 12; however, patients receiving CCX168 appeared to achieve remission faster than patients in the control group since more patients receiving CCX168 were in remission at Week 4 and stayed in remission through Week 12. The CCX168 groups showed a more rapid improvement in albuminuria compared to control, and eGFR and hematuria improved similarly across treatment groups, indicating that prednisone was not needed if patients were taking CCX168. Urinary monocyte chemoattractant protein-1 (MCP-1) excretion, a marker of renal inflammation, decreased more in patients receiving CCX168 compared to control. Health-related quality of life measurements, based on the

EuroQOL-5D-5L (EQ-5D-5L) and Short Form-36 version 2 (SF-36 v2) instruments, generally showed improvement in the CCX168 groups compared to control. Based on these results, chronic glucocorticoid use was successfully replaced with CCX168 and the efficacy profile was similar or better in patients receiving CCX168 compared to the high dose glucocorticoids SOC control group.

A second Phase 2 study in patients with AAV (CL003_168) was also conducted. In this study, two oral doses of CCX168, 10 mg and 30 mg twice daily, were tested on top of full-dose glucocorticoid plus either cyclophosphamide or rituximab standard of care. Results from this study showed that CCX168 appeared safe when given to standard of care treatment, and that the 30 mg CCX168 dose was appropriate for further study. Refer to the Investigator's Brochure for more details.

An open-label Phase 1 clinical trial in 6 healthy volunteers was conducted to evaluate mass balance and the metabolic disposition of CCX168 (CL004_168). Results showed that >86% of the dose was recovered, with hepatic metabolism and fecal excretion being the major route of elimination. Urinary excretion was a minor route of elimination. CCX168 was well tolerated in this study.

An open-label Phase 2 clinical trial in 7 patients with IgA nephropathy has been conducted (CL005_168). Proteinuria was decreased with CCX168 treatment in 6 of 7 patients. An open-label Phase 2 clinical trial was conducted in 6 patients with atypical hemolytic uremic syndrome (CL006_168). Preliminary results showed that serum collected from patients dosed with CCX168 has a substantial reduction in thrombogenic potential compared to control serum.

An open-label Phase 1 clinical trial in 16 healthy volunteers (CL007_168) has been conducted to evaluate the food effect and potential effect of CCX168 on ECG parameters. Results showed that a high-fat, high-calorie meal increased the T_{max} by ~4 hours, and the plasma AUC by ~2-fold. It is therefore recommended to take CCX168 with meals. Results also showed that CCX168 does not adversely affect the ECG parameters including the QTcF interval.

An open-label Phase 1 clinical trial in 32 healthy volunteers (CL008_168) to evaluate the drug-drug interaction potential of CCX168 has been completed. Results showed that co-administration of CCX168 with a potent cytochrome P450 3A4 (CYP3A4) inhibitor, itraconazole, increases that CCX168 plasma levels ~2-fold (i.e., a moderate effect), and co-administration of CCX168 with a potent CYP3A4 inducer, rifampicin, decreases the CCX168 plasma levels ~90% (i.e., a strong effect). Therefore, it is recommended that CCX168 not be co-administered with potent CYP3A4 inducers since this may decrease the CCX168 plasma exposure substantially.

For more detail regarding the pharmacology and toxicology, and in-depth descriptions of clinical studies conducted with CCX168, please refer to the Investigator's Brochure.

This clinical trial will be conducted in compliance with the protocol, good clinical practice (GCP), and applicable regulatory requirements.

The clinical trial will be conducted in patients with active newly-diagnosed or relapsing AAV, who need cyclophosphamide/azathioprine or rituximab treatment.

1.2. Rationale for the Study

AAV standard therapy includes cyclophosphamide (IV or oral), and glucocorticoids. Severe disease warrants plasma exchange. Results from clinical trials with rituximab (Jones et al, 2010 and Stone et al, 2010) indicated that rituximab could be used instead of cyclophosphamide followed by azathioprine, but that the incidence of adverse events and the mortality remain high with rituximab. Glucocorticoid use contributes significantly to these high morbidity and mortality rates (Robson et al, 2015; Little et al, 2010). Therefore, the medical need for alternate therapies remains high and it is important to find ways to reduce or eliminate chronic high dose glucocorticoid use in the treatment of patients with AAV.

Based on encouraging results from a Phase 2 clinical trial in 67 patients with AAV (CL002_168), as well as preclinical studies in a human C5aR knock-in transgenic mouse model of AAV (Xiao et al, 2014), CCX168 has the potential to be a glucocorticoid-sparing therapy for this disease, with potential safety and tolerability advantages. CCX168 also showed efficacy that was at least as good as the standard of care regimen that included high dose glucocorticoid treatment.

Hence, the clinical hypothesis of the current clinical trial is to test whether CCX168, as a glucocorticoid replacement therapy, in combination with cyclophosphamide followed by azathioprine, or in combination with rituximab is safe and effective in inducing and maintaining remission when compared to prednisone in combination with cyclophosphamide followed by azathioprine, or in combination with rituximab in patients with active AAV.

2. OBJECTIVES

2.1. Primary Objective

The primary objective is to evaluate the efficacy of CCX168 (avacopan) to induce and sustain remission in patients with active anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), when used in combination with cyclophosphamide followed by azathioprine, or in combination with rituximab. Disease remission is defined as achieving a Birmingham Vasculitis Activity Score (BVAS) of 0 and not taking glucocorticoids for treatment of AAV within 4 weeks prior to Week 26. Sustained remission is defined as remission at Week 26 without relapse to Week 52 (BVAS of 0 and not taking glucocorticoids for treatment of AAV for 4 weeks prior to Week 52).

2.2. Secondary Objectives

The secondary objectives of this study include:

1. Evaluation of the glucocorticoid-induced toxicity in the CCX168 plus rituximab or cyclophosphamide/azathioprine group, compared to prednisone plus rituximab or cyclophosphamide/azathioprine, based on the Glucocorticoid Toxicity Index (GTI; Miloslavsky et al, 2016);
2. Evaluation of rapidity of response in the CCX168 plus rituximab or cyclophosphamide/azathioprine group, compared to prednisone plus rituximab or cyclophosphamide/azathioprine, based on remission (BVAS of 0) at Week 4;

3. Evaluation of the safety of CCX168 plus rituximab or cyclophosphamide/azathioprine, compared to prednisone plus rituximab or cyclophosphamide/azathioprine based on the incidence of adverse events and changes in vital signs, physical examinations, clinical laboratory tests, and electrocardiograms (ECGs) in these patients;
4. Assessment of health-related quality-of-life changes based on the Medical Outcomes Survey Short Form-36 version 2 (SF-36 v2) and EuroQOL-5D-5L (EQ-5D-5L) with CCX168 plus rituximab or cyclophosphamide/azathioprine, compared to prednisone plus rituximab or cyclophosphamide/azathioprine;
5. Assessment of changes in parameters of renal disease including estimated glomerular filtration rate (eGFR), albuminuria, and urinary excretion of monocyte chemoattractant protein-1 (MCP-1) in patients with active renal disease at baseline with CCX168 plus rituximab or cyclophosphamide/azathioprine, compared to prednisone plus rituximab or cyclophosphamide/azathioprine;
6. Assessment of changes in cumulative organ damage based on the Vasculitis Damage Index (VDI) with CCX168 plus rituximab or cyclophosphamide/azathioprine, compared to prednisone plus rituximab or cyclophosphamide/azathioprine;
7. Assessment of changes in markers of pharmacodynamics in plasma and urine with CCX168 plus rituximab or cyclophosphamide/azathioprine, compared to prednisone plus rituximab or cyclophosphamide/azathioprine;
8. Evaluation of the pharmacokinetic profile of CCX168 in patients with AAV.

3. STUDY DESIGN

Standard therapy for patients with AAV, including granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), includes cyclophosphamide followed by azathioprine or rituximab, plus a tapering schedule of oral glucocorticoids. Severe disease may warrant the addition of IV glucocorticoids and/or plasma exchange. Glucocorticoid use in these patients is associated with an increased risk of serious adverse events such as infections.

Based on compelling results both from preclinical studies in a mouse model of AAV and Phase 2 clinical trial results, CCX168 has the potential to be an effective therapy for this disease that will also allow for glucocorticoid sparing or elimination. Hence, the clinical hypothesis of the trial is to test whether CCX168 is effective in inducing and then sustaining remission in patients with AAV who are also treated with either cyclophosphamide/azathioprine or rituximab.

This hypothesis will be tested in a randomized, double-blind, double-dummy, active-controlled, Phase 3 clinical trial in approximately 300 patients with newly diagnosed or relapsing AAV.

3.1. Stratification

To obtain balance across treatment groups, eligible patients will be stratified, prior to randomization, based on the following factors:

1. One of the following treatment regimens:
    a. IV rituximab

b. IV cyclophosphamide followed by oral azathioprine

c. Oral cyclophosphamide followed by oral azathioprine

2. Positive test for proteinase-3 (PR3) vs. myeloperoxidase (MPO) ANCA at diagnosis

3. Newly-diagnosed vs. relapsing disease

3.2. Randomization

Patients will be randomized with an interactive response technology (IRT) system and a minimization algorithm, using the stratification factors, in a 1:1 ratio to one of two treatment groups:

Group A: Placebo CCX168 plus cyclophosphamide/azathioprine or rituximab plus a full starting dose of prednisone;

Group B: CCX168 plus cyclophosphamide/azathioprine or rituximab plus placebo prednisone.

3.3. Study Treatments

Treatments for each group are shown in Table 1. The selection of IV cyclophosphamide, oral cyclophosphamide, or IV rituximab is at the discretion of the Investigator.

The treatment period is 52 weeks (364 days), followed by an 8-week (56 days) follow-up period.

Study drug and other medication for vasculitis will be taken as described in Section 5.3.

For study centers where enrollment of adolescents (12 to 17 years old) is approved, CCX168 or placebo dosing will initially be given based on body weight at screening and the dose will be adjusted based on CCX168 plasma levels on Day 1 as shown in Table 2.

Table 1: CCX168/Placebo, Prednisone/Placebo, and Cyclophosphamide/Azathioprine or Rituximab Treatments for the Two Study Groups

Group	CCX168 Active	CCX168-Matching Placebo	Prednisone Active	Prednisone-Matching Placebo	Cyclophosphamide (CYC)/azathioprine or Rituximab (RTX)
A	None	3 Placebo capsules orally twice daily	60 mg starting dose (or 45 mg for patients <55 kg) with standard tapering schedule; Adolescents who weigh ≤37 kg will start at a prednisone dose of 30 mg per day (see Section 12.6).	None	CYC: 15 mg/kg IV up to 1.2 g maximum every 2 to 3 weeks for 13 weeks, followed by azathioprine 1 mg/kg/day starting at Week 15, with titration up to 2 mg/kg/day or CYC 2 mg/kg/day orally for 14 weeks, followed by azathioprine 1 mg/kg/day starting at Week 15, with titration up to 2 mg/kg/day or RTX: 375 mg/m^2 IV weekly x 4 infusions.

Group	CCX168 Active	CCX168-Matching Placebo	Prednisone Active	Prednisone-Matching Placebo	Cyclophosphamide (CYC)/azathioprine or Rituximab (RTX)
B	3 x 10 mg CCX168 capsules orally twice daily	None	None	Placebo capsules	CYC: 15 mg/kg IV up to 1.2 g maximum every 2 to 3 weeks for 13 weeks, followed by azathioprine 1 mg/kg/day starting at Week 15, with titration up to 2 mg/kg/day or CYC 2 mg/kg/day orally for 14 weeks, followed by azathioprine 1 mg/kg/day starting at Week 15, with titration up to 2 mg/kg/day or RTX: 375 mg/m^2 IV weekly x 4 infusions.

Table 2: CCX168/Placebo Starting Dose and Dose Adjustments Based on CCX168 Plasma Exposure in Adolescents

Body weight	Initial CCX168/placebo dose	CCX168 Plasma AUC_{0-6} (ng•hr/mL) on Day 1	CCX168 Dose Adjustment
< 40 kg (88 lb)	10 mg (1 capsule) twice daily	≥351	None
		<351	Increase dose to 20 mg (2 capsules) twice daily
40-55 kg (88-121 lb)	20 mg (2 capsules) twice daily	351 to 699	None
		<351	Increase dose to 30 mg (3 capsules) twice daily
		>699	Decrease dose to 10 mg (1 capsule) twice daily
>55 kg (121 lb)	30 mg (3 capsules) twice daily	≤699	None
		>699	Decrease dose to 20 mg (2 capsules) twice daily

Only in 12 to 17 year old patients, blood samples will be taken pre-dosing and at Hours 0.5, 1, 2, 3, 4, and 6 after the first CCX168 dose on Day 1 and plasma samples will be sent for expeditious measurement of CCX168 and CCX168-M1 in these patients. Dose adjustments will be made based on AUC_{0-6} as shown in Table 2.

These AUC_{0-6} thresholds are based on the mean CCX168 plasma exposure (525 ng•hr/mL) and one standard deviation (174 ng•hr/mL) above or below the mean in adult patients from Phase 2 study CL002_168 in AAV. In order to maintain the blind, some adolescent patients on placebo will also be instructed to modify the number of placebo capsules taken. This will be done by a

designated person who is unblinded to the plasma CCX168 levels, and not by otherwise blinded study team members.

3.4. Study Visits and Procedures

All patients will visit the study center during the screening period, and, if eligible, on Day 1 and Weeks 1, 2, 3, 4, 7, 10, 13, 16, 20, 23**,** 26, 29, 32, 35, 39, 42, 45, 48, 52, and 60. CCX168/placebo will be taken orally in the morning, preferably with food, and in the evening, preferably with food.

The screening period will be kept as short as possible in order not to delay initiation of treatment. The screening period must not exceed 14 days. Screening procedures will include written informed consent, collecting demographic data, medical history, medication history, physical examination and vital signs, serum chemistry tests, hematology tests, serum pregnancy test (in women of childbearing potential: have experienced menarche and who is not permanently sterile or postmenopausal; postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause), urinalysis (including hematuria and albuminuria), 12-lead ECG, a test to exclude tuberculosis (interferon γ release assay [IGRA], tuberculin purified protein derivative [PPD] skin test, or chest radiography [X rays or CT scan]) if not done within 6 weeks prior to screening, viral screening (if not done within 6 weeks prior to screening), serology (anti-nuclear antibodies [ANA], anti-glomerular basement membrane [GBM] antibodies, IgG, IgM, and IgA) and complement (C3 and C4) measurements (if not done within the previous 12 months), eGFR based on serum creatinine (Modification of Diet in Renal Disease [MDRD] equation for adults, and modified Schwartz equation for adolescents), ANCA measurement (anti-PR3 and anti-MPO) if not done previously), BVAS and VDI assessments. The BVAS version 3 will be used in this study (Mukhtyar et al, 2009; Suppiah et al, 2011).

To expedite the screening process, blood and urine tests may be done at the local laboratories for only the Screening visit. Laboratory results from the local laboratories obtained within 72 hours of screening are acceptable in order to avoid unnecessary blood draws. Results from histology of renal biopsies (if performed within 4 weeks prior to Screening) will be recorded on standard histology forms.

Eligible patients must be ANCA-positive (having tested positive for antibodies to PR3 or MPO by ELISA or ALBIA, either at the time of enrollment or in the past), and must have at least one "major" item, or at least 3 minor items, or at least the two renal items of proteinuria and hematuria in the BVAS (see Section 12.3.2 for major, minor, and renal items). Care must be taken to ensure that the renal items are due to vasculitis activity and not other factors such as menses or cyclophosphamide-related cystitis. If a patient has "other" items, not specified in the BVAS, these need to be discussed with the Medical Monitor before enrollment.

Eligible patients will visit the study center on Day 1, after an overnight fast of at least 9 hours, for physical examination and vital signs, serum chemistry tests (including HbA1c and LDL cholesterol), hematology tests, serum pregnancy test (in women of childbearing potential), urinalysis (including hematuria, urinary albumin:creatinine ratio [UACR], and MCP-1:creatinine ratio assessment), eGFR, ANCA measurement (anti-PR3 and anti-MPO), SF-36 v2 and EQ-5D-5L assessment, Glucocorticoid Toxicity Index (GTI) baseline assessment (see Section 12.5 for details), baseline pharmacokinetic (PK) and pharmacodynamic (PD) blood sample collection,

stratification and randomization. Medication will be administered (IV) and dispensed (for oral medications). The patients will take the first dose of CCX168 or placebo, and prednisone or placebo while at the study center. A patient could be kept overnight in the hospital on Day 1, if necessary, based on the patient's clinical condition. This hospital stay may be extended, if the patient's condition requires it, and this hospital stay would not be considered a serious adverse event, unless other SAE criteria are met.

Twice daily dosing of CCX168 or placebo will continue for 364 days. At post-Day 1 study visits, study medication will be administered according to the protocol schedule, and blood and urine samples will be collected for safety and efficacy and PK/PD measurements. BVAS assessments will be made at Screening and Weeks 4, 10, 16, 26, 39, 52, and 60. VDI assessments will be made at Screening and Weeks 26, 52, and 60. SF-36 v2 and EQ-5D-5L will be completed on Day 1 and Weeks 4, 10, 16, 26, 39, 52, and 60. GTI assessments will be performed on Day 1 and at Weeks 13 and 26. If a patient consents, renal biopsy for histology will be performed at Week 52 or at the time of treatment discontinuation. Physical examinations, vital sign assessments, and ECG measurements will be performed throughout the study. Concomitant medication and adverse event assessments will be made at every study visit.

Patients will be discharged from the study when all the Study Week 60 visit procedures have been completed. Each patient's condition will be evaluated by the Investigator at the end of the clinical trial (Week 60) and appropriate standard of care medical treatment will be provided to all patients as needed.

To the extent possible, any adverse events that are deemed study drug-related and are ongoing at discharge will be followed to resolution or until a determination is made that the unresolved event is stable.

4. STUDY POPULATION

4.1. Size of the Population

The aim is to enroll approximately 300 patients in this clinical trial. Patients who drop out of the study prematurely will not be replaced.

4.2. Inclusion Criteria

Patients must meet all of the following inclusion criteria in order to enter the study:

1. Clinical diagnosis of granulomatosis with polyangiitis (GPA;Wegener's) or microscopic polyangiitis (MPA), consistent with Chapel-Hill Consensus Conference definitions (Jennette et al, 2013);
2. Aged at least 18 years, with newly-diagnosed or relapsed AAV where treatment with cyclophosphamide or rituximab is needed; where approved, adolescents (12-17 years old) may be enrolled; female patients of childbearing potential may participate if adequate contraception is used during the study, and for at least 6 months after the last cyclophosphamide dose (if receiving cyclophosphamide) and at least 12 months after the last rituximab dose (if receiving rituximab); male patients with partners of childbearing potential may participate in the study if they had a vasectomy at least 6 months prior to randomization

or if adequate contraception is used during the study, and for at least 6 months after the last cyclophosphamide dose (if receiving cyclophosphamide) and at least 12 months after the last rituximab dose (if receiving rituximab); Adequate contraception is defined as resulting in a failure rate of less than 1% per year (combined estrogen and progestogen [oral, intravaginal, or transdermal], or progestogen-only hormonal contraception [oral, injectable, or implantable], intra-uterine device, intra-uterine hormone releasing system, bilateral tubal occlusion, vasectomized partner, or true [absolute] sexual abstinence, i.e., in line with the preferred and usual lifestyle of the patient); for patients who will be receiving mycophenolate instead of azathioprine, a second form of birth control must be used if the first form of birth control is hormonal contraception, such as progestogen-only hormonal contraception, because mycophenolate reduces blood levels of the hormones in the oral contraceptive pill and could theoretically reduce its effectiveness; sperm donation for at least 6 months after the last cyclophosphamide dose (if receiving cyclophosphamide), and at least 12 months after the last rituximab dose (if receiving rituximab), must not be performed.

3. Positive test for anti-PR3 or anti-MPO (current or historic) antibodies;
4. At least one major item, or at least 3 minor items, or at least the 2 renal items of proteinuria and hematuria in the BVAS (see Section 12.3); care must be taken to ensure that the renal items are due to vasculitis activity, and not other factors such as menses or cyclophosphamide-related cystitis; if a patient has “other” items, not specified in the BVAS, these need to be discussed with the Medical Monitor before enrollment.
5. Estimated glomerular filtration rate ≥15 mL/minute/1.73 m^2 (using the MDRD method for adults, and modified Schwartz equation for adolescents; see Section 7.1.3) at screening;
6. Willing and able to give written Informed Consent and to comply with the requirements of the study protocol; written Informed Consent should be obtained from the legal guardian in accordance with regional laws or regulations for patients 12 to 17 years of age, and
7. Judged by the Investigator to be fit for the study, based on medical history, physical examination (including electrocardiogram [ECG]), and clinical laboratory assessments. Patients with clinical laboratory values that are outside of normal limits (other than those specified in the Exclusion Criteria) and/or with other abnormal clinical findings that are judged by the Investigator not to compromise patient participation in the study, may be entered into the study.

4.3. Exclusion Criteria

1. Pregnant or breast-feeding;
2. Alveolar hemorrhage requiring invasive pulmonary ventilation support anticipated to last beyond the screening period of the study;
3. Any other known multi-system autoimmune disease including eosinophilic granulomatosis with polyangiitis (Churg-Strauss), systemic lupus erythematosus, IgA vasculitis (Henoch-Schönlein), rheumatoid vasculitis, Sjögren's syndrome, anti-glomerular basement membrane disease, or cryoglobulinemic vasculitis;
4. Required dialysis or plasma exchange within 12 weeks prior to screening;

5. Have had a kidney transplant;
6. Received cyclophosphamide within 12 weeks prior to screening; if on azathioprine, mycophenolate, or methotrexate at the time of screening, these drugs must be withdrawn prior to receiving the cyclophosphamide or rituximab dose on Day 1;
7. Received intravenous glucocorticoids, >3000 mg methylprednisolone equivalent, within 4 weeks prior to screening;
8. Have been taking an oral daily dose of a glucocorticoid of more than 10 mg prednisone-equivalent for more than 6 weeks continuously prior to the screening visit;
9. Received rituximab or other B-cell antibody within 52 weeks of screening or 26 weeks provided B cell reconstitution has occurred (i.e., CD19 count > $0.01x10^9$/L); received anti-TNF treatment, abatacept, alemtuzumab, IVIg, belimumab, tocilizumab, or eculizumab within 12 weeks prior to screening; immunosuppressive drugs not listed here must be discussed with the Medical Monitor;
10. Currently taking a strong inducer of the cytochrome P450 3A4 (CYP3A4) enzyme, such as carbamazepine, phenobarbital, phenytoin, rifampin, or St. John's wort;
11. Any of the following within 12 weeks prior to screening: symptomatic congestive heart failure requiring prescription medication, unstable angina (unless successfully treated with stent or bypass surgery), clinically significant cardiac arrhythmia, myocardial infarction or stroke;
12. History or presence of any form of cancer within the 5 years prior to screening, with the exception of excised basal cell or squamous cell carcinoma of the skin, or carcinoma in situ such as cervical or breast carcinoma in situ that has been excised or resected completely and is without evidence of local recurrence or metastasis;
13. Evidence of tuberculosis based on interferon γ release assay (IGRA), tuberculin purified protein derivative (PPD) skin test, or chest radiography (X rays or CT scan) done at screening or within 6 weeks prior to screening;
14. HBV, HCV, or HIV viral screening test showing evidence of active or chronic viral infection done at screening or within 6 weeks prior to screening;
15. Received a live vaccine within 4 weeks prior to screening;
16. WBC count less than 3500/μL, or neutrophil count less than 1500/μL, or lymphocyte count less than 500/μL before start of dosing;
17. Evidence of hepatic disease: AST, ALT, alkaline phosphatase, or bilirubin > 3 times the upper limit of normal before start of dosing;
18. Clinically significant abnormal ECG during screening, e.g., QTcF greater than 450 msec;
19. Known hypersensitivity to CCX168 or inactive ingredients of the CCX168 capsules ([redacted], cyclophosphamide or its metabolites (for patients scheduled to receive cyclophosphamide), or known Type I hypersensitivity or anaphylactic reactions to murine proteins, Chinese Hamster Ovary cell proteins, or to any component of rituximab (for patients scheduled to receive rituximab), or any contraindications or hypersensitivity to the use of azathioprine, cyclophosphamide,

mycophenolate, or prednisone, or excipients, where applicable, as per the local prescribing information; for patients who will receive azathioprine, concomitant use with allopurinol is contraindicated;

20. For patients scheduled to receive cyclophosphamide treatment, urinary outflow obstruction, active infection (especially varicella zoster infection), or platelet count < 50,000/μL before start of dosing;
21. Participated in any clinical study of an investigational product within 30 days prior to screening or within 5 half-lives after taking the last dose;
22. Participated previously in a CCX168 study; and
23. History or presence of any medical condition or disease which, in the opinion of the Investigator, may place the patient at unacceptable risk for study participation.

4.4. Removal of Patients from Therapy of Assessment

Investigators must clearly distinguish between study drug treatment discontinuation and study withdrawal. Patients who discontinue study drug treatment or who initiate medication changes (including those prohibited by the protocol) will not be automatically withdrawn from the study, but all efforts must be made to continue to follow the patients for all regularly scheduled visits.

Investigators must take appropriate measures to make sure that patients are motivated to comply with all requirements of the protocol in order to minimize the amount of missing data. Patients who discontinue study treatment early or initiate medication changes (including those prohibited by the protocol) should continue to be followed for all regularly scheduled visits for safety and efficacy assessments. Investigators and their staff must take measures to actively maintain contact with their patients in the study, such as telephone calls, texts, or emails between visits, and offers for transportation support to visit the study site.

Patients may be withdrawn from the study for only one of the following two reasons:

1. Patient withdrawal of consent to contribute additional outcome information;
2. Loss to follow-up.

Patients may discontinue study drug treatment for any of the following reasons:

1. Patient withdrawal of consent;
2. The Investigator may discontinue study drug treatment if, in his/her clinical judgment, it is in the best interest of the patient;
3. The Sponsor may request discontinuation of study drug treatment for safety reasons.

If a patient develops a Grade 3 or higher adverse event considered possibly related to study medication (CCX168/placebo), the study medication needs to be suspended, and may only be re-started if the event has resolved and the Investigator considers it appropriate to do so.

If a patient develops Grade 3 or greater increased hepatic transaminases (>5 times the upper limit of normal), or if a patient develops Grade 2 or greater increased transaminases (>3 times the upper limit of normal) with elevation of bilirubin to >2 times the upper limit of normal,

dosing with study drug (CCX168/placebo) must be paused in this patient, and evaluation for possible drug-induced liver injury must be undertaken.

Study medication (CCX168 or placebo) must be permanently discontinued if any of the following markers of hepatic injury and/or impaired liver synthetic activity are observed, and cannot be attributed to a reversible etiology unrelated to study medication (e.g. cholelithiasis):

- ALT or AST >8xULN
- ALT or AST >5xULN for more than 2 weeks
- ALT or AST >3xULN and (Total Bilirubin >2xULN or INR >1.5)
- ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

If drug induced hepatic toxicity is ruled out following complete evaluation and if all labs have returned to normal, then resumption of study drug may be considered only after discussion with and the agreement of the Medical Monitor. If study drug is resumed, hepatic transaminases and bilirubin are to be monitored closely.

If a patient develops Grade 3 or greater leukopenia (WBC count < 2 x 10^9/L) or neutropenia (< 1 x 10^9/L), or grade 4 lymphopenia (< 0.2 x 10^9/L), then study drug must be paused in this patient. In addition, if a patient develops Grade 2 leukopenia (WBC count <3 x 10^9/L, but ≥2 x 10^9), the patient must be followed closely for infection and for further significant reduction (reduction by an additional 0.5 x 10^9/L, or to < 2 x 10^9/L) in WBC count; if either occurs, then study drug must be paused in this patient. Study drug may be resumed only if the abnormal value returns to normal and the Investigator deems resumption to be appropriate.

If a patient develops grade 3 or worse CPK increase (>5 times the upper limit of normal), dosing with study drug must be paused in this patient. Study drug may be resumed only if the CPK returns to normal levels.

In the event of early withdrawal from the study, the tests and evaluations listed for the Early Termination visit in Section 6.27 will be performed, whenever possible. Data collected at this visit will be designated as an “Early Termination” visit in the EDC. The Sponsor should be notified of all study drug treatment and study withdrawals in a timely manner.

Extra glucocorticoid treatment, i.e., that was not provided as study medication must be avoided as much as possible during the study. However, patients who experience a *relapse* of their AAV during the study may be treated with IV glucocorticoids (typically 0.5 to 1 g methylprednisolone per day for 3 days) and/or oral glucocorticoids, tapered according to the patient's condition. A *relapse* is defined as worsening of disease, after having previously achieved remission (BVAS = 0), that involves:

- one or more major item in the BVAS, or
- three or more minor items in the BVAS, or
- one or two minor items in the BVAS recorded at two consecutive study visits.

These patients may continue study drug treatment and should continue in the study.

Patients who experience worsening of disease that involves a major item in the BVAS may be treated with IV glucocorticoids (typically 0.5 to 1 g methylprednisolone per day for 3 days) and/or oral glucocorticoids, tapered according to the patient's condition. Worsening not involving a major item in the BVAS may be treated with a short burst (i.e., not more than 2 weeks) of oral glucocorticoids, at a maximum dose of 20 mg prednisone equivalent. Patients experiencing worsening of disease may continue study drug treatment and should continue in the study.

Patients who have one or more major items in the BVAS before study entry, and who do not show an improvement or stabilization of these items within the first 4 weeks of the study, may receive additional IV or oral glucocorticoids, tapered according to the patient's condition.

Patients who relapse may require additional immunosuppressive therapy. If the Investigator considers giving other medications, such as additional rituximab or cyclophosphamide treatment, these should be discussed with the Medical Monitor. These patients may continue study drug treatment and should continue in the study.

Refer to Section 12.6.2 for more detail on use of non-study supplied glucocorticoids prior to the screening period, during the screening period, and during the treatment period.

5. STUDY MEDICATION/TREATMENT

5.1. Product Characteristics

CCX168 will be administered orally as hard gelatin capsules containing 10 mg CCX168. The capsules are manufactured under current good manufacturing practice. All doses of study medication will be administered orally. The CCX168 capsules will be supplied to the study centers in plastic bottles containing 180 capsules. This is sufficient for 30 days of dosing at 30 mg CCX168 twice daily.

CCX168-matching placebo will be administered orally as matching hard gelatin capsules containing no CCX168. The capsules are manufactured under current good manufacturing practice. All doses of study medication will be administered orally. The placebo capsules will be supplied to the study centers in plastic bottles containing 180 capsules. This is sufficient for 30 days of twice daily dosing.

Prednisone will be administered orally as hard gelatin capsules containing either 20 mg or 5 mg prednisone. The capsules are manufactured under current good manufacturing practice. All doses of prednisone will be administered orally. The prednisone capsules will be supplied to the study centers in plastic bottles containing 30 capsules of either 20 mg or 5 mg prednisone. The dose of prednisone will be tapered according to a standard schedule (see Section 12.6).

Prednisone-matching placebo will be administered orally as hard gelatin capsules containing placebo tablets. The capsules are manufactured under current good manufacturing practice. All doses of prednisone-matching placebo will be administered orally. The prednisone-matching placebo capsules will be supplied to the study centers in plastic bottles containing 30 capsules, matching either 20 mg or 5 mg prednisone capsules.

5.2. Randomization and Method of Treatment Assignment

Eligible patients will be enrolled, stratified based on three stratification factors (i.e., IV rituximab, IV cyclophosphamide, or oral cyclophosphamide use, anti-PR3 or anti-MPO AAV, and newly-diagnosed or relapsing disease), and then randomized to one of the two treatment groups in a ratio of 1:1, control:CCX168. Randomization will be performed centrally via an interactive response technology (IRT) system and minimization algorithm, using the stratification factors. In order to protect the blinding, the randomization schedule will not be accessible to study personnel who have contact with study centers or who are involved in data management and analysis.

5.3. Doses and Regimens

Treatments for each group are shown in Table 2.

Adult patients will receive 30 mg CCX168 or matching placebo twice daily. For patients who are 12 to 17 years old, initial CCX168 or placebo doses will be selected based on body weight, and further refined based on CCX168 plasma exposure according to Table 2.

The treatment period is 52 weeks (364 days), followed by an 8-week (56 days) follow-up period.

Study drug and other medication for vasculitis will be taken as follows by study patients:

Group A (control group):

- Three CCX168-matching placebo capsules in the morning, preferably with food, and 3 in the evening, preferably with food, approximately 12 hours after the morning dose, daily for 52 weeks (364 days).
- Prednisone 60 mg orally per day if the patient's body weight is ≥55 kg, or 45 mg per day if the patient's body weight is <55 kg, starting on Day 1 with tapering according to the protocol-specified schedule. Adolescents who weigh ≤37 kg will start at a prednisone dose of 30 mg per day (see Section 12.6).
- If a patient is in the IV cyclophosphamide stratum, cyclophosphamide 15 mg/kg IV up to 1.2 g maximum will be given on Day 1 and also at the Week 2, 4, 7, 10, and 13 study visits. The cyclophosphamide dose will be adjusted based on the patient's age, eGFR, and WBC count according to protocol-specified criteria (see Section 12.7). Starting at Week 15, all patients will receive oral azathioprine at a starting dose of 1 mg/kg/day, with titration up to a target dose of 2 mg/kg/day at 2 weeks (see Section 12.7 . If azathioprine is not tolerated, mycophenolate mofetil at a target dose of 2 g/day may be given. If mycophenolate mofetil is not tolerated or not available, enteric coated mycophenolate sodium may be given at a target dose of 1440 mg/day.
- If a patient is in the oral cyclophosphamide stratum, cyclophosphamide 2 mg/kg/day (maximum 200 mg/day) will be given orally starting on Day 1 and continuing up to the day before Week 15. The cyclophosphamide dose will be adjusted based on the patient's age, eGFR, and WBC count according to protocol-specified criteria (see Section 12.7). Starting at Week 15, all patients will receive oral azathioprine at a starting dose of 1 mg/kg/day, with titration up to a target dose of 2 mg/kg/day at 2 weeks (see Section 12.7). If azathioprine is not tolerated, mycophenolate mofetil at a target dose of 2

g/day may be given. If mycophenolate mofetil is not tolerated or not available, enteric coated mycophenolate sodium may be given at a target dose of 1440 mg/day.

- If in the rituximab stratum, rituximab IV will be given on Day 1, and then Weeks 1, 2, and 3 at a dose of 375 mg/m^2 at each visit for a total of 4 weekly infusions (see Section 12.8).

Group B (CCX168):

- Three 10 mg CCX168 capsules in the morning, preferably with food, and 3 in the evening, preferably with food, approximately 12 hours after the morning dose, daily for 52 weeks (364 days).
- Prednisone-matching placebo capsules equivalent to 60 mg orally per day if the patient's body weight is ≥55 kg, or 45 mg per day if the patient's body weight is <55 kg, starting on Day 1 with tapering according to a protocol-specified schedule. Adolescents who weigh ≤37 kg will start at a prednisone-matching placebo dose of 30 mg per day (see Section 12.6).
- If a patient is in the IV cyclophosphamide stratum, cyclophosphamide 15 mg/kg IV up to 1.2 g maximum will be given on Day 1 and also at the Week 2, 4, 7, 10, and 13 study visits. The cyclophosphamide dose will be adjusted based on the patient's age, eGFR, and WBC count according to protocol-specified criteria (see Section 12.7). Starting at Week 15, all patients will receive oral azathioprine at a starting dose of 1 mg/kg/day, with titration up to a target dose of 2 mg/kg/day at 2 weeks (see Section 12.7). If azathioprine is not tolerated, mycophenolate mofetil at a target dose of 2 g/day may be given. If mycophenolate mofetil is not tolerated or not available, enteric coated mycophenolate sodium may be given at a target dose of 1440 mg/day.
- If a patient is in the oral cyclophosphamide stratum, cyclophosphamide 2 mg/kg/day (maximum 200 mg/day) will be given orally starting on Day 1 and continuing up to the day before Week 15. The cyclophosphamide dose will be adjusted based on the patient's age, eGFR, and WBC count according to protocol-specified criteria (see Section 12.7). Starting at Week 15, all patients will receive oral azathioprine at a starting dose of 1 mg/kg/day, with titration up to a target dose of 2 mg/kg/day at 2 weeks (see Section 12.7). If azathioprine is not tolerated, mycophenolate mofetil at a target dose of 2 g/day may be given. If mycophenolate mofetil is not tolerated or not available, enteric coated mycophenolate sodium may be given at a target dose of 1440 mg/day.
- If in the rituximab stratum, rituximab IV will be given on Day 1, and then Weeks 1, 2, and 3 at a dose of 375 mg/m^2 at each visit for a total of 4 weekly infusions (see Section 12.8).

The dose regimens selected for oral prednisone, IV cyclophosphamide, oral cyclophosphamide, IV rituximab, oral azathioprine, and oral mycophenolate are in line with current standard clinical practice.

The study will be double-blind, double-dummy, i.e., placebo capsules will be identical in appearance to the CCX168 capsules, and prednisone capsules will also have matching placebo capsules.

Patients in Group A will receive one bottle of CCX168-matching placebo capsules on Day 1 and Weeks 4, 7, 10, and 13, and two bottles at the Week 16, 20, 26, 32, 39, and 45 visits. Patients will be asked to take 3 capsules every morning, preferably with food, and 3 capsules every evening, preferably with food, as instructed. Patients will be asked to bring all bottles, whether empty or not, to the study center at each study visit. Capsules will be taken with water. Patients in Group A will also take prednisone capsules as indicated in Section 12.6.

Patients in Group B will receive one bottle of CCX168 capsules on Day 1 and Weeks 4, 7, 10, and 13, and two bottles at the Week 16, 20, 26, 32, 39, and 45 visits. Patients will be asked to take 3 capsules every morning, preferably with food, and 3 capsules every evening, preferably with food, as instructed. Patients will be asked to bring all bottles, whether empty or not, to the study center at each study visit. Capsules will be taken with water. Patients in Group B will also take prednisone-matching placebo capsules as indicated in Section 12.6.

Prednisone will be given as tablets, over-encapsulated with hard gelatin capsules in order to maintain the blind. Two dose strengths of prednisone will be provided, 20 mg and 5 mg. Prednisone-matching placebo will be given as matching hard gelatin capsules with inert contents. Each patient will receive one or more bottles containing prednisone or placebo prednisone on Study Day 1, and Week 1, 2, 3, 4, 7, 10, 13, and 16 visits. Each bottle will contain either 20 mg or 5 mg prednisone capsules, or matching placebo capsules. Patients will be provided with detailed instructions regarding the number of capsules to take each day from each bottle (see Section 12.6 for more detail). The dose of prednisone in Group A will be tapered over the course of the study (see Section 12.6 for the tapering schedule).

Please refer to Section 12.6.2 for non-study supplied glucocorticoid use.

5.4. Rationale for Dose Selection

Single doses of 1 mg up to 100 mg CCX168 were studied in a Phase 1 study (CL001_168) in 48 healthy volunteers, and once daily doses of 1, 3, and 10 mg CCX168 and twice daily doses of 30 mg and 50 mg for up to 7 days were studied in the multiple dose period of the study. Doses from 3 mg up to 100 mg twice daily for 7 days were tested in 16 healthy volunteers in Phase 1 study CL007_168, and 30 mg single doses and 30 mg twice daily doses for 17 days in Phase 1 study CL008_168. All these CCX168 doses were found to be safe in these studies.

A dose of 30 mg CCX168 twice daily given for 12 weeks was studied in clinical trial CL002_168 in patients with AAV. This dose regimen was shown to be effective and safe in study CL002_168. Doses of 10 mg and 30 mg CCX168 twice daily given for 12 weeks were studied in clinical trial CL003_168 in patients with AAV and found to be safe.

A dose of 30 mg CCX168 twice daily has been selected for this Phase 3 study in patients with AAV, which is lower than the maximum dose of 100 mg twice daily tested in study CL007_168. A dose regimen of 30 mg CCX168 twice daily provides trough (C_{min}) plasma CCX168 concentrations that provide at least 95% C5aR blockade on blood neutrophils continuously throughout the day. This level of C5aR coverage is deemed appropriate to achieve optimal pharmacology based on blockade of C5a-induced CD11b upregulation and C5a-induced migration of neutrophils in in vitro assays conducted in whole blood samples obtained from subjects in Phase 1 clinical trial CL001_168.

Based on the favorable safety profile observed in the long-term toxicology studies (26 weeks in rats and 44 weeks in cynomolgus monkeys), and on the safety and tolerability results from the clinical trials conducted to date, the risk for serious or unanticipated untoward events associated with CCX168 occurring in this clinical trial is considered low.

5.5. Drug Supply

5.5.1. Packaging and Labeling

CCX168 capsules containing 10 mg CCX168 and identical appearing placebo capsules will be packaged in high density polyethylene (HDPE) bottles with child-resistant screw caps and provided to the study sites for dispensing. Each bottle will contain 180 capsules.

Prednisone capsules containing either 20 mg or 5 mg prednisone, and identical appearing placebo capsules will be packaged in HDPE bottles with child-resistant screw caps and provided to the study sites. Each bottle will contain 30 capsules.

Cyclophosphamide (oral or IV), azathioprine, mycophenolate (if needed), and rituximab will be prescribed and provided by the study centers.

5.5.2. Storage

CCX168 and CCX168-matching placebo capsules, as well as prednisone and prednisone-matching placebo capsules will be stored according to label instructions. Access should be restricted to pharmacy staff or to the designated responsible member of the Investigator's staff, and to the study monitor. The Investigator agrees that neither s/he nor any of the study staff will supply study medication to any persons other than those enrolled in the study.

5.6. Blinding

This study is double-blind, double-dummy. Blinding of the study will be achieved by the following measures:

1. The study drug bottles and capsule appearance for CCX168 and its matching placebo, as well as prednisone and its matching placebo, will be identical;
2. Limited access to the randomization code; Sponsor personnel, study site personnel, study patients, personnel responsible for study monitoring, and biostatisticians and data managers involved in data analysis of the study will remain blinded to treatment assignment for the duration of the study;
3. While laboratory personnel conducting the PK assays will not be blinded to treatment assignment, unblinded CCX168 plasma concentration results will not be shared with the study site personnel or study staff who have direct contact with study sites during the study;
4. Efficacy data that could potentially be unblinding, i.e., urinary MCP-1:creatinine ratio, UACR, HbA1c, LDL cholesterol, and WBC and neutrophil count data within the normal range will not be made available to study site personnel, study patients, personnel responsible for study monitoring, and biostatisticians and data managers during the study unless for safety monitoring. Investigators will be provided with safety laboratory data reports, flagging abnormally high and low values to make informed decisions regarding patient care.

Treatment assignments for individual patients will remain blinded to the study team, investigators, and patients until after the study database has been cleaned and locked. Designated study staff will be provided with instructions regarding how to unblind an individual patient treatment assignment. An individual patient treatment assignment may be unblinded only in the case of an adverse event that requires knowledge of the study medication received by the patient in order to provide appropriate treatment or management of the adverse event. The study monitor and Sponsor should be notified as soon as possible in the event that unblinding of an individual patient's treatment assignment occurs prior to study completion.

An external data monitoring committee (DMC) will be constituted prior to start of the study (see Section 7.6). The DMC members will review data periodically over the course of the study in an unblinded manner. The DMC will provide recommendations to the Sponsor regarding further conduct of the study. The DMC will operate according to a charter developed prior to study initiation.

5.7. Drug Accountability

The study pharmacist and Investigator must maintain accurate records of dates and quantities of product(s) received, to whom dispensed (patient-by-patient accounting), and accounts of any product accidentally or deliberately destroyed. The Investigator must retain all unused and/or expired study supplies until the study monitor has confirmed the accountability data.

5.8. Treatment Compliance

The CCX168 and CCX168-matching placebo capsules, and prednisone and prednisone-matching placebo capsules, will be self-administered by participating study patients. The morning dose of study drug on Day 1 will be taken in the presence of study site personnel. Patients will be provided with dosing instructions at the start of the study, and will be encouraged by study site personnel to take the study medication according to the instructions for the duration of the study. Patients will be instructed to bring the assigned bottles of study medication to the site staff at each study visit, whether empty or not. The study drug dispensed will be checked, and a capsule count will be done from Week 4 through Week 52 of any remaining CCX168 or placebo capsules and from Week 1 through 20 of prednisone or matching placebo capsules. This information will be recorded and entered into the electronic data capture (EDC) system.

CCX168 plasma concentration measurements over the course of the study may also be used to assess patient compliance. Any events of non-compliance to the protocol will be documented in the study records.

5.9. Concomitant Medications and Restrictions

Use of any drug other than protocol-specified CCX168 or CCX168-matching placebo, oral prednisone or prednisone-matching placebo supplied as part of the study medication, IV or oral cyclophosphamide or rituximab, azathioprine, medication to treat relapses, worsening of disease, or non-responders, or prophylactic medicine as described below is prohibited over the course of the study. This includes use of mycophenolate (except if used instead of azathioprine), methotrexate, anti-TNF treatment, abatacept, alemtuzumab, IVIg, belimumab, tocilizumab, eculizumab, or other experimental or immunosuppressive drugs.

Drugs that are strong inducers of CYP3A4 enzyme, such as carbamazepine, phenobarbital, phenytoin, rifampin, or St. John's wort are prohibited during the study, because these drugs may substantially reduce the plasma concentrations of CCX168 and reduce its effectiveness.

Substances that are strong inhibitors of CYP3A4, such as boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole, and grapefruit juice should be avoided during the study, because these may modestly increase (~2-fold) the plasma concentrations of CCX168. However, these are not absolutely contra-indicated. In case it is inevitable to use these concomitantly with CCX168, patients should be monitored carefully for any untoward side effects.

Patients need to receive appropriate prophylactic therapy during the course of the study. This includes prophylaxis against *Pneumocystis jirovecii* (formerly *carinii*) infections (sulfamethoxazole 400 mg-trimethoprim 80 mg daily or sulfamethoxazole 800 mg-trimethoprim 160 mg every second day; atovaquone 1500 mg/day orally (once daily or divided twice daily, with food), aerosolized pentamidine 300 mg every 4 weeks, or oral dapsone 100 mg/day may be given in case sulfamethoxazole-trimethoprim is contra-indicated), osteoporosis, nausea, and therapy for gastroprotection.

Please refer to Section 12.6.2 for more detailed guidance regarding allowed non-study supplied glucocorticoid use.

All concomitant medications taken during the course of the study must be recorded meticulously on the concomitant medication pages of the CRF.

Patients will be receiving various concomitant therapies in this trial, e.g., rituximab, IV or oral cyclophosphamide, and azathioprine or mycophenolate. There are precautions listed in the prescribing information for each of these drugs. The local prescribing information for each concomitant drug must be consulted prior to its use, so that these precautions can be taken into consideration. Adverse events observed with these drugs are summarized in Section 12.10 for prednisone, Section 12.9 for cyclophosphamide, Section 12.11 for rituximab, Section 12.12 for azathioprine, and Section 12.13 for mycophenolate mofetil.

6. STUDY PROCEDURES

6.1. Screening and Enrollment

Informed Consent must be obtained prior to performance of any study-specific tests or evaluations. It is important to complete the screening procedures in the shortest time possible to allow patients to start treatment. Within a period not to exceed 14 days prior to randomization, patients will undergo the following evaluations to determine their eligibility for study participation:

- Recording of demographic data and medical history in the EDC;
- Recording of all prior medications for AAV for the 12-month period prior to screening in the EDC;

- Recording of all other prior medications for the 6-month period prior to screening in the EDC;
- Recording of all other concomitant medications on the screening day(s) in the EDC;
- In order to expedite the screening process, blood may be collected for testing at the local laboratory for the following:
  - Urinalysis, serum chemistry and hematology tests (results from tests done within 72 hours prior to screening may be used for eligibility assessment);
  - Serum pregnancy test (in women of childbearing potential: have experienced menarche and who is not permanently sterile or postmenopausal; postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause);
  - An estimated glomerular filtration rate will be calculated based on the following Modification of Diet in Renal Disease (MDRD) study equation for adults, and modified Schwartz equation (Schwartz et al, 2009) for adolescents:

    MDRD: eGFR (mL/min/1.73 m^2) = 175 x (serum creatinine in mg/dL)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.212 if African-American/Black).

    Modified Schwartz: eGFR = (0.413 x Height [in cm]) / Serum creatinine (in mg/dL)
  - ANCA measurement (anti-PR3 and anti-MPO antibody levels) if not done previously;
  - Virology assessments as detailed in Section 7.2.2, unless done within 6 weeks prior to screening;
  - Serology and complement assessments as detailed in Section 7.2.2. These tests do not need to be performed if results are available from tests done within the past 12 months prior to the Screening visit. Results from the prior tests must be recorded in the EDC.
- Results from tests that have been performed prior to screening may be used to determine study eligibility if these tests were performed as part of the practice of medicine and were done whether or not study entry was contemplated, such as for diagnosis or treatment of the patient's condition. Results from the prior tests must be recorded in the EDC.
- BVAS assessment (see Section 12.3); to be eligible for enrollment, a patient must have:
  - At least one "major" item (see bold italicized items in Section 12.3.2) in BVAS, or
  - At least three minor items in BVAS, or
  - At least the two renal items of proteinuria and hematuria due to vasculitis (and not other factors such as menses or cyclophosphamide-related cystitis), i.e.:

- Proteinuria >1+ on urinalysis or >0.2 g/g creatinine, and
- Hematuria ("moderate" on urinalysis or ≥10 RBC per high power field, usually accompanied by RBC casts).

If a patient has "other" items, not specified in the BVAS, these need to be discussed with the Medical Monitor before enrollment.

- VDI assessment (see Section 12.4);
- A clean catch, midstream urine sample will be collected and may be sent to the local laboratory, instead of the central laboratory, to expedite screening in order to perform urinalysis for hematuria, RBC casts, and proteinuria;
- A physical examination will be performed; body weight, height, and body mass index will be determined;
- Vital signs (temperature, blood pressure, heart rate) will be measured after at least 3 minutes of rest;
- A 12-lead ECG, after at least 3 minutes of rest, will be recorded and assessed for any clinically significant abnormality;
- At least one of the following tests to exclude tuberculosis: interferon γ release assay (IGRA), tuberculin purified protein derivative (PPD) skin test, or chest radiography (X rays or CT scan); tests performed within 6 weeks prior to screening are allowed to assess eligibility; chest radiography may also be needed for BVAS and VDI assessment;
- If a renal biopsy has been performed within 4 weeks prior to screening, or during screening, the standard Histology Form will be completed and data entered into EDC; a copy of the biopsy results will be kept in the study records.
- Please refer to Section 12.6.2.2 for allowable glucocorticoid use during the screening period.
- After all screening procedures have been completed, and the patient satisfies all eligibility criteria, the study schedule will be discussed with the patient and the schedule will be provided to the patient to ensure compliance with the study visits.
- The patient will be reminded to come to the clinic after an overnight fast of at least 9 hours prior to the Day 1 study visit for the LDL cholesterol measurement.

6.2. Study Day 1

If eligible for the study, the patient will visit the study center on Day 1, after an overnight fast of at least 9 hours for the LDL cholesterol measurement. The following procedures will be performed before taking the first dose of CCX168 or placebo:

- Stratification and randomization in the IVRS;

- A physical examination including body weight; height will also be measured in 12-17 year old patients;
- Vital signs (temperature, blood pressure, heart rate) after at least 3 minutes of rest;
- Blood samples will be collected for shipment to the central laboratory for serum chemistry, hematology, serum pregnancy test (in women of childbearing potential), ANCA (anti-PR3 and anti-MPO ELISA) measurement, HbA1c, LDL cholesterol, PK and PD baseline measurements;
- A blood sample will also be taken for an expedited WBC count at the local laboratory in order to determine the appropriate cyclophosphamide dose for patients who are in the cyclophosphamide strata (see Section 12.7);
- Patients will be asked to complete the SF-36 v2 and EQ-5D-5L;
- Items will be collected to support calculation of the Glucocorticoid Toxicity Index (GTI; see Section 12.5);
- Any pre-treatment adverse events (from time of the screening visit) will be recorded;
- A clean catch, midstream urine sample will be collected, aliquoted, and sent to the central laboratory for urinalysis (including blood, protein, and nitrites; if positive for blood, protein, or nitrites, a microscopic assessment for RBC casts and RBC count will be performed), albumin, MCP-1, and creatinine measurement (for UACR and MCP-1:creatinine), and urinary PD markers related to inflammation and the complement system;
- A saliva sample will be collected for genetic marker assessments in patients who have provided consent.

The patient will be stratified and randomized, and the following procedures will be performed:

- Study medication (1 bottle of CCX168 or CCX168-matching placebo, and 1 bottle of 20 mg prednisone and/or prednisone-matching placebo if ≥55 kg, and 1 bottle of 20 mg prednisone and/or prednisone-matching placebo plus 1 bottle of 5 mg prednisone and/or prednisone-matching placebo if <55 kg) will be provided to the patient with dosing instructions (see Section 12.6);
- The patient will be asked to take the first doses of study medication while at the study center;
- The time of the dosing of CCX168 or CCX168-matching placebo, as well as the time of dosing of prednisone or prednisone-matching placebo, will be recorded;
- If the patient is 12 to 17 years old, blood samples will be taken at Hour 0.5, 1, 2, 3, 4, and 6 after the first dose of CCX168 and plasma samples will be frozen and sent for expeditious measurement of CCX168 and metabolite plasma concentrations;

- Cyclophosphamide IV or oral dose will be given after receipt of the local WBC count (see Section 12.7) to patients in the cyclophosphamide strata; The start and end times of the infusion and the dose time of the oral dose will be recorded;
- Rituximab will be given to patients in the rituximab stratum (see Section 12.8); A dose of 375 mg/m^2 will be given IV; The start and end times of the infusion will be recorded;
- Any changes in concomitant medication use will be recorded;
- If the patient is on non-study supplied glucocorticoids, the dose on Day 1 may not exceed 20 mg prednisone-equivalent, and the patient will be provided with instructions regarding tapering to a dose of zero within a period of 4 weeks from Day 1; if glucocorticoids cannot be tapered to a dose of zero due to adrenal insufficiency the adverse event of adrenal insufficiency and treatment administered must be recorded, along with the evidence supporting the diagnosis;
- Any post-dosing adverse events will be recorded;
- A patient could be kept overnight in the hospital on Day 1, and longer, if necessary. This hospital stay would not be considered a serious adverse event, unless other SAE criteria are met;
- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 1 study visit;
  - Store the study medications in a cool and dry place according to label instructions for the duration of the study;
  - Take the CCX168 or matching placebo, prednisone or matching placebo, as well as oral cyclophosphamide, if applicable, as instructed, and
  - Continue taking all their other concomitant medications as usual.

6.3. Study Week 1 (Day 8)

The Study Week 1 visit must occur within ± 2 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination including body weight; height will also be measured in 12 to17 year-old patients;
- Vital signs (temperature, blood pressure, heart rate) after at least 3 minutes of rest;
- Blood samples will be collected for shipment to the central laboratory for serum chemistry, hematology, PK, and PD measurements;
- The date and time of the last dose of CCX168/placebo prior to collection of the PK sample will be recorded;

- If the patient has not yet taken the morning dose of CCX168/placebo for this day, the patient will be asked to take the dose;
- A clean catch, midstream urine sample will be collected and aliquoted for urinalysis, UACR, urinary MCP-1:creatinine ratio, and PD assessment, and sent to the central laboratory.
- The bottle of study medication will be checked to make sure the patient is taking the study medication as instructed;
- Drug accountability will be performed on the study-supplied prednisone bottles;
- One bottle of 20 mg prednisone or matching placebo and one bottle of 5 mg prednisone or matching placebo will be dispensed with appropriate dosing instructions (see Section 12.6);
- If on oral cyclophosphamide, the patient will be questioned to confirm compliance; any change in cyclophosphamide dose, based on WBC count and eGFR, will be recorded;
- Rituximab will be given to patients in the rituximab stratum (see Section 12.8); A dose of 375 mg/m^2 will be given IV; The start and end times of the infusion will be recorded;
- Any changes in concomitant medication use will be recorded;
- If the patient is on non-study supplied glucocorticoids, the tapering schedule will be discussed with the patient to ensure that tapering to a dose of zero occurs within a period of 4 weeks from Day 1; if glucocorticoids cannot be tapered to a dose of zero due to adrenal insufficiency the adverse event of adrenal insufficiency and treatment administered must be recorded, along with the evidence supporting the diagnosis.
- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 2 study visit;
  - Store the study medications in a cool and dry place according to label instructions for the duration of the study;
  - Take the CCX168 or matching placebo, prednisone or matching placebo, as well as oral cyclophosphamide, if applicable, as instructed, and
  - Continue taking all their other concomitant medications as usual.

6.4. Study Week 2 (Day 15)

The Study Week 2 visit must occur within ± 2 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination including body weight; height will also be measured in 12-17 year old patients;
- Vital signs (temperature, blood pressure, heart rate) after at least 3 minutes of rest;
- A 12-lead ECG, after at least 3 minutes of rest, will be recorded and assessed for any clinically significant abnormality;
- Blood samples will be collected for shipment to the central laboratory for serum chemistry, hematology, PK, and PD measurements;
- The date and time of the last dose of CCX168/placebo prior to collection of the PK sample will be recorded;
- If the patient has not yet taken the morning dose of CCX168/placebo for this day, the patient will be asked to take the dose;
- A blood sample will also be taken for an expedited WBC count at the local laboratory in order to determine the appropriate cyclophosphamide dose (see Section 12.7) for patients who are in the cyclophosphamide strata;
- A clean catch, midstream urine sample will be collected and aliquoted for urinalysis, UACR, urinary MCP-1:creatinine ratio, and PD assessment, and sent to the central laboratory.
- The bottle of study medication will be checked to make sure the patient is taking the study medication as instructed;
- Drug accountability will be performed on the study-supplied prednisone bottles;
- One bottle of 20 mg prednisone or matching placebo and one bottle of 5 mg prednisone or matching placebo will be dispensed with appropriate dosing instructions (see Section 12.6);
- Cyclophosphamide IV dose will be given after receipt of the local WBC count (see Section 12.7) to patients in the IV cyclophosphamide stratum; The start and end times of the infusion will be recorded;
- If on oral cyclophosphamide, the patient will be questioned to confirm compliance; any change in cyclophosphamide dose, based on WBC count and eGFR, will be recorded;
- Rituximab will be given to patients in the rituximab stratum (see Section 12.8); A dose of 375 mg/m^2 will be given; The start and end times of the infusion will be recorded;
- Any changes in concomitant medication use will be recorded;
- If the patient is on non-study supplied glucocorticoids, the tapering schedule will be discussed with the patient to ensure that tapering to a dose of zero occurs within a period of 4 weeks from Day 1; if glucocorticoids cannot be tapered to a dose of zero due to

adrenal insufficiency the adverse event of adrenal insufficiency and treatment administered must be recorded, along with the evidence supporting the diagnosis

- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 3 study visit;
  - Store the study medications in a cool and dry place according to label instructions for the duration of the study;
  - Take the CCX168 or matching placebo, prednisone or matching placebo, as well as oral cyclophosphamide, if applicable, as instructed, and
  - Continue taking all their other concomitant medications as usual.

6.5. Study Week 3 (Day 22)

The Study Week 3 visit must occur within ± 2 days of the scheduled date. During this visit, the following study procedures will be performed:

- Vital signs (temperature, blood pressure, heart rate) after at least 3 minutes of rest;
- Blood samples will be collected for shipment to the central laboratory for serum chemistry, and hematology measurements;
- If the patient has not yet taken the morning dose of CCX168/placebo for this day, the patient will be asked to take the dose;
- A clean catch, midstream urine sample will be collected for urinalysis at the central laboratory;
- The bottle of study medication will be checked to make sure the patient is taking the study medication as instructed;
- Drug accountability will be performed on the study-supplied prednisone bottles;
- The bottle of 20 mg prednisone or matching placebo dispensed at the Week 2 visit will be re-dispensed and one new bottle of 5 mg prednisone or matching placebo will be dispensed with appropriate dosing instructions (see Section 12.6);
- If on oral cyclophosphamide, the patient will be questioned to confirm compliance; any change in cyclophosphamide dose, based on WBC count and eGFR, will be recorded;
- Rituximab will be given to patients in the rituximab stratum (see Section 12.8); A dose of 375 mg/m^2 will be given; The start and end times of the infusion will be recorded;
- Any changes in concomitant medication use will be recorded;
- If the patient is on non-study supplied glucocorticoids, the tapering schedule will be discussed with the patient to ensure that tapering to a dose of zero occurs within a period

of 4 weeks from Day 1; if glucocorticoids cannot be tapered to a dose of zero due to adrenal insufficiency the adverse event of adrenal insufficiency and treatment administered must be recorded, along with the evidence supporting the diagnosis

- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 4 study visit;
  - Store the study medications in a cool and dry place according to label instructions for the duration of the study;
  - Take the CCX168 or matching placebo, prednisone or matching placebo, as well as oral cyclophosphamide, if applicable, as instructed, and
  - Continue taking all their other concomitant medications as usual.

6.6. Study Week 4 (Day 29)

The Study Week 4 visit must occur within ± 2 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination including body weight; height will also be measured in 12to17 years old patients;
- Vital signs (temperature, blood pressure, heart rate) after at least 3 minutes of rest;
- Chest radiograms will be acquired if necessary for BVAS;
- Blood samples will be collected for shipment to the central laboratory for serum chemistry, hematology, serum pregnancy test (in women of childbearing potential), PK, and PD measurements;
- The date and time of the last dose of CCX168/placebo prior to collection of the PK sample will be recorded;
- If the patient has not yet taken the morning dose of CCX168/placebo for this day, the patient will be asked to take the dose;
- A blood sample will also be taken for an expedited WBC count at the local laboratory in order to determine the appropriate cyclophosphamide dose (see Section 12.7) for patients who are in the cyclophosphamide strata;
- A clean catch, midstream urine sample will be collected and aliquoted for urinalysis, UACR, urinary MCP-1:creatinine ratio, and PD assessment, and sent to the central laboratory;
- BVAS assessment (see Section 12.3); For this assessment, the disease activity status within 7 days prior to the Week 4 visit will be scored;
- Patients will be asked to complete the SF-36 v2 and EQ-5D-5L;

- Drug accountability will be performed on the returned CCX168/placebo bottle;
- A new bottle of CCX168/placebo will be dispensed;
- Drug accountability will be performed on the study-supplied prednisone bottles;
- One bottle of 20 mg prednisone or matching placebo will be dispensed and the bottle of 5 mg prednisone or matching placebo provided at the Week 3 visit will be re-dispensed with appropriate dosing instructions (see Section 12.6);
- Cyclophosphamide IV dose will be given after receipt of the local WBC count (see Section 12.7) to patients in the IV cyclophosphamide stratum; The start and end times of the infusion will be recorded;
- If on oral cyclophosphamide, the patient will be questioned to confirm compliance; any change in cyclophosphamide dose, based on WBC count and eGFR, will be recorded;
- Any changes in concomitant medication use will be recorded;
- If the patient was on non-study supplied glucocorticoids, confirm that the patient has stopped this glucocorticoid use; if glucocorticoids cannot be tapered to a dose of zero due to adrenal insufficiency the adverse event of adrenal insufficiency and treatment administered must be recorded, along with the evidence supporting the diagnosis
- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Change the prednisone or matching placebo dose, starting on Day 43;
  - Come to the study center for the Week 7 study visit;
  - Store the study medications in a cool and dry place according to label instructions for the duration of the study;
  - Take the CCX168 or matching placebo, prednisone or matching placebo, as well as oral cyclophosphamide, if applicable, as instructed, and
  - Continue taking all their other concomitant medications as usual.

6.7. Study Week 6 (Day 43)

The study site personnel will contact the patients prior to this time point to remind them of the prednisone/placebo dose change from one 20 mg/placebo capsule and one 5 mg/placebo capsule per day to only one 20 mg/placebo capsule per day, starting on Day 43.

6.8. Study Week 7 (Day 50)

The Study Week 7 visit must occur within ± 3 days of the scheduled date. During this visit, the following study procedures will be performed:

- Vital signs (temperature, blood pressure, heart rate) after at least 3 minutes of rest;

- A 12-lead ECG, after at least 3 minutes of rest, will be recorded and assessed for any clinically significant abnormality;
- Blood samples will be collected for shipment to the central laboratory for serum chemistry, hematology, and PK measurements;
- The date and time of the last dose of CCX168/placebo prior to collection of the PK sample will be recorded;
- If the patient has not yet taken the morning dose of CCX168/placebo for this day, the patient will be asked to take the dose;
- A blood sample will also be taken for an expedited WBC count at the local laboratory in order to determine the appropriate cyclophosphamide dose (see Section 12.7) for patients who are in the cyclophosphamide strata;
- A clean catch, midstream urine sample will be collected for urinalysis at the central laboratory;
- Drug accountability will be performed on the returned CCX168/placebo bottle;
- A new bottle of CCX168/placebo will be dispensed;
- Drug accountability will be performed on the study-supplied prednisone bottles;
- Three bottles of 5 mg prednisone or matching placebo will be dispensed with appropriate dosing instructions (see Section 12.6);
- Cyclophosphamide IV dose will be given after receipt of the local WBC count (see Section 12.7) to patients in the IV cyclophosphamide stratum; The start and end times of the infusion will be recorded;
- If on oral cyclophosphamide, the patient will be questioned to confirm compliance; any change in cyclophosphamide dose, based on WBC count and eGFR, will be recorded;
- Any changes in concomitant medication use will be recorded;
- Record any AAV relapse events in patients who have previously achieved remission (BVAS = 0); relapse is defined as return of at least one major item, or three or more minor items, or one or two minor items recorded at two consecutive visits in the BVAS;
- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Change the prednisone or matching placebo dose, starting on Day 57;
  - Come to the study center for the Week 10 study visit;

- Store the study medications in a cool and dry place according to label instructions for the duration of the study;
- Take the CCX168 or matching placebo, prednisone or matching placebo, as well as oral cyclophosphamide, if applicable, as instructed, and
- Continue taking all their other concomitant medications as usual.

6.9. Study Week 8 (Day 57)

The study site personnel will contact the patients prior to this time point to remind them of the prednisone/placebo dose change from four 5 mg/placebo capsules per day to three 5 mg/placebo capsules per day, starting on Day 57.

6.10. Study Week 10 (Day 71)

The Study Week 10 visit must occur within ± 3 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination including body weight; height will also be measured in 12-17 year old patients;
- Vital signs (temperature, blood pressure, heart rate) after at least 3 minutes of rest;
- Chest radiograms will be acquired if necessary for BVAS;
- Blood samples will be collected for shipment to the central laboratory for serum chemistry, hematology, and serum pregnancy test (in women of childbearing potential);
- If the patient has not yet taken the morning dose of CCX168/placebo for this day, the patient will be asked to take the dose;
- A blood sample will also be taken for an expedited WBC count at the local laboratory in order to determine the appropriate cyclophosphamide dose (see Section 12.7) for patients who are in the cyclophosphamide strata;
- A clean catch, midstream urine sample will be collected for urinalysis at the central laboratory;
- BVAS assessment (see Section 12.3);
- Patients will be asked to complete the SF-36 v2 and EQ-5D-5L;
- Drug accountability will be performed on the returned CCX168/placebo bottle;
- A new bottle of CCX168/placebo will be dispensed;
- Drug accountability will be performed on the study-supplied prednisone bottles;

- Two bottles of 5 mg prednisone or matching placebo will be dispensed with appropriate dosing instructions (see Section 12.6);
- Cyclophosphamide IV dose will be given after receipt of the local WBC count (see Section 12.7) to patients in the IV cyclophosphamide stratum; The start and end times of the infusion will be recorded;
- If on oral cyclophosphamide, the patient will be questioned to confirm compliance; any change in cyclophosphamide dose, based on WBC count and eGFR, will be recorded;
- Any changes in concomitant medication use will be recorded;
- Record any AAV relapse events in patients who have previously achieved remission;
- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 13 study visit;
  - Store the study medications in a cool and dry place according to label instructions for the duration of the study;
  - Take the CCX168 or matching placebo, prednisone or matching placebo, as well as oral cyclophosphamide, if applicable, as instructed, and
  - Continue taking all their other concomitant medications as usual.
  - The patient will be reminded to come to the clinical after an overnight fast of at least 9 hours prior to the visit for the LDL cholesterol measurement.

6.11. Study Week 13 (Day 92)

The patient must be fasting for at least 9 hours prior to this visit for the LDL cholesterol measurement. The Study Week 13 visit must occur within ± 3 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination including body weight and BMI calculation; height will also be measured in 12-17 year old patients;
- Vital signs (temperature, blood pressure, heart rate) after at least 3 minutes of rest;
- A 12-lead ECG, after at least 3 minutes of rest, will be recorded and assessed for any clinically significant abnormality;
- Blood samples will be collected for shipment to the central laboratory for serum chemistry, hematology, ANCA (anti-PR3 and anti-MPO ELISA) measurement, HbA1c, LDL cholesterol, PK, and PD measurements;
- The date and time of the last dose of CCX168/placebo prior to collection of the PK sample will be recorded;

- Items will be collected to support calculation of the GTI (see Section 12.5);
- If the patient has not yet taken the morning dose of CCX168/placebo for this day, the patient will be asked to take the dose;
- A blood sample will also be taken for an expedited WBC count at the local laboratory in order to determine the appropriate cyclophosphamide dose (see Section 12.7) for patients who are in the IV cyclophosphamide stratum;
- A clean catch, midstream urine sample will be collected and aliquoted for urinalysis, UACR, urinary MCP-1:creatinine ratio, and PD assessment, and sent to the central laboratory;
- Drug accountability will be performed on the returned CCX168/placebo bottle;
- A new bottle of CCX168/placebo will be dispensed;
- Drug accountability will be performed on the study-supplied prednisone bottles;
- Two bottles of 5 mg prednisone or matching placebo will be dispensed with appropriate dosing instructions (see Section 12.6);
- Cyclophosphamide IV dose will be given after receipt of the local WBC count (see Section 12.7) to patients in the IV cyclophosphamide stratum; The start and end times of the infusion will be recorded;
- If the patient is in the IV cyclophosphamide stratum, the patient will be instructed to start taking oral azathioprine on the 14th day after the Week 13 visit at a starting dose of 1 mg/kg/day (see Section 12.7.2);
- If the patient is in the oral cyclophosphamide stratum, the patient will be instructed to continue taking oral cyclophosphamide for an additional 13 days after the Week 13 visit. Then, on the 14th day after the Week 13 visit, the patient will be instructed to stop taking oral cyclophosphamide and start taking azathioprine orally at a starting dose of 1 mg/kg/day (see Section 12.7.2);
- Any changes in concomitant medication use will be recorded;
- Record any AAV relapse events in patients who have previously achieved remission;
- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Change the prednisone or matching placebo dose, starting on Day 99;
  - Come to the study center for the Week 16 study visit;
  - Store the study medications in a cool and dry place according to label instructions for the duration of the study;

- Take the CCX168 or matching placebo, as well as prednisone or matching placebo as instructed, and
- Continue taking all their other concomitant medications as usual.

6.12. Study Week 14 (Day 99)

The study site personnel will contact the patients prior to this time point to remind them of the prednisone/placebo dose change from two 5 mg/placebo capsules per day to one 5 mg/placebo capsule per day, starting on Day 99.

6.13. Study Week 15 (Day 106)

For patients who are in the oral or IV cyclophosphamide strata, the study site personnel will contact the patients prior to this time point to remind them to start taking azathioprine at a starting dose of 1 mg/kg/day, or if azathioprine is not suitable, to start taking mycophenolate mofetil at a starting dose of 500 mg twice daily (1 g/day). If mycophenolate mofetil is not tolerated or not available, enteric coated mycophenolate sodium may be given at a starting dose of 720 mg/day.

6.14. Study Week 16 (Day 113)

The Study Week 16 visit must occur within ± 3 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination including body weight; height will also be measured in 12-17 year old patients;
- Vital signs (temperature, blood pressure, heart rate) after at least 3 minutes of rest;
- Chest radiograms will be acquired if necessary for BVAS;
- Blood samples will be collected for shipment to the central laboratory for serum chemistry, hematology, and serum pregnancy test (in women of childbearing potential);
- If the patient has not yet taken the morning dose of CCX168/placebo for this day, the patient will be asked to take the dose;
- A clean catch, midstream urine sample will be collected for urinalysis at the central laboratory;
- BVAS assessment (see Section 12.3);
- Patients will be asked to complete the SF-36 v2 and EQ-5D-5L;
- Drug accountability will be performed on the returned CCX168/placebo bottle;
- Two new bottles of CCX168/placebo will be dispensed;
- Drug accountability will be performed on the study-supplied prednisone bottles;

- Two bottles of 5 mg prednisone or matching placebo will be dispensed with appropriate dosing instructions (see Section 12.6);
- As indicated in Section 6.11, patients in the IV and oral cyclophosphamide strata will start taking oral azathioprine at Week 15 (see Section 12.7 for dosing instructions); The dose of azathioprine will be titrated up to a dose of 2 mg/kg/day;
- Any changes in concomitant medication use will be recorded;
- Record any AAV relapse events in patients who have previously achieved remission;
- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 20 study visit;
  - Store the study medications in a cool and dry place according to label instructions for the duration of the study;
  - Take the CCX168 or matching placebo, as well as prednisone or matching placebo as instructed, and
  - Continue taking all their other concomitant medications as usual.

6.15. Study Week 20 (Day 141)

The Study Week 20 visit must occur within ± 3 days of the scheduled date. During this visit, the following study procedures will be performed:

- Vital signs (temperature, blood pressure, heart rate) after at least 3 minutes of rest;
- Blood samples will be collected for shipment to the central laboratory for serum chemistry and hematology;
- If the patient has not yet taken the morning dose of CCX168/placebo for this day, the patient will be asked to take the dose;
- A clean catch, midstream urine sample will be collected for urinalysis at the central laboratory and a local urine pregnancy test;
- Drug accountability will be performed on the returned CCX168/placebo bottle;
- Two new bottles of CCX168/placebo will be dispensed;
- Drug accountability will be performed on the study-supplied prednisone bottles;
- For the cyclophosphamide strata, compliance with azathioprine dosing will be checked;
- Any changes in concomitant medication use will be recorded;
- Record any AAV relapse events in patients who have previously achieved remission;

- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 23 study visit;
  - Store the study medication in a cool and dry place according to label instructions for the duration of the study;
  - Take the CCX168 or matching placebo, as well as azathioprine, if applicable, as instructed, and
  - Continue taking all their other concomitant medications as usual.
  - The patient will be reminded to come to the clinical after an overnight fast of at least 9 hours prior to the visit for the LDL cholesterol measurement.

6.16. Study Week 23 (Day 162)

The Study Week 23 visit must occur within ± 7 days of the scheduled date. During this visit, the following study procedures will be performed:

- Blood samples will be collected for shipment to the central laboratory for hematology, and for liver function measurements (AST, ALT, Bilirubin and Alkaline Phosphatase)
- Any changes in concomitant medication use will be recorded;
- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 26 study visit;
  - Store the study medications in a cool and dry place according to label instructions for the duration of the study;
  - Take the CCX168 or matching placebo, as well as prednisone or matching placebo as instructed; and
  - Continue taking all their other concomitant medications as usual.

6.17. Study Week 26 (Day 183)

The patient must be fasting for at least 9 hours prior to this visit for the LDL cholesterol measurement. The Study Week 26 visit must occur within ± 3 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination including body weight and BMI calculation; height will also be measured in 12-17 year old patients;
- Vital signs (temperature, blood pressure, heart rate) after at least 3 minutes of rest;
- A 12-lead ECG, after at least 3 minutes of rest, will be recorded and assessed for any clinically significant abnormality;
- Chest radiograms will be acquired if necessary for BVAS;

- Blood samples will be collected for shipment to the central laboratory for serum chemistry, hematology, serum pregnancy test (in women of childbearing potential), ANCA (anti-PR3 and anti-MPO ELISA) measurement, HbA1c, LDL cholesterol, PK, and PD measurements;
- The date and time of the last dose of CCX168/placebo prior to collection of the PK sample will be recorded;
- If the patient has not yet taken the morning dose of CCX168/placebo for this day, the patient will be asked to take the dose;
- A clean catch, midstream urine sample will be collected and aliquoted for urinalysis, UACR, urinary MCP-1:creatinine ratio, and PD assessment, and sent to the central laboratory;
- BVAS assessment (see Section 12.3);
- VDI assessment (see Section 12.4);
- Patients will be asked to complete the SF-36 v2 and EQ-5D-5L;
- Items will be collected to support calculation of the GTI (see Section 12.5);
- Drug accountability will be performed on the returned CCX168/placebo bottles;
- Two new bottles of CCX168/placebo will be dispensed;
- For the cyclophosphamide strata, compliance with azathioprine dosing will be checked;
- Any changes in concomitant medication use will be recorded;
- Record any AAV relapse events in patients who have previously achieved remission;
- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 29 study visit;
  - Store the study medication in a cool and dry place according to label instructions for the duration of the study;
  - Take the CCX168 or matching placebo as well as azathioprine, if applicable, as instructed, and
  - Continue taking all their other concomitant medications as usual

6.18. Study Week 29 (Day 204)

The Study Week 29 visit must occur within ± 7 days of the scheduled date. During this visit, the following study procedures will be performed:

- Blood samples will be collected for shipment to the central laboratory for hematology, and for liver function measurements (AST, ALT, Bilirubin and Alkaline Phosphatase)
- Any changes in concomitant medication use will be recorded;
- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 32 study visit;
  - Store the study medications in a cool and dry place according to label instructions for the duration of the study;
  - Take the CCX168 or matching placebo, as well as prednisone or matching placebo as instructed; and
  - Continue taking all their other concomitant medications as usual.

6.19. Study Week 32 (Day 225)

The Study Week 32 visit must occur within ± 3 days of the scheduled date. During this visit, the following study procedures will be performed:

- Vital signs (temperature, blood pressure, heart rate) after at least 3 minutes of rest;
- Blood samples will be collected for shipment to the central laboratory for serum chemistry and hematology;
- If the patient has not yet taken the morning dose of CCX168/placebo for this day, the patient will be asked to take the dose;
- A clean catch, midstream urine sample will be collected for urinalysis at the central laboratory and a local urine pregnancy test;
- Drug accountability will be performed on the returned CCX168/placebo bottle;
- Two new bottles of CCX168/placebo will be dispensed;
- For the cyclophosphamide strata, compliance with azathioprine dosing will be checked;
- Any changes in concomitant medication use will be recorded;
- Record any AAV relapse events in patients who have previously achieved remission;
- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 35 study visit;
  - Store the study medication in a cool and dry place according to label instructions for the duration of the study;
  - Take the CCX168 or matching placebo as well as azathioprine, if applicable, as instructed, and
  - Continue taking all their other concomitant medications as usual.

6.20. Study Week 35 (Day 246)

The Study Week 35 visit must occur within ± 7 days of the scheduled date. During this visit, the following study procedures will be performed:

- Blood samples will be collected for shipment to the central laboratory for hematology, and for liver function measurements (AST, ALT, Bilirubin and Alkaline Phosphatase)
- Any changes in concomitant medication use will be recorded;
- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 39 study visit;
  - Store the study medications in a cool and dry place according to label instructions for the duration of the study;
  - Take the CCX168 or matching placebo, as well as prednisone or matching placebo as instructed; and
  - Continue taking all their other concomitant medications as usual.

6.21. Study Week 39 (Day 274)

The Study Week 39 visit must occur within ± 3 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination including body weight; height will also be measured in 12-17 year old patients;
- Vital signs (temperature, blood pressure, heart rate) after at least 3 minutes of rest;
- A 12-lead ECG, after at least 3 minutes of rest, will be recorded and assessed for any clinically significant abnormality;
- Chest radiograms will be acquired if necessary for BVAS;
- Blood samples will be collected for shipment to the central laboratory for serum chemistry and hematology, serum pregnancy test (in women of childbearing potential), ANCA (anti-PR3 and anti-MPO ELISA) measurement, PK and PD measurements;
- The date and time of the last dose of CCX168/placebo prior to collection of the PK sample will be recorded;
- If the patient has not yet taken the morning dose of CCX168/placebo for this day, the patient will be asked to take the dose;
- A clean catch, midstream urine sample will be collected and aliquoted for urinalysis, UACR, urinary MCP-1:creatinine ratio, and PD assessment, and sent to the central laboratory;
- BVAS assessment (see Section 12.3);

- Patients will be asked to complete the SF-36 v2 and EQ-5D-5L;
- Drug accountability will be performed on the returned CCX168/placebo bottles;
- Two new bottles of CCX168/placebo will be dispensed;
- For the cyclophosphamide strata, compliance with azathioprine dosing will be checked;
- Any changes in concomitant medication use will be recorded;
- Record any AAV relapse events in patients who have previously achieved remission;
- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 42 study visit;
  - Store the study medication in a cool and dry place according to label instructions for the duration of the study;
  - Take the CCX168 or matching placebo as well as azathioprine, if applicable, as instructed, and
  - Continue taking all their other concomitant medications as usual.

6.22. Study Week 42 (Day 295)

The Study Week 42 visit must occur within ± 7 days of the scheduled date. During this visit, the following study procedures will be performed:

- Blood samples will be collected for shipment to the central laboratory for hematology, and for liver function measurements (AST, ALT, Bilirubin and Alkaline Phosphatase)
- Any changes in concomitant medication use will be recorded;
- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 45 study visit;
  - Store the study medications in a cool and dry place according to label instructions for the duration of the study;
  - Take the CCX168 or matching placebo, as well as prednisone or matching placebo as instructed; and
  - Continue taking all their other concomitant medications as usual.

6.23. Study Week 45 (Day 316)

The Study Week 45 visit must occur within ± 3 days of the scheduled date. During this visit, the following study procedures will be performed:

- Vital signs (temperature, blood pressure, heart rate) after at least 3 minutes of rest;

- Blood samples will be collected for shipment to the central laboratory for serum chemistry and hematology;
- If the patient has not yet taken the morning dose of CCX168/placebo for this day, the patient will be asked to take the dose;
- A clean catch, midstream urine sample will be collected for urinalysis at the central laboratory and a local urine pregnancy test;
- Drug accountability will be performed on the returned CCX168/placebo bottles;
- Two new bottles of CCX168/placebo will be dispensed;
- For the cyclophosphamide strata, compliance with azathioprine dosing will be checked;
- Any changes in concomitant medication use will be recorded;
- Record any AAV relapse events in patients who have previously achieved remission;
- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 48 study visit;
  - Store the study medication in a cool and dry place according to label instructions for the duration of the study;
  - Take the CCX168 or matching placebo as well as azathioprine, if applicable, as instructed, and
  - Continue taking all their other concomitant medications as usual.

6.24. Study Week 48 (Day 337)

The Study Week 48 visit must occur within ± 7 days of the scheduled date. During this visit, the following study procedures will be performed:

- Blood samples will be collected for shipment to the central laboratory for hematology, and for liver function measurements (AST, ALT, Bilirubin and Alkaline Phosphatase)
- Any changes in concomitant medication use will be recorded;
- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 52 study visit;
  - Store the study medications in a cool and dry place according to label instructions for the duration of the study;
  - Take the CCX168 or matching placebo, as well as prednisone or matching placebo as instructed; and
  - Continue taking all their other concomitant medications as usual.

6.25. Study Week 52 (Day 365)

The Study Week 52 visit must occur within ± 3 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination including body weight; height will also be measured in 12-17 year old patients;
- Vital signs (temperature, blood pressure, heart rate) after at least 3 minutes of rest;
- A 12-lead ECG, after at least 3 minutes of rest, will be recorded and assessed for any clinically significant abnormality;
- Chest radiograms will be acquired if necessary for BVAS;
- Blood samples will be collected for shipment to the central laboratory for serum chemistry, hematology, serum pregnancy test (in women of childbearing potential), ANCA (anti-PR3 and anti-MPO ELISA) measurement, PK, and PD measurements;
- The date and time of the last dose of CCX168/placebo prior to collection of the PK sample will be recorded;
- A clean catch, midstream urine sample will be collected and aliquoted for urinalysis, UACR, urinary MCP-1:creatinine ratio, and PD assessment, and sent to the central laboratory;
- If a patient consents, a renal biopsy will be obtained to assess histologic changes; the standard Histology Form will be completed; the biopsy needs to be performed within a 14-day window prior to or after the Week 52 visit;
- BVAS assessment (see Section 12.3);
- VDI assessment (see Section 12.4);
- Patients will be asked to complete the SF-36 v2 and EQ-5D-5L;
- Drug accountability will be performed on the returned CCX168/placebo bottles;
- For the cyclophosphamide strata, compliance with azathioprine dosing will be checked;
- Any changes in concomitant medication use will be recorded;
- Record any AAV relapse events in patients who have previously achieved remission;
- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 60 study visit;
  - Take the azathioprine, if applicable, as instructed, and
  - Continue taking all their other concomitant medications as usual.

6.26. Study Week 60 (Day 421)

The Study Week 60 visit must occur within ± 3 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination including body weight; height will also be measured in 12-17 year old patients;
- Vital signs (temperature, blood pressure, heart rate) after at least 3 minutes of rest;
- A 12-lead ECG, after at least 3 minutes of rest, will be recorded and assessed for any clinically significant abnormality;
- Chest radiograms will be acquired if necessary for BVAS;
- Blood samples will be collected for shipment to the central laboratory for serum chemistry, hematology, serum pregnancy test (in women of childbearing potential), ANCA (anti-PR3 and anti-MPO ELISA) measurement, and PD measurements;
- A clean catch, midstream urine sample will be collected and aliquoted for urinalysis, UACR, urinary MCP-1:creatinine ratio, and PD assessment, and sent to the central laboratory;
- BVAS assessment (see Section 12.3);
- VDI assessment (see Section 12.4);
- Patients will be asked to complete the SF-36 v2 and EQ-5D-5L;
- For the cyclophosphamide strata, compliance with azathioprine dosing will be checked;
- Any changes in concomitant medication use will be recorded;
- Record any AAV relapse events in patients who have previously achieved remission;
- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be discharged from the study. The patient's condition will be evaluated by the Investigator at the end of the clinical trial (Week 60) and appropriate standard of care medical treatment will be provided to all patients as needed.

6.27. Early Termination Visit

If a patient will be withdrawn early from the study, the following termination procedures must be completed whenever possible:

- A physical examination including body weight; height will also be measured in 12-17 year old patients;
- Vital signs (temperature, blood pressure, heart rate) after at least 3 minutes of rest;
- A 12-lead ECG, after at least 3 minutes of rest, will be recorded and assessed for any clinically significant abnormality;
- Chest radiograms will be acquired if necessary for BVAS;

- Blood samples will be collected for shipment to the central laboratory for serum chemistry, hematology, serum pregnancy test (in women of childbearing potential), and ANCA (anti-PR3 and anti-MPO ELISA) measurement;
- A clean catch, midstream urine sample will be collected and aliquoted for urinalysis, UACR, and urinary MCP-1:creatinine ratio and sent to the central laboratory;
- BVAS assessment (see Section 12.3);
- VDI assessment (see Section 12.4) if early termination occurs prior to Study Week 60;
- If the early withdrawal occurs within the first 26 weeks of the study, items will be collected to support calculation of the GTI, including HbA1c and LDL cholesterol tests (see Section 12.5);
- Patients will be asked to complete the SF-36 v2 and EQ-5D-5L if early termination occurs prior to Week 60;
- Drug accountability will be performed on the returned CCX168/placebo and prednisone/placebo bottles;
- Any changes in concomitant medication use will be recorded;
- Record any AAV relapse events or progression/worsening of disease activity in patients who were in remission or had stable disease at the previous visit; and
- Any adverse events will be recorded. If an adverse event remains unresolved at the conclusion of the study, a clinical assessment will be made by the Investigator and the Sponsor's Medical Monitor to determine whether continued follow-up of the adverse event is warranted.

7. STUDY ASSESSMENTS

7.1. Efficacy Assessments

7.1.1. BVAS

The BVAS form will be completed according to the schedule provided in the Time and Events Table. In Section 12.3, instructions for completion, and the BVAS organ systems and items within each system are provided. The "major" BVAS items are listed in bold italics. Data need to be recorded in the EDC system. Calculation of the BVAS score does not need to be performed by the investigators, but will be performed in the EDC system. BVAS data recorded by investigators will be adjudicated, according to an adjudication charter, before data finalization and unblinding. The adjudicated data will be used in the final analysis.

7.1.2. Urinary Measurements

A clean catch midstream urine sample needs to be collected according to instructions provided separately. The screening urine sample may be sent to the local laboratory, instead of the central

laboratory, for proteinuria assessment, as well as a microscopic examination for RBC casts and RBC count to determine patient eligibility.

Starting on Day 1, the urine samples will be sent to the central laboratory for analysis. The following analyses will be performed according to the Time and Events Table:

- Urinalysis including blood, protein, and nitrites; if positive for blood, protein, or nitrites, a microscopic assessment for RBC casts and RBC count will be performed;
- Quantitative albumin and creatinine measurements to calculate the urinary albumin:creatinine ratio (UACR);
- Quantitative MCP-1 measurements to calculate the MCP-1:creatinine ratio;
- Other urinary markers related to inflammation and the complement system may also be performed.

Microscopic review is triggered if a urinary dipstick test is positive for blood, nitrite, or protein. When microscopy is performed, hematuria will be categorized as follows: None, Occasional (Occ), 1 - 2, 3 - 5, 6 - 9, 10 - 15, 16 - 29, 30 - 49, 50 - 75, and >75 RBCs per high power field.

Proteinuria will be assessed by measuring the albumin and creatinine concentrations and calculating the UACR. Results will be expressed as mg albumin/g creatinine.

Urine MCP-1 will be measured by specific ELISA assay. Urine MCP-1 levels will be standardized to urine creatinine and expressed as pg MCP-1/mg creatinine.

Other inflammation and complement markers will be measured using validated assay methodology.

7.1.3. Estimated Glomerular Filtration Rate

Estimated glomerular filtration rate (eGFR) will be calculated from serum creatinine measurements at all applicable study visits using the following MDRD equation for adults, and modified Schwartz equation (Schwartz et al, 2009) for adolescents:

MDRD: eGFR (mL/min/1.73 m^2) = 175 x (serum creatinine in mg/dL)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.212 if African-American/Black)

Modified Schwartz: eGFR = (0.413 x Height [in cm]) / Serum creatinine (in mg/dL)

7.1.4. Health-Related Quality of Life Assessments

The SF-36 v2 and EQ-5D-5L will be completed by study patients at visits specified in the Time and Events Table to measure changes from baseline in health-related quality of life. Proven translations will be used for non-English speaking patients, whenever possible. An administrator will facilitate completion of the questionnaires by the patients, but will not complete the forms for the patients. The administrator will establish a rapport with the patient, emphasize the importance of completing the form, and serve to answer questions and address concerns. The questionnaires should be completed by patients before seeing the Investigator at the visit.

7.1.5. Vasculitis Damage Index (VDI)

The VDI form will be completed at the visits specified in the Time and Events Table. In Section 12.4, instructions for completion, the organ systems with individual damage items, and the scoring of the VDI are provided. Data need to be recorded in the EDC. Investigators do not need to calculate the VDI. This will be done within the EDC system. VDI data will be adjudicated before finalization and unblinding according to an adjudication charter. The adjudicated data will be used in the final analysis.

7.1.6. Disease Relapse

A relapse is defined as worsening of disease, after having previously achieved remission at week 26 (BVAS = 0 and having received no glucocorticoids for treatment of vasculitis for 4 weeks), that involves:

- one or more major item in the BVAS, or
- three or more minor items in the BVAS, or
- one or two minor items in the BVAS recorded at two consecutive study visits.

Major items are indicated in bold italics in Section 12.3.2. Patients who experience a relapse during the study may be treated with glucocorticoids at a dose and regimen according to the patient's condition. Refer to Section 12.6.2.3 for detailed guidance. These patients should continue to be followed in the study if at all possible. In patients experiencing a relapse, the study-supplied prednisone/matching placebo may be temporarily halted during the IV and/or oral course of glucocorticoids, and if the patient's condition stabilizes, the study-supplied prednisone/matching placebo may be restarted according to the original study visit schedule. The CCX168/matching placebo may also continue during the treatment for the relapse, or restarted when interrupted, at the discretion of the PI.

7.1.7. Renal Histology

Kidney biopsies are optional procedures for this study. A standard Histology Form will be provided to investigators to document histologic findings in a standard manner for all patients from whom renal biopsies are taken. This will be completed for available baseline and Week 52 renal biopsies. Data will be entered into the EDC. If a sufficient number of biopsies have been performed, changes from baseline in typical histologic findings, e.g., percentage of glomeruli with crescents or necrosis will be summarized by treatment group. Efficacy outcomes in patients, based on baseline histologic findings, may be assessed, if appropriate.

7.2. Safety Assessments

7.2.1. Physical Examinations, Vital Signs, and ECGs

A complete physical examination (including evaluation of general appearance/mental status, HEENT [head, eyes, ears, nose, throat], and the following body systems: dermatologic, cardiovascular, respiratory, gastrointestinal, musculoskeletal and neurologic) for safety, BVAS, GTI, and VDI assessments will be performed at visits indicated in the Time and Events Table.

Physical examinations must be sufficiently comprehensive to include ALL components of the BVAS, VDI, and GTI (see Section 12.3, Section 12.4, and Section 12.5). Findings must be recorded in the source documents.

Any new or worsening findings upon physical examination need to be recorded as adverse events, and also be captured in the BVAS, VDI, and GTI, as appropriate.

Body weight will be measured as part of the physical examinations. Height needs to be recorded at screening only, except for adolescents (12-17 years old) in whom height will also be included as part of all physical examinations. BMI will be calculated from the body weight and height measurements.

Vital signs will be measured during screening and on each scheduled study day as indicated in the Time and Events Table. Blood pressure, pulse rate, and body temperature will be measured. All vital signs assessments will be performed after the patient has rested for at least three minutes.

Twelve-lead ECGs, after resting for at least 3 minutes, will be acquired according to the schedule in the Time and Events Table. All ECGs will be assessed for any clinically significant abnormalities. All abnormalities will be recorded in the EDC system.

7.2.2. Clinical Safety Laboratory Assessments

The following tests will be performed at the visits identified in the Time and Events Table.

- Hematology: hemoglobin, hematocrit, RBC count, WBC count with differential, platelet count, mean cell hemoglobin, mean cell hemoglobin concentration, mean corpuscular volume;
- Local laboratory WBC counts will be performed prior to administration of cyclophosphamide or azathioprine for potential dose adjustments;
- Serum Chemistry: liver panel (bilirubin, lactate dehydrogenase [LDH], AST, ALT), renal panel (BUN, creatinine), creatine phosphokinase (CPK), albumin, sodium, potassium, magnesium, bicarbonate, chloride, calcium, inorganic phosphorus, glucose, total protein, alkaline phosphatase, total cholesterol, uric acid, serum amylase, and serum lipase; at a subset of visits only AST, ALT, bilirubin and alkaline phosphatase will be assessed. Visits should be scheduled so that laboratory tests are measured at a frequency not to exceed 1 month between assessments.
- Hemoglobin A1c and LDL cholesterol;
- Urinalysis: At the central laboratory, nitrite, blood, and protein, will be tested. If positive, microscopy will be performed;
- Virology (measured only at screening and may be measured at the local laboratory): hepatitis B surface antigen, hepatitis C antibodies, HIV 1 and 2 antibodies; virology tests done within 6 weeks prior to screening are acceptable for eligibility assessment;
- Serology and Complement (measured only at screening and may be measured at the local laboratory): anti-nuclear and anti-GBM antibody levels, C3, C4, IgG, IgM, and IgA.

These tests do not need to be performed if results are available from tests done within the past 12 months prior to the screening visit. Results from these prior tests must be recorded in the EDC system.

- TB screen: Only one of the following is needed: interferon γ release assay (IGRA), tuberculin purified protein derivative (PPD) skin test, or chest radiograms (X rays or CT scan); chest radiography done within 6 weeks prior to screening is allowed for eligibility assessment. Chest radiography at subsequent visits will only be performed if deemed clinically necessary by the Investigator for BVAS, VDI, or GTI assessment, or to assess safety.

7.2.3. Anti-Neutrophil Cytoplasmic Antibody (ANCA) Assessments

Tests for anti-PR3 and anti-MPO will be performed according to the Time and Events Table. If necessary to determine eligibility, anti-PR3 and anti-MPO tests during screening may be performed at the local laboratory if more time-efficient. ELISA or ALBIA (Addressable Laser Bead ImmunoAssay) assays at local laboratories will be allowed for eligibility assessment. Starting on Day 1, ELISA assays will be performed by a central laboratory.

7.2.4. Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event could therefore be any unfavorable and/or unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the use of the drug, whether or not considered related to the drug. This definition includes intercurrent illnesses or injuries, and exacerbation of pre-existing conditions.

An unexpected adverse event is an adverse event that is not identified in nature, severity, or frequency in the current Investigator's Brochure, or that is of greater severity than expected based on the information in the Reference Safety Information listing within the Investigator's Brochure.

All adverse events occurring in patients who have been randomized to treatment will be recorded in the EDC system and will be reported in accordance with regulatory requirements. Adverse events reported prior to commencement of administration of study medication will be considered pre-treatment events.

All adverse events will be monitored until resolution or, if the adverse event is determined to be chronic, until a cause is identified. If an adverse event remains unresolved at the conclusion of the study, a clinical assessment will be made by the Investigator and the Sponsor's Medical Monitor to determine whether continued follow-up of the adverse event is warranted.

7.2.4.1. Adverse Event Severity Assessment

The severity of each adverse event will be determined by the investigator using the following scale:

- Mild (Grade 1): no limitation of usual activities

- Moderate (Grade 2): some limitation of usual activities
- Severe (Grade 3): inability to carry out usual activities
- Life-threatening (Grade 4): an immediate risk of death
- Death (Grade 5)

7.2.4.2. Causality Assessment

The relationship of CCX168/placebo to an adverse event will be determined by the Investigator and Sponsor based on the following definitions:

- Probably Not Related: the adverse event was more likely explained by causes other than CCX168/placebo.
- Possibly Related: there is evidence for a reasonable possibility that CCX168/placebo administration caused the adverse event.

The relationship of glucocorticoid use, cyclophosphamide, rituximab, and azathioprine or mycophenolate use to an adverse event will also be determined by the Investigator and Sponsor based on the following definitions:

- Probably Not Related: the adverse event was more likely explained by causes other than glucocorticoid, cyclophosphamide, rituximab, azathioprine, or mycophenolate use.
- Possibly Related: there is evidence for a reasonable possibility that the glucocorticoid, cyclophosphamide, rituximab, azathioprine, or mycophenolate administration caused the adverse event.

7.2.4.3. Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening (i.e., the patient was, in the opinion of the Investigator, at immediate risk of death from the event as it occurred);
- Requires or prolongs hospitalization;
- Results in persistent or significant disability or incapacity;
- Is a congenital anomaly or birth defect;
- Is an important and significant medical event that, based on appropriate medical judgment, may jeopardize the patient and/or may require medical or surgical intervention to prevent one of the other outcomes defining serious.

Elective surgery already known during screening to occur in the course of the study, and elective hospitalizations for convenience of the patient which are clearly unrelated to any medical

condition, and agreed upon between the Investigator and the patient prior to randomization, will not have to be reported as SAEs. Hospital stays on the evening of Day 1 (or beyond) will also not be considered an SAE, unless other SAE criteria are met.

7.2.4.4. Infections

Any adverse events of infections are of particular importance in this study, since infections are one of the more common adverse events associated with current therapies for AAV. For medically important infections, the organism(s) involved in the infection needs to be determined whenever possible. As a selective C5aR antagonist, CCX168 does not appear to affect formation of the C5b-9 membrane attack complex, a defense mechanism against infection by encapsulated bacteria such as *Neisseria meningitidis*. Nevertheless, any such events need to be clearly documented in the EDC and all local and national vaccination recommendations should be followed.

Glucocorticoids are often associated with fungal and Herpes infections. These need to be meticulously documented in the EDC.

7.2.4.5. SARs and SUSARs

A serious adverse reaction (SAR) is defined as an SAE for which there is at least a reasonable possibility that the study drug (CCX168/placebo) caused the event.

A suspected unexpected serious adverse reaction (SUSAR) is defined as an SAE for which there is at least a reasonable possibility that the study drug (CCX168/placebo) caused the event, and the SAE is 'unexpected', i.e., not described in terms of nature, severity, or frequency in the Reference Safety Information within the current Investigator's Brochure.

'Reasonable possibility' means that there is evidence to suggest a causal relationship between the study drug and the adverse event. Within the reporting requirements, the following examples illustrate the types of evidence that would suggest a causal relationship:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

Patients with AAV are often elderly and have many co-morbidities. Therefore, single occurrences of SAEs that are considered more likely related to the underlying disease or concomitant medications would typically not be considered reasonably related to CCX168.

The therapies used to treat patients with AAV, i.e., cyclophosphamide, rituximab, glucocorticoids, azathioprine, and mycophenolate are often associated with adverse events. A list of reported adverse events observed with cyclophosphamide use is provided in Section 12.9, with glucocorticoid use in Section 12.10, with rituximab use in Section 12.11, with azathioprine use in Section 12.12, and with mycophenolate mofetil use in Section 12.13. In assessing potential causality of adverse events to CCX168/placebo, the known association between cyclophosphamide, glucocorticoids, rituximab, azathioprine, and mycophenolate to these adverse events will be taken into account.

Events related to the underlying disease, such as relapses or worsening of disease, will not be considered as SUSARs, unless there is a reasonable possibility that CCX168 use was associated with these events.

7.2.4.6. Laboratory Abnormalities

Safety laboratory tests are performed frequently over the course of the study. Laboratory reports with abnormal findings will be reviewed by the Investigator and the Medical Monitor. The Investigator may be advised to take appropriate steps, such as increasing the frequency of monitoring, or potentially discontinuing study medication, in case the abnormalities persist.

If a patient develops Grade 3 or greater increased hepatic transaminases (> 5 times the upper limit of normal), or if a patient develops Grade 2 or greater increased transaminases (> 3 times the upper limit of normal) with elevation of bilirubin to > 2 times the upper limit of normal, dosing with study drug (CCX168/placebo) must be paused in this patient, and evaluation for possible drug-induced liver injury must be undertaken.

Study medication (CCX168 or placebo) must be permanently discontinued if any of the following markers of hepatic injury and/or impaired liver synthetic function are observed, and cannot be attributed to a reversible etiology unrelated to study medication (e.g. cholelithiasis):

- ALT or AST >8xULN
- ALT or AST >5xULN for more than 2 weeks
- ALT or AST >3xULN and (Total Bilirubin >2xULN or INR >1.5)
- ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

If drug induced hepatic toxicity is ruled out following complete evaluation and if all laboratory values have returned to normal, then resumption of study drug may be considered only after discussion with and the agreement of the Medical Monitor. If study drug is resumed, hepatic transaminases and bilirubin are to be monitored closely.

If a patient develops Grade 3 or greater leukopenia (WBC count < 2 x 10^9/L) or neutropenia (< 1 x 10^9/L), or grade 4 (< 0.2 x 10^9/L), then study drug must be paused in this patient. In addition, if a patient develops Grade 2 leukopenia (WBC count <3 x 10^9/L, but ≥2 x 10^9), the patient must be followed closely for infection and for further significant reduction (reduction by an additional 0.5 x 10^9/L, or to < 2 x 10^9/L) in WBC; if either occurs, then study drug must be paused in this patient. Study drug may be resumed only if the abnormal value returns to normal and the Investigator deems resumption to be appropriate.

If a patient develops grade 3 or worse CPK increase (>5 times the upper limit of normal), dosing with study drug must be paused in this subject. Study drug may be resumed only if the CPK returns to normal levels.

7.2.4.7. Pregnancies

Any pregnancies that occur in female patients or partners of male study patients must be reported to the Safety team within 24 hours of awareness as indicated in Section 7.2.5. All pregnancies must be followed up until conclusion and the outcome of the pregnancy reported within 24 hours of awareness to the Safety team as indicated in Section 7.2.5.

7.2.5. Serious Adverse Event Reporting

Any SAE occurring from screening through the end of the follow-up period, whether or not considered study related, will be reported immediately (within 24 hours) to the Safety team. Reporting is done by completing the SAE form in the EDC system. If it is not possible to access the EDC system, the Investigator will send an email to the appropriate regional clinical safety mailbox (see information below) or call their regional SAE hotline and fax the completed SAE report form within 24 hours of awareness.

Contact details are as follows:

[redacted]

[redacted]

Any medication or other therapeutic measures used to treat the event, in addition to the outcome of the adverse event, will be recorded in the EDC system.

Follow-Up Reports

The investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.

Within 24 hours of receipt of follow-up information, the investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., patient discharge summary or autopsy reports) to [redacted] via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

The Sponsor or its representatives will report all SUSARs to national health authorities and ethics committees in an expedited manner in accordance with Clinical Trial Directive, Articles 16 and 17, ICH Guideline E2A and ENTR CT3 on the reporting of all SUSARs.

7.3. Pharmacokinetic Assessments

Concentrations of CCX168 (and metabolites) will be determined in plasma according to the schedule in the Time and Events Table. The samples on Day 1 will be collected prior to the first dose of CCX168/placebo on that day. Only for patients 12 to 17 years of age, samples will also be taken at Hours 0.5, 1, 2, 3, 4, and 6 following the first dose of CCX168/placebo on Day 1. The blood samples collected on the other study days do not need to be collected prior to the CCX168/placebo dose on those days. However, the date and time of the last dose of CCX168/placebo prior to the sample collections must be recorded in the EDC system. Population PK analysis will be performed based on the CCX168 and metabolite plasma concentrations.

Total plasma concentrations of CCX168 (and metabolites) will be determined using validated analytical methods. These plasma samples may also be used to measure cytokines, complement fragments, or other markers associated with AAV.

7.4. Pharmacodynamic Assessments

Blood samples will be collected according to the schedule in the Time and Events Table for PD marker measurements in plasma, including, for example, cystatin C, complement fragments, and inflammatory cytokine and chemokine levels. Blood samples collected may be used for lymphocyte subset counts including B cells, T cells, and natural killer cells, and for DNA and other biomarker assessments by RNA analysis. The complete blood cell (CBC) count results from the hematology samples will also be included in the PD assessments. The PK plasma samples may be used for these PD marker measurements.

Urine samples will also be collected according to the schedule in the Time and Events Table for biomarker assessments including, for example, renal injury and inflammation markers (e.g., kidney injury molecule-1 [KIM-1] and neutrophil gelatinase-associated lipocalin [NGAL]), soluble CD163, complement fragments, inflammatory chemokine and cytokine levels.

A saliva sample will be collected on Day 1 from patients who have provided Informed Consent for assessment of genetic markers of AAV as well as the complement pathway. Potential markers include *HLA DPB1*0401*, *SERPINA1*, *PRTN3*, and *HLA-DQ*. C5aR polymorphisms may also be investigated.

7.5. Study Completion and Withdrawal

The Week 60 visit will be the last Study Day for all patients. Procedures for this day will be completed per the Time and Events Table. Each patient's condition will be evaluated by the Investigator at the end of the clinical trial and appropriate standard of care medical treatment will be prescribed for to all patients as needed. For early withdrawals from the study, the procedures for the Early Termination visit will be performed, when possible (see Section 6.27).

The clinical trial will be terminated early if there is a safety concern that cannot be addressed by a modification of the protocol.

7.6. Data Monitoring Committee

In addition to continuous safety monitoring by the Medical Monitor and clinical staff, an external Data Monitoring Committee (DMC) will monitor the safety of patients over the course of the study. The DMC will consist of external physicians and a biostatistician. A DMC charter will be developed before start of the study and the DMC will function according to the charter.

It is anticipated that the DMC will have regular meetings, once every 3 to 6 months, depending on study enrollment rate. Ad hoc meetings may be scheduled if unanticipated safety events occur. After review of data at each meeting, the DMC will make recommendations about further conduct of the study.

8. STATISTICS

Details of the statistical analysis will be provided in a separate statistical analysis plan (SAP), which will be written, finalized, and approved prior to unblinding of the study. Additional details will be provided in the SAP; in all cases the SAP will take precedence over the analyses described in the protocol. (as described below).

The SAP will supersede the statistical analysis methods described in this clinical protocol. Any deviation from the protocol will be documented and described in the final report. If changes to principal features stated in the protocol are required, these will be documented in a protocol amendment. The final SAP will take into account any amendment to the protocol. Data analysis and writing of a clinical study report (CSR) for all study data will be performed by the designated CRO in accordance with its standard operating procedures (SOPs). Analysis of PK and PD data, and writing of PK and PD reports will be performed by designated PK and PD teams in accordance with their SOPs.

8.1. Patient Populations

8.1.1. Intent-to-Treat Population

For the purposes of data analysis, the ITT Population will include all patients who have provided written informed consent and are randomized in the study and who received at least one dose of blinded study drug.

8.1.2. Per Protocol Population

The Per Protocol (PP) population will consist of all randomized patients who receive at least one dose of study drug and do not have protocol deviations that could significantly affect the interpretation of the results for the primary endpoints. Patients' inclusion/exclusion from the PP population will be determined and documented prior to the database lock and unblinding.

8.1.3. Safety Population

The safety population will include all patients who are randomized and have received at least one dose of study drug.

8.2. Efficacy Endpoints

8.2.1. Primary Endpoints

The primary efficacy endpoints are:

1. The proportion of patients achieving disease remission at Week 26, defined as a BVAS of 0 and not taking glucocorticoids for treatment of AAV within 4 weeks prior to Week 26.
2. The proportion of patients achieving sustained disease remission, defined as remission at Week 26 without relapse to Week 52 (BVAS of 0 and not taking glucocorticoids for treatment of AAV within 4 weeks prior to Week 52).

8.2.2. Secondary Endpoints

Secondary efficacy endpoints include:

1. Glucocorticoid-induced toxicity as measured by change from baseline over the first 26 weeks in the glucocorticoid toxicity index;
2. Early remission, defined as BVAS of 0 at Week 4;
3. Change from baseline over 52 weeks in health-related quality-of-life as measured by the domains and component scores of the SF-36 v2 and EQ-5D-5L VAS and index;
4. Proportion of patients and time to experiencing a relapse after previously achieving remission at Week 26 in the study; relapse is defined as occurrence of at least one major item in the BVAS, or three or more minor items in the BVAS, or one or two minor items in the BVAS recorded at two consecutive visits, after having achieved remission at Week 26 (BVAS = 0 and no glucocorticoids for treatment of AAV within 4 weeks) in the study;
5. In patients with renal disease at baseline (based in the BVAS renal component), the change in eGFR from baseline over 52 weeks;
6. In patients with renal disease at baseline (based in the BVAS renal component), the percent change in UACR from baseline over 52 weeks;
7. In patients with renal disease at baseline (based in the BVAS renal component), the percent change in urinary MCP-1:creatinine ratio from baseline over 52 weeks;
8. Change in the VDI from baseline over 52 weeks.

8.3. Safety Endpoints

Safety endpoints, other than glucocorticoid-induced toxicity listed under the efficacy endpoints, include:

1. Patient incidence of treatment-emergent serious adverse events, adverse events, and withdrawals due to adverse events;
2. Change from baseline and shifts from baseline in all safety laboratory parameters;
3. Change from baseline in vital signs, and
4. Incidence of clinically significant ECG changes from baseline.

8.4. Pharmacokinetic Endpoints

CCX168 (and metabolite) plasma concentration results will be used to calculate trough plasma concentrations (C_{min}) over the course of the clinical trial. If sufficient data are available, population PK analyses may also be performed to determine PK parameters for CCX168 and significant metabolites.

The C_{max}, T_{max}, and AUC_{0-6} will be determined for patients 12 to 17 years old based on CCX168 and metabolite plasma concentration data on Day 1.

8.5. Pharmacodynamic Endpoints

The following PD endpoints may be assessed:

1. Change and percent change from baseline in plasma biomarkers such as cystatin C, complement fragments, inflammatory chemokine and cytokine levels. The cystatin C levels may be used in calculating eGFR changes from baseline using the following equation:

   $eGFR_{cys}$ (mL/min/1.73 m^2) = 127.7 x (cystatin C in mg/L)$^{-1.17}$ x (Age)$^{-0.13}$ x (0.91 if female) x (1.06 if African-American/Black)

2. Change and percent change from baseline in urine biomarkers such as renal injury and inflammation markers (e.g., KIM-1 and NGAL), soluble CD163, complement fragments, inflammatory chemokine and cytokine levels;
3. Change from baseline in CBC count (especially WBCs, neutrophils, and lymphocytes) and lymphocyte subset counts including B cells, T cells, and natural killer cells;
4. Change from baseline in blood cell gene expressions such as neutrophil functional status markers.

The effect of polymorphism in genetic markers such as *HLA DPB1*0401*, *SERPINA1*, *PRTN3*, and *HLA-DQ*, as well as C5aR polymorphism may also be investigated.

8.6. Statistical Analysis Methodology

A statistical analysis plan with specific details of all the planned analyses and sensitivity analyses will be generated and approved before unblinding the data for analysis.

All statistical testing will be two-sided, with the type I error rate at α=0.05.

The efficacy analyses for the efficacy endpoints will be performed in the ITT and PP populations, with the ITT analysis being the primary analysis.

The analysis of the efficacy endpoints will be conducted when all patients have completed at least the Week 52 study visit. Individual patient group assignment will remain blinded to investigators and patients until after the analysis of the data in order to maintain study integrity.

Baseline is defined as the last value prior to start of dosing with study medication (typically the Day 1 pre-dose value). For BVAS and VDI, baseline will be from the Screening visit.

8.6.1. Patient Disposition

The number of patients who were screened, who screen failed (by reason), who were randomized, who completed Week 26, Week 52, and Week 60 of the study, who withdrew early from the study, along with the reasons for withdrawal, will be presented by treatment group.

8.6.2. Demographics and Baseline Characteristics

All patient baseline characteristics and demographic data, i.e., age, gender, race, ethnicity, weight, height, body mass index, anti-PR3 and anti-MPO status, GPA vs. MPA, newly-diagnosed vs. relapsing disease, IV cyclophosphamide vs. oral cyclophosphamide vs. IV rituximab use, vasculitis disease duration (from time of diagnosis), BVAS, VDI, GTI, SF-36 v2, EQ-5D-5L, eGFR, hematuria status, UACR, urinary MCP-1:creatinine ratio, will be listed and summarized by treatment group.

Glomerular histopathology (if biopsy was taken), physical examination abnormalities, and medical history will be listed and, where applicable, summarized by treatment group.

8.6.3. Prior and Concomitant Medications

All prior (within 12 months of screening for AAV medications, and within 6 months of screening for all other medications) and concomitant medications (including vasculitis medication) will be listed and summarized by Anatomic Therapeutic Chemistry (ATC) classification. All patients who received prior IV or oral glucocorticoids, concomitant IV or oral non-study supplied glucocorticoids, as well as other non-study supplied treatments for AAV during the study will be listed and summarized by treatment group.

8.6.4. Study Drug Exposure and Compliance

Patient drug exposure will be calculated based on the study drug dispensing and return records, as well as CCX168 plasma concentrations over the course of the study. The CCX168/placebo and prednisone/placebo compliance will be calculated comparing the study drug dispensed and the study drug returned. The study drug exposure (duration, total dose, and average daily dose) and compliance will be summarized and/or listed.

8.6.5. Efficacy Analyses

Summary statistics will be calculated for each of the efficacy endpoints. For categorical endpoints, numbers and percentages will be calculated. For continuous variables, numbers, means, medians, ranges, standard deviations, and standard error of means will be calculated. Geometric means will be calculated for UACR and urinary MCP-1:creatinine, and other data that are not normally distributed.

Results will be presented by treatment group. Results will be presented by stratum for each of the three stratification factors, IV rituximab vs. IV cyclophosphamide vs. oral cyclophosphamide use, anti-PR3 vs. anti-MPO positive ANCA, and newly-diagnosed vs. relapsing patients, as well as GPA vs. MPA. Results will be presented for patients with renal AAV and those without renal AAV at baseline, as well as those who received IV glucocorticoids upfront compared to those who did not. Data will also be presented by geographic distribution, sex, age group (including a

separate analysis in 12-17 year old patients), race, and ethnicity for at least the primary endpoints.

The overall efficacy hypothesis in this study is that CCX168 treatment will be effective in treatment of patients with AAV based on inducing and then sustaining remission without requiring chronic oral prednisone treatment.

The primary efficacy endpoints are:

1. The proportion of patients in disease remission at Week 26, defined as BVAS score of 0 and not taking glucocorticoids for treatment of AAV within 4 weeks prior to Week 26, and
2. The proportion of patients achieving sustained remission, defined as remission at Week 26 without relapse to Week 52 (BVAS of 0 and not taking glucocorticoids for treatment of AAV within 4 weeks prior to Week 52).

The proportion of patients achieving disease remission at Week 26 will be calculated as the number of patients with a BVAS of 0 during the 4-week period preceding the Week 26 visit, and having not received any glucocorticoid treatment during the 4-week period preceding and including the Week 26 visit, divided by the total number of patients randomized to the particular treatment group and who received at least 1 dose of blinded study drug.

The proportion of patients achieving sustained disease remission at Week 52 will be calculated as the number of patients who achieved remission at Week 26 (with a BVAS of 0 during the 4-week period preceding the Week 26 visit, and having not received any glucocorticoid treatment during the 4-week period preceding and including the Week 26 visit) AND who have also achieved remission at Week 52 (with a BVAS of 0 during the 4-week period preceding the Week 52 visit, and having not received any glucocorticoid treatment for AAV during the 4-week period preceding and including the Week 52 visit), divided by the total number of patients randomized to the particular treatment group and who received at least 1 dose of blinded study drug.

The following hypotheses will be tested for the first primary efficacy endpoint:

- The non-inferiority null hypothesis ($H1_0$) is that the CCX168 group is inferior to the control group when comparing the remission rate based on BVAS at Week 26.
- The non-inferiority alternative hypothesis ($H1_1$) is that the CCX168 group is not inferior to the control group when comparing the remission rate at Week 26.
- The superiority null hypothesis ($H2_0$) is that the CCX168 group is not different from the control group when comparing the remission rate at Week 26.
- The superiority alternative hypothesis ($H2_1$) is that the CCX168 group is superior to the control group when comparing the remission rate at Week 26.

The following hypotheses will be tested for the second primary efficacy endpoint:

- The non-inferiority null hypothesis ($H3_0$) is that the CCX168 group is inferior to the control group when comparing the sustained remission rate based on remission at Week 26 without relapse to Week 52.

- The non-inferiority alternative hypothesis ($H3_1$) is that the CCX168 group is not inferior to the control group when comparing the sustained remission rate based on remission at Week 26 without relapse to Week 52.
- The superiority null hypothesis ($H4_0$) is that the CCX168 group is not different from the control group when comparing the sustained remission rate based on remission at Week 26 without relapse to Week 52.
- The superiority alternative hypothesis ($H4_1$) is that the CCX168 group is superior to the control group when comparing the sustained remission rate at Week 26 without relapse to Week 52.

The two primary endpoints will be tested sequentially using a gatekeeping procedure to preserve the Type I error rate at 0.05. The sequence of testing will be as follows:

1. Test for non-inferiority ($H1_0$) of the CCX168 group compared to the control group regarding remission at Week 26; if the p-value for non-inferiority is < 0.05, proceed to step 2;
2. Test for non-inferiority ($H3_0$) of the CCX168 group compared to the control group regarding sustained remission at Week 52; if the p-value for non-inferiority is < 0.05, proceed to step 3;
3. Test for superiority ($H4_0$) of the CCX168 group compared to the control group regarding sustained remission at Week 52; if the p-value for superiority is < 0.05, proceed to step 4;
4. Test for superiority ($H2_0$) of the CCX168 group compared to the control group regarding remission at Week 26.

For the non-inferiority test of the first primary efficacy endpoint, if the lower bound of the 95% confidence interval is greater than -0.20 (i.e., $P < 0.05$ for the non-inferiority test) and the control group disease remission rate is at least 40% at Week 26, the CCX168 group will be considered not inferior to the control group. For the superiority test, if the lower bound of the 95% confidence interval is greater than 0.0 (i.e., $P < 0.05$ for the superiority test), the CCX168 group will be considered superior to the control group in achieving the disease remission at Week 26.

The disease remission rate at Week 26 in the control group is based on a meta-analysis of 20 published studies in patients treated with rituximab plus glucocorticoids or cyclophosphamide plus glucocorticoids. The lower bound of the 95% confidence interval for the remission rate was approximately 60%. The non-inferiority margin of -0.20 was selected to demonstrate that the CCX168 group retains at least 50% of the control group benefit.

For the second primary endpoint, the proportion of patients in disease remission at Week 26 without relapse to Week 52, and the two-sided 95% confidence interval for the difference in proportion (CCX168 minus control) will be estimated for the comparison between the CCX168 group and the control group. For the non-inferiority test of the second primary endpoint, if the lower bound of the 95% confidence interval is greater than -0.20 (i.e., $P < 0.05$ for the non-inferiority test), the CCX168 group will be considered not inferior to the control group. For the superiority test, if the lower bound of the 95% confidence interval is greater than 0.0 (i.e., $P < 0.05$ for the superiority test), the CCX168 group will be considered superior to the control group in achieving the disease remission at Week 26 without relapse to Week 52.

Patients who relapse after Week 26 and before Week 52 will be considered treatment failures for the sustained remission analysis at Week 52. A relapse is defined as worsening of disease that

involves at least one major item, or three or more minor items, or one or two minor items recorded at two consecutive visits in the BVAS, after having previously achieved remission at Week 26 (BVAS = 0 and not receiving glucocorticoids for treatment of AAV within 4 weeks)

The confidence intervals for the difference in proportions will be calculated using the Newcombe hybrid-score method for the common difference from the stratified contingency tables.

The secondary endpoints will be tested in parallel and nominal p-values will be provided.

The proportion of patients with early remission (Week 4) and the proportion of patients with relapse events will be analyzed using the same method as for the primary endpoints.

If there are a sufficient number of relapse events, time from achieving remission at Week 26 to relapse will be analyzed by Kaplan Meier methodology and log rank testing of the differences between treatment groups.

Continuous variables will be analyzed using a mixed effects model for repeated measures (MMRM) with treatment group, visit, treatment-by-visit interaction, and randomization strata (IV rituximab, IV or oral cyclophosphamide, anti-PR3 or anti-MPO ANCA, and newly-diagnosed AAV or relapsed AAV) as factors, and baseline as covariate. Patients will be considered as repeated measure units over visits. Point estimates and corresponding 95% confidence intervals will be estimated for the difference across 52 weeks using simple contrast from the model. Continuous variables include change and/or percent change from baseline in GTI, eGFR, UACR, urinary MCP-1:creatinine ratio, SF-36 v2 (component scores and domains) and EQ-5D-5L VAS and index, VDI, and pharmacodynamic markers. Data that are not normally distributed, e.g., UACR will be log-transformed before analysis. In the MMRM model, missing data will not be imputed. This analysis is unbiased under the missing at random (MAR) assumption. A Toeplitz covariance matrix will be used to model the within-patient variance-covariance deviation. A sensitivity analysis will be carried out using analysis of covariance (ANCOVA) with missing data imputed by last observation carried forward (LOCF).

The Week 60 follow-up data will be summarized with no formal statistical testing.

8.6.6. Handling of Missing Data

Missing remission data at Week 26 and Week 52 will be imputed as remission not achieved for the primary endpoints. Time to relapse will be censored at the time when the first data point is missing. Missing data in the continuous variables will not be imputed for the MMRM analysis. As a sensitivity analysis, missing data in the continuous variables will be imputed with LOCF and analyzed using analysis of covariance (ANCOVA). Other sensitivity analysis may be added in the statistical analysis plan (SAP) to further explore the robustness of the treatment effect.

8.6.7. Covariates and Subgroups

The analysis of the efficacy endpoints may be adjusted by the following variables in the form of covariate analysis, stratified analysis, and/or subgroup analysis:

- Randomization stratification variables
  - IV rituximab, IV cyclophosphamide, or oral cyclophosphamide
  - Anti-PR3 or anti-MPO ANCA

  - Newly diagnosed AAV or relapsed AAV
- Sex
- BMI
- Age at diagnosis of AAV
- Age at study entry; a subgroup analysis will be performed in 12-17 year old patients, if feasible.
- Duration of AAV
- Patient's age, race, and ethnicity (if plausible)
- GPA vs. MPA
- Renal disease or not
- Baseline BVAS
- Baseline VDI
- Baseline GTI
- Baseline eGFR
- Baseline hematuria
- Baseline UACR
- Baseline urinary MCP-1:creatinine ratio
- Geographic distribution (North America vs. Europe and Rest of World)

8.6.8. Safety Analyses

Analysis of change from baseline in the glucocorticoid toxicity index is discussed in Section 8.6.5. In addition to the GTI, the proportion of patients who had any of the items in the "Specific List" will be summarized by specific item, treatment group, and study visit.

All clinical safety and tolerability data will be listed by treatment group and by patient, and will be summarized by treatment group.

All reported adverse events will be coded using MedDRA and listed by System Organ Class, preferred term, and verbatim term.

Treatment-emergent adverse events will be listed and summarized by System Organ Class, by relatedness and by maximum severity, and by treatment group.

Serious adverse events and adverse events leading to withdrawal will be summarized by treatment group. This will include serious infections.

Individual vital signs and change from baseline in vital signs will be listed by treatment group, patient, and study visit, and summarized by treatment group.

Laboratory data (actual values and change from baseline) will be listed by treatment group, patient, and study visit. Abnormal laboratory values will be flagged. Laboratory data will also be summarized by treatment group and study visit. Shift tables will be generated for shifts in laboratory parameters by study visit.

Abnormal ECG findings will be listed by treatment group and study visit, and clinical significance of abnormalities indicated.

8.6.9. Pharmacokinetic and Pharmacodynamic Marker Analysis

Individual plasma concentrations of CCX168 and significant metabolites will be listed, plotted, and summarized descriptively and graphically. PK parameters such as C_{max}, T_{max}, and $AUC_{0\text{-}6hr}$ will be calculated in adolescents for CCX168 based on plasma concentrations for samples collected on Day 1. Plasma levels of significant metabolites may also be determined and PK parameters calculated. Population PK modeling may be performed to calculate PK parameters.

Plasma and urinary PD markers will be summarized and may be analyzed using methods analogous to the efficacy parameters.

The relationship between PK parameters and renal function based on eGFR will also be evaluated. The data may also be used to evaluate the PK/PD relationship of CCX168 treatment. To this end, the change and/or percent change from baseline in eGFR, VDI, UACR, urinary MCP-1:creatinine ratio, or other biomarkers may be used as PD markers.

8.7. Sample Size Justification

The proportion of patients in the control group achieving clinical remission at Week 26 is estimated to be ~60%, a blended proportion of 64% and 53% observed in the rituximab and cyclophosphamide/azathioprine groups, respectively, in the largest prior registration study in AAV (Stone et al, 2010).

A non-inferiority margin of -20 percentage points has been derived for the difference between CCX168 and control groups, and a one-sided alpha level of 0.025. This non-inferiority margin is based on a thorough review and meta-analysis of all previous clinical trials conducted in patients with AAV, as well as precedent (Stone et al, 2010).

A sample size of 150 patients per group (300 in total) is estimated to provide more than 90% power for the non-inferiority test. This sample size provides 90% power to detect approximately 18% superiority in the proportion of patients achieving clinical remission at Week 26 if the control group remission rate is 60%.

The proportion of patients in the control group with sustained remission at Week 52 is estimated to be ~45%, a blended proportion observed in a prior study comparing rituximab and cyclophosphamide/azathioprine in AAV (Specks et al, 2013).

A sample size of 150 patients per group (300 in total) is estimated to provide 85% power to detect approximately 18% superiority if the control group sustained remission rate at Week 52 is 45%.

8.8. Interim Analysis

Safety data from the study will be summarized for review by the DMC at various points over the course of the study (see Section 7.6). The DMC charter will include details of these reviews.

No Type I error adjustment will be made based on the DMC review of the data, since these reviews will focus on safety assessment.

8.9. Protocol Deviations

Significant protocol deviations will be listed and summarized by category. The effect of significant protocol deviations on the safety and efficacy outcomes will be assessed by conducting sensitivity analyses excluding patients and/or study visits with significant protocol deviations. This will be determined and documented before unblinding the study.

The Sponsor will assess any protocol deviation and decide whether any of these should be reported to Competent Authorities as a serious breach of GCP and the protocol. Protocol waivers are not acceptable.

9. STUDY COMPLETION AND TERMINATION

9.1. Study Completion

A patient has completed the study when s/he has completed the study procedures per protocol.

9.2. Study Termination

The end of study is defined as the last study visit of the last clinical trial patient.

10. REGULATORY AND ADMINISTRATIVE REQUIREMENTS

10.1. Investigator Responsibilities

Prior to trial initiation, the Investigator will provide the Sponsor with a fully executed and signed FDA Form 1572, a Financial Disclosure Form, and a curriculum vitae. Financial Disclosure Forms also will be completed for all Sub-Investigators listed on the Form 1572 who will be involved directly in the treatment or evaluation of research patients in this trial.

The study will be conducted in accordance with the Declaration of Helsinki (amended by the 59th World Medical Association General Assembly, October 2008) and Good Clinical Practice (GCP) according to International Conference on Harmonisation (ICH) guidelines. Specifically, the study is based on adequately performed laboratory and animal experimentation; the study will be conducted under a protocol reviewed by a properly constituted IRB/EC; the study will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the patients will be respected; and each patient or his/her legal guardian will give his/her written Informed Consent before any protocol-specific tests or evaluations are performed.

10.2. Institutional Review Board or Ethics Committee

Prior to initiating the study, the Investigator will obtain written confirmation from the IRB/EC that the IRB/EC was properly constituted and met the definition of all United States Code of Federal Regulations Title 21, Section 312.3(b) and Part 56, and/or the applicable local, regional or national Regulatory requirements. A copy of the confirmation will be provided to the Sponsor. The Principal Investigator will provide the IRB/EC with all appropriate materials, including the protocol and Informed Consent documents. The trial will not be initiated until IRB/EC approval

of the protocol, the Informed Consent document, and all recruiting materials are obtained in writing by the Investigator and copies are received by the Sponsor. Appropriate reports on the progress of the study will be made to the IRB/EC and the Sponsor by the Principal Investigator in accordance with applicable governmental regulations and in agreement with the policy established by the Sponsor.

10.3. Informed Consent

A properly executed, written, and appropriately explained Informed Consent Form, in compliance with the Declaration of Helsinki, ICH GCP, and US Code of Federal Regulations for Protection of Human Patients (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 46, Subpart A), will be signed by each patient or his/her legal guardian prior to entering the trial. Either the Investigator or the Investigator's designee will obtain the consent of the study patient. The patient will be provided as much time as necessary to review the document, to inquire about details of the trial, and to decide whether or not to participate in the study. The Informed Consent will be signed and dated by the study patient and by the person who conducted the Informed Consent discussion. The Investigator will provide a copy of the signed Informed Consent Form to each patient and will maintain a copy in the patient's record file.

10.4. Protocol Modifications

Only the Sponsor may modify the protocol. The only exception is when the Investigator considers that a patient's safety would be compromised without immediate action. In this circumstance, immediate approval of the chairperson of the IRB/EC must be sought, and the Investigator should inform the Sponsor's Medical Monitor and the full IRB/EC within five working days after the emergency occurred. All other amendments that have an impact on patient risk or the study objectives, and/or that require revision of the Informed Consent Form, must receive approval from the IRB/EC prior to their implementation, except when the changes involve only logistical or administrative aspects of the trial. The IRB/EC must be notified of changes that are made to study contact personnel, but IRB/EC review or approval of these changes is not required. If protocol amendments are substantial and are likely to have an impact on the safety of the trial patients or to change the interpretation of the scientific documents in support of the conduct of the trial, or if they are otherwise significant, the sponsor shall notify the FDA and other competent authorities concerned of the reasons for, and content of, these amendments according to the European Directive "Detailed guidance on the request to the competent authorities for authorization of a clinical trial on a medical products for human use, the notification of substantial amendments and the declaration of the end of trial (CT-1)(2010/C 82/01)" and other regulatory guidance. In case of a substantial amendment to the protocol, approval will be sought from Competent Authorities before implementation.

10.5. Regulatory Documentation

All regulatory documentation including regulatory submissions, 1572 forms, and correspondence regarding this study will be kept by the Sponsor. The CRO that will conduct the study on behalf of the Sponsor will maintain all study documentation according to their SOPs. Clinical trial related documents will be archived for the longest of:

1. 10 years according to national Swedish and EU regulations (LVFS 2003:3), or

2. For 2 years following the date a full marketing application is approved, or
3. For 2 years after the FDA is notified that the IND is discontinued if there is no marketing application.

10.6. Patient Identification Register

The Investigator agrees to complete a patient identification register, which will be used for the purpose of long term follow-up, if needed. This form will be treated as confidential, and will be filed by the Investigator in a secure locked place. Otherwise, all reports and communications relating to the study will identify participants by initials and/or assigned number only.

10.7. Record Retention

The Investigator must retain all study records required by the Sponsor and by the applicable regulations in a secure and safe facility. The Investigator must consult a Sponsor CRA before disposal of any study records, and must notify the Sponsor of any change in the location, disposition, or custody of the study files. Clinical trial related documents will be archived for the longest of:

1. 10 years according to national Swedish and EU regulations (LVFS 2003:3), or
2. For 2 years following the date a full marketing application is approved, or
3. For 2 years after the FDA is notified that the IND is discontinued if there is no marketing application.

10.8. Case Report Form Completion

Electronic Case Report Forms (CRFs) will be generated for each patient. The electronic data capture (EDC) system will comply with CFR 21 Part 11.

It is the policy of the Sponsor that study data must be verifiable to the source data, which necessitates access to all original recordings, laboratory reports, and patients' records. The Investigator must therefore agree to allow access to patients' records, and source data must be made available for all study data. The patients (or their legal representatives) must also allow access to the patients' medical records, and they will be informed of this requirement and will indicate their agreement when giving Informed Consent. Upon completion of the study, electronic copies of the CRFs will be provided to the investigators and should be included as part of his/her study files and retained as per FDA or local regulations.

10.9. Monitoring

At intervals during the study, as well as after the completion of patient enrollment at the study center, the study center will be monitored by a CRA for compliance, which will include ensuring that accurate and complete data are promptly recorded in EDC, and reviewing source documentation and drug accountability records. The study will be conducted according to the principles of GCP as accepted in the United States and according to CPMP/ICH/135/95.

10.10. On-site Visits and Audits

The Sponsor's representatives will visit the study center prior to initiation of the study to review with the center personnel information regarding the investigational agent, protocol requirements, monitoring requirements, and reporting of serious adverse events.

In certain circumstances, a secondary audit may be conducted by members of a Quality Assurance group designated by the Sponsor. The Investigator will be informed if this is to take place and advised as to the nature of the audit. Representatives of the Food and Drug Administration (FDA) and/or representatives of other regulatory authorities may also conduct an audit of the study. If informed of such an audit, the Investigator should notify the Sponsor immediately.

10.11. Use of Information and Publication

It is understood by the Investigator that the information generated in this study will be used by the Sponsor in connection with the development of the product and therefore may be disclosed to government agencies in various countries. To allow for the use of information derived from the study, it is understood that the Investigator is obliged to provide the Sponsor with complete test results, all study data, and access to all study records.

The Sponsor recognizes the importance of communicating study data and will disclose or publish the results in a suitable form regardless of outcome. The Sponsor will post the clinical trial information on appropriate registries, e.g., clinicaltrials.gov prior to enrollment of the first patients, and publish the results of this study in scientific journals, at seminars or conferences, and/or in other manner(s) it so chooses. Results from this study shall not be made available to any third party by the investigating team without the express permission of the Sponsor.

11. REFERENCES

Exley AR, et al. 1997 Development and initial validation of the VDI. Arthritis Rheum 40:371-380.

Jennette JC, et al. 2013 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 65:1–11.

Johnson TN, et al. Prediction of the clearance of eleven drugs and associated variability in neonates, infants and children. Clin Pharmacokinet 2006; 45:931–956.

Jones JH, et al. 2010 Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med 363:211-220.

Little M, et al. 2010 Early mortality in systemic vasculitis: relative contribution of adverse events and active vasculitis. Ann Rheum Dis 69:1036−1043.

Miloslavsky EM, et al. 2016 Development of a Glucocorticoid Toxicity Index (GTI) using multicriteria decision analysis. Ann Rheum Dis 2016;0:1–4. doi:10.1136/annrheumdis-2016-210002.

Momper JD, et al. Adolescent Dosing and Labeling Since the Food and Drug Administration Amendments Act of 2007. JAMA Pediatr 2013;167:926–932.

Mukhtyar C, et al. 2009 Modification and validation of the Birmingham Vasculitis Activity Score (version 3) Ann Rheum Dis 68:1827–1832.

Robson J, et al. 2015 Glucocorticoid treatment and damage in the anti-neutrophil cytoplasm antibody-associated vasculitides: long-term data from the European Vasculitis Study Group trials. Rheumatol 54:471-481.

Schwartz GJ, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol 2009;20:629–637.

Specks U, et al. 2013 Efficacy of remission-induction regimens for ANCA-associated vasculitis. N Engl J Med 369:417-427.

Stone JH, et al. 2010 Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 363:221-232.

Suppiah R, et al. 2011 A cross-sectional study of the Birmingham Vasculitis Activity Score version 3 in systemic vasculitis. Rheumatol 50:899-905.

Xiao H, et al. C5a receptor (CD88) blockade protects against MPO-ANCA GN. J Am Soc Nephrol 2014;25:225–231.

12. APPENDICES

12.1. Statement of Obligations of Sponsor, Monitor, and Clinical Investigator

Sponsor and Monitor

If the Sponsor is not familiar with the Study Site, the Sponsor or its designated representative, will:

A. Conduct a pre-study visit to:

1. Establish the acceptability of the facility, the recruitment potential and the standard of patient care at this site, and record this in a written report.
2. Discuss the proposed clinical trial with the Investigator, review the CRF requirements, and supply the Investigator's Brochure and the draft protocol for review and approval.
3. Discuss with the Investigator FDA and other regulatory requirements with respect to Informed Consent, competent authority (CA) and ethics committee (EC) approval of the trial, the protocol, protocol amendments, and Informed Consent changes.

B. Conduct periodic site visits to:

1. Assure adherence to the protocol.
2. Review CRFs and medical records for accuracy and completeness of information.
3. Examine pharmacy records for documentation of quantity and date of receipt of investigational supplies, dispensation and accountability data for administration to each patient, loss of materials, contamination, and unused supplies.
4. Record and report observations on the progress of the trial and continued acceptability of the facilities in a Site Visit Report.
5. Review Investigator files for required documents, e.g., protocols, protocol amendments, CA and EC approvals (protocols, amendments, Informed Consent, etc.), EC charter and membership, and communications between the EC and the Investigator.

Clinical Investigator

A. EC

The Investigator must assure the monitor that the EC:

1. Meets FDA regulations as defined in 21 CFR Part 56 and other applicable ICH and GCP requirements.
2. Has authority delegated by the parent institution and found in EC by-laws, operation guidelines, or charter to approve or disapprove clinical trials and protocols, including Informed Consent Forms and other documents (protocol amendments, information to be supplied to patients concerning Informed Consent, etc.).
3. Complies with proper personnel makeup of an EC and maintains an active up-to-date roster of all EC members participating in the meetings.

4. Convenes meetings using acceptable rules of order for making decisions, recording such decisions, and implementing them.
5. Files contain (a) documentation of its decisions such as are found in EC minutes and correspondence, (b) written guidelines or by-laws governing EC functions, (c) protocols, (d) protocol information to be supplied to the patient, (e) correspondence between the EC and the Investigator (Informed Consent Form changes, protocol amendments, etc.).

B. Informed Consent of Human Patients.

The Principal Investigator must assure the monitor that the Informed Consent Form:

1. Meets FDA regulations as defined in 21 CFR Part 50 Informed Consent, and other applicable ICH and GCP requirements.
2. Has been approved by the EC, including, when required, information to be given to the patient regarding the trial in which s/he is enrolled.
    a. The Informed Consent Form includes the Basic Elements and any Additional Elements necessary.
    b. The patient and a study center representative sign the Informed Consent Form and the patient is given a copy.

C. Storage and Dispensing of Study Supplies.

The Investigator (or pharmacist or pharmacy technician) must demonstrate to the monitor that:

1. Adequate and accurate written records show receipt and disposition of all study supplies, including dates, serial or lot numbers, quantities received, and each quantity dispensed, administered, or used, with identification of each patient.
2. Purpose and reasons are given in written records for study material disposal, e.g., the amount contaminated, broken, or lost, and the quantity returned to the Sponsor.

D. Case Report Forms.

The Investigator must assure the monitor that:

1. Case report forms, when complete, accurately reflect the medical records on each patient.
2. Case report forms and medical records will be accessible to the monitor or FDA and other Regulatory inspectors during site visits.

E. Files and Records.

The Investigator must assure the quality, integrity, and content of his or her files that will be inspected by the monitor and regulatory inspectors. The files must contain, at a minimum:

1. Correspondence between the EC and the Investigator.
2. The following documents:
    a. EC-approved protocols.
    b. EC-approved protocol amendments.
    c. EC-approved Informed Consent Form and information supplied to the patient.
    d. EC charter, membership, and qualifications.

3. Clinical supplies:
    a. Record of receipt, date and quantity, and batch or lot number.
    b. Disposition dates and quantity administered to each patient.
    c. Inventory records.

Clinical trial related documents will be archived for the longest of:

1. 10 years according to national Swedish and EU regulations (LVFS 2003:3), or
2. For 2 years following the date a full marketing application is approved, or
3. For 2 years after the FDA is notified that the IND is discontinued if there is no marketing application.

12.2. Informed Consent Form

In seeking Informed Consent, the following information shall be provided to each patient:

1. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the patient's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
2. A description of any reasonably foreseeable risks or discomforts to the patient.
3. A description of any benefits to the patient or to others that may reasonably be expected from the research.
4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient.
5. A statement describing the extent, if any, to which confidentiality of records identifying the patient will be maintained and that notes the possibility that the Food and Drug Administration or other regulatory agency may inspect the records.
6. For research involving more than minimal risk, an explanation as to whether any compensation and as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
7. An explanation of who to contact for answers to pertinent questions about the research and research patients' rights, and who to contact in the event of a research related injury to the patient.
8. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits to which the patient is otherwise entitled.

ADDITIONAL ELEMENTS OF INFORMED CONSENT

1. A statement that the particular treatment or procedure may involve risks to the patient (or to the embryo or fetus if the patient is or may become pregnant) which are currently unforeseeable.

2. Anticipated circumstances under which the patient's participation may be terminated by the Investigator without regard to the patient's consent.
3. Any additional costs to the patient that may result from participation in the research.
4. The consequences of a patient's decision to withdraw from the research and procedures for orderly termination of participation by the patient.
5. A statement that significant new findings developed during the course of the research which may relate to the patient's willingness to continue participation will be provided to the patient.
6. The approximate number of patients involved in the study.

12.3. Birmingham Vasculitis Activity Score (BVAS) Version 3

12.3.1. Instructions

The BVAS was previously validated (Mukhtyar et al, 2009; Suppiah et al, 2011).

The following instructions need to be followed to complete the BVAS according to the Time and Events Table.

1. Record BVAS items and enter the data into the EDC for this study;
2. Record only symptoms/signs ascribed to the presence of active AAV (GPA or MPA) on this form;
3. Check "none" for category only if there are no disease activity for the category;
4. "Major" items are indicated in bold italics;
5. For the Week 4 BVAS assessment, record the disease activity present within the 7 days prior to the visit. For all the other study visits, record the disease activity present within the 28 days prior to the visit.

12.3.2. AAV Organ Systems and Activity Items in BVAS

There are 9 organ systems, plus an "Other" category in the BVAS. Major items are indicated in bold italics. For study eligibility, a patient must have at least one major item, at least 3 minor items, or at least the two renal items of hematuria and proteinuria. If a patient has "other" items, not specified in the BVAS, these need to be discussed with the Medical Monitor before enrollment.

1. General
    - Myalgia
    - Arthralgia / arthritis
    - Fever ≥38 °C
    - Weight loss ≥2 kg
2. Cutaneous
    - Infarct

- Purpura
- Ulcer
- ***Gangrene***
- Other skin vasculitis

3. Mucous membranes / eyes
   - Mouth ulcers
   - Genital ulcers
   - Adnexal inflammation
   - Significant proptosis
   - ***Scleritis / Episcleritis***
   - Conjunctivitis / Blepharitis / Keratitis
   - Blurred vision
   - Sudden visual loss
   - Uveitis
   - ***Retinal changes (vasculitis / thrombosis / exudate / haemorrhage)***
4. ENT
   - Bloody nasal discharge / crusts / ulcers / granulomata
   - Paranasal sinus involvement
   - Subglottic stenosis
   - Conductive hearing loss
   - ***Sensorineural hearing loss***
5. Chest
   - Wheeze
   - Nodules or cavities
   - Pleural effusion / pleurisy
   - Infiltrate
   - Endobronchial involvement
   - ***Massive haemoptysis / alveolar haemorrhage***
   - ***Respiratory failure***
6. Cardiovascular
   - Loss of pulses

- Valvular heart disease
- Pericarditis
- Ischaemic cardiac pain
- Cardiomyopathy
- Congestive cardiac failure

7. Abdominal
   - Peritonitis
   - Bloody diarrhoea
   - ***Ischaemic abdominal pain***
8. Renal
   - Hypertension
   - Proteinuria >1+ or >0.2 g/g creatinine
   - Haematuria ≥10 RBCs/hpf
   - Serum creatinine 125-249 μmol/L
   - Serum creatinine 250-499 μmol/L
   - Serum creatinine ≥500 μmol/L
   - ***Rise in serum creatinine >30% or fall in creatinine clearance >25%***
9. Nervous system
   - Headache
   - ***Meningitis***
   - Seizures (not hypertensive)
   - ***Cerebrovascular accident***
   - Organic confusion
   - ***Spinal cord lesion***
   - ***Cranial nerve palsy***
   - ***Sensory peripheral neuropathy***
   - ***Mononeuritis multiplex***
10. Other
    - ***RBC casts and/or glomerulonephritis***

12.3.3. Scoring of BVAS

The Investigators will not be required to calculate the BVAS. This will be done programmatically in the EDC according to Mukhtyar et al, 2009.

12.4. Vasculitis Damage Index

12.4.1. Instructions

The Vasculitis Damage Index (VDI) was developed by Exley et al, 1997 and is for recording organ damage that has occurred in patients since the onset of vasculitis.

Damage is defined as the presence of non-healing scars and does not give any indication of current disease activity. Damage items in the VDI are often the direct result of previous disease activity (captured in the BVAS). Damage is defined as having been present or currently present for at least 3 months. It is therefore possible for abnormalities to have occurred in the past, not be currently present, but to still count as damage.

Patients often have co-morbidity before they develop vasculitis, which must not be scored.

Record features of active disease using the BVAS, not the VDI.

New patients 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.

The VDI item list can only deteriorate or be stable over time (damage is defined as irreversible in this scoring system). For each item in turn, record all features which have occurred since the onset of vasculitis, regardless of the cause. For specific events, such as GI surgery, damage can be scored as positive if the procedure was undertaken at least three months prior to the assessment (and also must have occurred after the onset of the disease). The same time frame is applied to all the damage items. If the patient is seen for the first time, and their vasculitis onset date is within three months of the assessment, then by definition, the patient cannot be recorded as having any damage. However, any features which are observed can be recorded as ascribable to damage after the arbitrary time of three months has elapsed.

12.4.2. AAV Organ Systems in VDI

There are 11 organ systems in the VDI:

1. Musculoskeletal
    a. Significant muscle atrophy or weakness
    b. Deforming / erosive arthritis
    c. Osteoporosis / vertebral collapse
    d. Avascular necrosis
    e. Osteomyelitis
2. Skin/Mucous Membranes
    a. Alopecia
    b. Cutaneous ulcers
    c. Mouth ulcers
3. Ocular

a. Cataract
b. Retinal change
c. Optic atrophy
d. Visual impairment / diplopia
e. Blindness in one eye
f. Blindness in a second eye
g. Orbital wall destruction

4. Ear, Nose & Throat

a. Hearing loss
b. Nasal blockage / chronic discharge/crusting
c. Nasal bridge collapse / septal perforation
d. Chronic sinusitis / radiological damage
e. Subglottic stenosis (no surgery)
f. Subglottic stenosis (with surgery)

5. Pulmonary

a. Pulmonary hypertension
b. Pulmonary fibrosis
c. Pulmonary infarction
d. Pleural fibrosis
e. Chronic asthma
f. Chronic breathlessness
g. Impaired lung function

6. Cardiovascular

a. Angina angioplasty
b. Myocardial infarction
c. Subsequent myocardial infarction
d. Cardiomyopathy
e. Valvular disease
f. Pericarditis ≥3 months or pericardectomy
g. Diastolic BP ≥95 or requiring antihypertensives

7. Peripheral Vascular Disease

a. Absent pulses in one limb
b. Second episode of absent pulses in one limb
c. Major vessel stenosis
d. Claudication >3 months
e. Minor tissue loss
f. Major tissue loss

g. Subsequent major tissue loss
h. Complicated venous thrombosis

8. Gastrointestinal

a. Gut infarction / resection
b. Mesenteric insufficiency / pancreatitis
c. Chronic peritonitis
d. Esophageal stricture / surgery

9. Renal

a. Estimated / measured GFR ≤50
b. Proteinuria **≥0.5** g/24 hours
c. End stage renal disease

10. Neuropsychiatric

a. Cognitive impairment
b. Major psychosis
c. Seizures
d. Cerebrovascular accident
e. 2nd Cerebrovascular accident
f. Cranial nerve lesion
g. Peripheral neuropathy
h. Transverse myelitis

11. Other

a. Gonadal failure
b. Marrow failure
c. Diabetes
d. Chemical cystitis
e. Malignancy
f. Etc.

12.4.3. Scoring of VDI

The number of positive items is added for the total VDI score. Any previously scored items on the VDI must be carried forward to subsequent visits. The VDI score cannot decrease over time. The investigators will not need to calculate the VDI. This will be done in the EDC.

12.5. Glucocorticoid Toxicity Index (GTI)

The GTI was developed to quantify toxicity associated with glucocorticoid use (Miloslavsky et al, 2016). The Index consists of the components in Table 3.

Table 3: The Glucocorticoid Toxicity Index

Composite GTI [1]	Item Weight	Specific List [2]
BMI		
Improvement in BMI	-8	Major increase in BMI (>8 units and above 24.9 kg/m^2)
No change in BMI	0	
Moderate increase in BMI	21	
Major increase in BMI	36	
Glucose tolerance		
Improvement in glucose tolerance	-8	Diabetic retinopathy
No change in glucose tolerance	0	Diabetic nephropathy
Worsening of glucose intolerance	32	Diabetic neuropathy
Worsening of glucose intolerance despite treatment	44	
Blood pressure		
Improvement in blood pressure	-10	Hypertensive emergency (or posterior reversible encephalopathy syndrome)
No change in blood pressure	0	Posterior reversible encephalopathy syndrome
Worsening hypertension	19	
Worsening hypertension despite treatment	44	
Lipids		
Improvement in lipids	-9	
No change in lipids	0	
Worsening hyperlipidaemia	10	
Worsening hyperlipidaemia despite treatment	30	
Bone density [3]		
Improvement in bone density	-1	Major decrease in bone density
No change in bone density	0	Insufficiency fracture
Decrease in bone density	29	
Steroid myopathy		
No steroid myopathy	0	Severe steroid myopathy or tendon rupture
Mild steroid myopathy	9	
Moderate steroid myopathy or greater	63	
Skin toxicity		

Composite GTI [1]	Item Weight	Specific List [2]
No skin toxicity	0	Severe skin toxicity
Mild skin toxicity	8	
Moderate skin toxicity or greater	26	
Neuropsychiatric toxicity		
No neuropsychiatric symptoms	0	Psychosis (hallucinations, delusions, or disorganized thought processes, occurring in the absence of mania, delirium, or depression)
Mild neuropsychiatric symptoms	11	Glucocorticoid-induced violence towards self or others
Moderate neuropsychiatric symptoms or greater	74	Other severe neuropsychiatric symptoms
Infection		
No significant infection	0	Grade IV infection
Oral/vaginal candidiasis or uncomplicated zoster	19	Grade V infection (death from infection)
Grade III infection or greater	93	
Endocrine		Symptomatic adrenal insufficiency
Gastrointestinal		Perforation (occurring in the absence of regular nonsteroidal anti-inflammatory drug use)
		Peptic ulcer disease confirmed by endoscopy (excluding *H. pylori*)
Musculoskeletal		Avascular necrosis
		Tendon rupture
Ocular		Central serous retinopathy
		New onset or worsened elevation of intraocular pressure requiring treatment or change in treatment.
		Posterior subcapsular cataract (or history of the same)
Total	**-35 to 410**	

[1] See Section 12.5.1 for definitions of each item in the GTI.

[2] See Section 12.5.2 for definitions of each specific list item.

[3] Since the last assessment of the GTI will be performed at Week 26, and bone density assessments are typically performed annually, the osteoporosis component will not be included in the GTI for this study, according to the authors' recommendation.

12.5.1. Definitions of Items Comprising the GTI

Definitions for each of the items in the first column in Table 3 are provided below.

Body Mass Index (BMI) (compared to baseline)

a. Improvement in the direction of the normal range by more than 2 BMI units (normal range = 18.5-24.9 kg/m^2);
b. No significant change (BMI remains within ± 2 BMI units compared with baseline) OR BMI remains within the normal range;
c. Moderate increase in BMI (increase by more than 2 but less than 5 BMI units, to above the upper limit of normal BMI [24.9 kg/m^2]);
d. Major increase in BMI (increase by at least 5 but less than 8 BMI units above normal BMI [24.9 kg/m^2]).

Glucose Tolerance (compared to baseline)

a. Improvement in glucose tolerance:
   - HbA1c declined >10% from baseline without medication increase OR
   - Decrease in diabetic medication without an increase in HbA1c of >10% or HbA1c < 5.7%.
b. No significant change in glucose tolerance:
   - HbA1c within 10% of baseline or HbA1c <5.7% AND no change in medication, OR
   - HbA1c increased to >10% of baseline with a decrease in medication, OR
   - HbA1c decreased by >10% of baseline with an increase in medication.
c. Worsening of glucose tolerance or medication status:
   - HbA1c >5.7% and increased to >10% of baseline without a change in medication, OR
   - Increase in diabetic medication with <10% increase in HbA1c.
d. Worsening of glucose tolerance despite increased treatment:
   - HbA1c >5.7% AND increased to >10% of baseline AND an increase in diabetic medication.

Blood Pressure (BP) (compared to baseline)

a. Improvement in BP:
   - Decrease in BP of >10% of baseline without medication increase, unless baseline systolic BP ≤120 and diastolic BP ≤85, OR
   - Decrease in medication without an increase in BP of >10%, unless baseline systolic BP ≤120 and diastolic BP ≤85.
b. No significant change in BP:
   - BP within 10% of baseline or systolic BP ≤120 and diastolic BP ≤85 AND no change in medication, OR
   - Increase in either systolic or diastolic BP >10% with a decrease in medication, OR
   - Improvement in systolic or diastolic BP of >10% with an increase in medication.
c. Worsening of hypertension:

- Increase in BP of >10% such that the systolic BP exceeds 120 mmHg or the diastolic BP exceeds 85 mmHg without a change in medication, OR
- An increase in anti-hypertensive medication accompanied by stability or no significant change in both the systolic and diastolic BP.

d. Worsening of hypertension despite treatment:

- Increase in BP of >10% such that the systolic BP exceeds 120 mmHg or the diastolic BP exceeds 85 mmHg AND an increase in medication.

Lipid metabolism (low-density lipoprotein [LDL] compared to baseline)

a. Improvement in lipids:

- Decrease in LDL concentration >10% of baseline toward the target range without medication increase, OR
- Decrease in medication without an increase in LDL of >10% or LDL remains within target range.

b. No significant change in LDL:

- LDL within 10% of baseline or within the target range for patient AND no change in medication, OR
- Increase in LDL >10% with a decrease in medication, OR
- Improvement in LDL of >10% with an increase in medication.

c. Worsening of LDL or medication status:

- Increase in LDL of >10% to above target range without a change in medication, OR
- Increase in medication with <10% change in LDL.

d. Worsening of LDL despite treatment:

- Increase in LDL of >10% AND an increase in medication.

Glucocorticoid-induced myopathy

Glucocorticoid-induced myopathy is defined as mild symmetrical weakness of the proximal muscles and/or neck flexors associated with steroid therapy, and NOT due to any other apparent cause. Muscle enzymes are typically within normal limits.

a. No steroid myopathy;
b. Mild steroid myopathy (Grade 4 weakness WITHOUT functional limitation); “Grade 4 weakness” is defined as weaker than normal, but greater than antigravity strength against resistance;
c. Moderate steroid myopathy (weakness WITH functional limitation, enough to interfere with normal daily activities).

Note that a person may have muscle weakness consistent with glucocorticoid-induced myopathy that is detectable on physical examination but might not be aware of it or have any corresponding functional limitation - this would be classified as mild.

Severe glucocorticoid-induced myopathy (defined as weakness of Grade 3 or less, which means no more than antigravity strength and unable to overcome any resistance or any degree weaker) is included in the Specific List (see Table 3). People who are severely weak may have difficulty rising from a chair without assistance or other major functional limitations but the formal categorization for severe should be based on the degree of weakness on strength testing.

Skin

Manifestations to be considered:

- Acneiform rash
- Easy Bruising
- Hirsutism
- Atrophy/striae
- Erosions/tears/ulcerations

Severity is graded as shown in Table 4.

Table 4: Severity of Glucocorticoid Toxicity in the Skin

Manifestation	Mild	Moderate	Severe
Acneiform rash	Papules and/or pustules covering ≤30% body surface area (BSA), which may or may not be associated with symptoms of pruritus or tenderness; OR associated with psychosocial impact; OR limiting instrumental activities of daily living (ADL).	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; OR limiting self-care ADL; OR associated with local superinfection with oral antibiotics indicated.	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; OR life-threatening consequences.
Easy Bruising	Localized or in a dependent area.	Generalized	
Hirsutism; In women, increase in length, thickness or density of hair in a male distribution	Hirsutism that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair.	Hirsutism that requires daily shaving or consistent destructive means of hair removal to camouflage; OR associated with psychosocial impact.	
Atrophy/striae	Covering <10% BSA; OR associated with telangiectasias or changes in skin color.	Covering 10 - 30% BSA; OR associated with striae or adnexal structure loss.	Covering >30% BSA; OR associated with ulceration.

Manifestation	Mild	Moderate	Severe
Erosions/tears/ulcerations	Combined area of ulcers <1 cm; OR nonblanchable erythema of intact skin associated with warmth or erythema.	Combined area of ulcers 1 to 2 cm; OR partial thickness skin loss involving skin or subcutaneous fat.	Combined area of ulcers >2 cm; OR full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia.

Neuropsychiatric Toxicity

Manifestations to be considered:

- Insomnia
- Mania
- Cognitive Impairment
- Depression

Severity is graded as shown in Table 5.

Table 5: Severity of Neuropsychiatric Glucocorticoid Toxicity

Manifestation	Mild	Moderate	Severe
Insomnia; Dissatisfaction with sleep quality and difficulty initiating or maintaining sleep or early morning awakening	Not associated with functional impairment.	Associated with functional impairment.	
Mania	Slightly or occasionally elevated or irritable mood and 0-1 mild or occasional additional symptoms of inflated self-esteem, decreased need for sleep, increased talkativeness, feeling that thoughts are faster than usual, distractibility, increased activity or agitation, and impulsive actions.	Frequent or moderately elevated or irritable mood and 2-3 mild additional symptoms of inflated self-esteem, decreased need for sleep, increased talkativeness, feeling that thoughts are faster than usual, distractibility, increased activity or agitation, and impulsive actions.	Severe or constantly elevated or irritable mood and 4 or more additional symptoms of inflated self-esteem, decreased need for sleep, increased talkativeness, feeling that thoughts are faster than usual, distractibility, increased activity or agitation, and impulsive actions.
Cognitive impairment	Minor cognitive complaints, no objective findings on mental status examination (i.e., not apparent to the examiner) that were not present before initiating steroids.	New moderate cognitive deficits that were not present before initiating steroids.	Frank delirium

Manifestation	Mild	Moderate	Severe
Depression	Feeling slightly down or depressed and 0-2 mild or occasional addition symptoms of loss of interest, low energy, guilt, poor concentration, insomnia, restlessness, or change in appetite.	Frequent or moderate feelings of being down or depression and/or 3-4 symptoms of loss of interest, low energy, guilt, poor concentration, insomnia, restlessness, or change in appetite.	Severe constant feeling of being down or depression and/or 5 or more symptoms of loss of interest, low energy, guilt, poor concentration, insomnia, restlessness, or change in appetite and/or suicidal thoughts.

Infection

a. No significant infection = No specific infections or serious infections, Grade 3 or greater
b. Specific Infections <Grade 3 – Oral or vaginal candidiasis or zoster infections without post-herpetic neuralgia or eye involvement
c. Grade 3 or complicated herpes zoster

- Grade 3 – Intravenous antibiotic, antifungal, or antiviral intervention or hospitalization indicated, OR radiologic or operative intervention indicated, OR herpes zoster complicated by post-herpetic neuralgia or eye involvement.
- Grade 4 or 5 - Life-threatening consequences; urgent intervention indicated, OR death from infection (included in the Specific List; see Table 3).

12.5.2. Definitions of Specific List Items

Definitions of each of the Specific List Items in the third column in Table 3 are provided below:

Hypertensive emergency: The blood pressure has reached levels that are damaging organs. Hypertensive emergencies generally occur at blood pressure levels exceeding 180 mmHg systolic OR 120 mmHg diastolic, but can occur at even lower levels in patients whose blood pressure have not been elevated before. Complications can include: stroke, loss of consciousness, memory loss, myocardial infarction, hypertensive retinopathy or nephropathy, aortic dissection, angina, pulmonary edema.

Posterior reversible leukoencephalopathy syndrome (PRES): A clinical radiological entity. Clinical features may include headaches, altered mental status, seizures, and visual loss, depending on the affected neuroanatomy. Characteristic Magnetic Resonance Imaging (MRI) findings include vasogenic edema involving the white matter that predominantly affects the posterior occipital and parietal lobes of the brain, although other brain regions may also be affected. Confirmation by MRI is required as is exclusion of other potential causes (including hypertensive emergency).

Severe glucocorticoid myopathy: Grade 3 or worse myopathic weakness or respiratory myopathic weakness attributable to glucocorticoid myopathy.

Central serous retinopathy: a fluid detachment of macula layers from their supporting tissue. Requires formal ophthalmology examination, typically accompanied by optical coherence tomography and/or fluorescein angiography for diagnostic confirmation.

Grade 4 infection: Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis).

Diabetic nephropathy: Macroalbuminuria; i.e., a urinary albumin excretion >300 mg in a 24-hour collection or a urinary protein: creatinine ratio >300mg/g.

Diabetic neuropathy: Any of four types of peripheral neuropathy occurring in the setting of diabetes mellitus, namely: 1) a distal sensory polyneuropathy; 2) autonomic neuropathy (hypoglycemia unawareness, bladder or bowel problems, erectile dysfunction, and other autonomic nervous system issues); 3) diabetic amyotrophy (muscle infarction); or 4) mononeuritis (e.g., foot drop attributed to diabetic neuropathy).

12.6. Prednisone Dose Schedule

12.6.1. Study-Supplied Prednisone

Patients who are randomized to the control group will receive prednisone according to a standardized tapering schedule over the course of the study. Patients who are randomized to the CCX168 group will receive prednisone-matching placebo capsules, with the type and number of capsules matching the type and number of capsules taken by the control group patients over the course of the study.

Patients with a body weight of ≥55 kg, who are randomized to the control group, will start at an oral prednisone dose of 60 mg per day and will taper the dose down to zero over 20 weeks (140 days). Adult patients with a body weight less than 55 kg will start at an oral prednisone dose of 45 mg per day and will taper the dose down to zero over 20 weeks. Adolescents with a body weight >37 kg will start at an oral prednisone dose of 45 mg per day and will taper the dose down to zero over 20 weeks, and adolescents with a body weight ≤37 kg will start at an oral prednisone dose of 30 mg per day and will taper the dose down to zero over 20 weeks.

The tapering schedule for patients in the control group is provided in Table 6.

Table 6: Prednisone/Matching Placebo Schedule for the Control Group

Study Day	CCX168 Group	Control Group			
	Daily Prednisone Dose				
	All	Adults		Adolescents	
		≥55 kg	<55 kg	>37 kg	≤37 kg
Day 1 to 7	0	60 mg	45 mg	45 mg	30 mg
Day 8 to 14	0	45 mg	45 mg	45 mg	30 mg
Day 15 to 21	0	30 mg	30 mg	30 mg	30 mg
Day 22 to 42	0	25 mg	25 mg	25 mg	25 mg
Day 43 to 56	0	20 mg	20 mg	20 mg	20 mg
Day 57 to 70	0	15 mg	15 mg	15 mg	15 mg
Day 71 to 98	0	10 mg	10 mg	10 mg	10 mg

Day 99 to 140	0	5 mg	5 mg	5 mg	5 mg
≥ Day 141	0	0	0	0	0

Patients will receive prednisone bottles containing either 20 mg prednisone/matching capsules or 5 mg prednisone/matching capsules or both, depending on the study visit, and will take prednisone/matching placebo capsules each day as shown in Table 7.

Table 7: Prednisone/Matching Placebo Dosing by Study Day

Study Day	Prednisone dose	Dosing instructions for 20 mg/ matching placebo bottle	Dosing instructions for 5 mg/ matching placebo bottle
Day 1 to 7 (for adults ≥55 kg)	60 mg	Take 3 capsules per day	NA
Day 1 to 7 (for adults <55 kg and adolescents >37 kg)	45 mg	Take 2 capsules per day	Take 1 capsule per day
Day 1 to 7 (for adolescents ≤37 kg)	30 mg	Take 1 capsule per day	Take 2 capsules per day
Day 8 to 14 (for all adults and adolescents >37 kg)	45 mg	Take 2 capsules per day	Take 1 capsule per day
Day 8 to 14 (for adolescents ≤37 kg)	30 mg	Take 1 capsule per day	Take 2 capsules per day
Day 15 to 21 (all)	30 mg	Take 1 capsule per day	Take 2 capsules per day
Day 22 to 42 (all)	25 mg	Take 1 capsule per day	Take 1 capsule per day
Day 43 to 49 (all)	20 mg	Take 1 capsule per day	Not applicable
Day 50 to 56 (all)	20 mg	Not applicable	Take 4 capsules per day
Day 57 to 70 (all)	15 mg	Not applicable	Take 3 capsules per day
Day 71 to 98 (all)	10 mg	Not applicable	Take 2 capsules per day
Day 99 to 140 (all)	5 mg	Not applicable	Take 1 capsule per day
≥ Day 141 (all)	0	Not applicable	Not applicable

Note that all patients will take prednisone or matching placebo capsules in order to maintain the study blinding. The appropriate number of 20 mg prednisone/matching placebo capsule bottles, and 5 mg prednisone/matching placebo capsule bottles will be dispensed to patients at each study visit, with detailed dosing instructions.

12.6.2. Non-Study Supplied Glucocorticoid Use

Extra glucocorticoids, i.e., that which is not supplied as study drug, must be avoided as much as possible during the study. The following sections provide guidance for non-study supplied glucocorticoid use.

12.6.2.1. Prior to the Screening Period

Patients with severe AAV will be allowed to have received IV glucocorticoids at a cumulative dose up to 3 g methylprednisolone equivalent in the 4-week period prior to screening.

Patients will also be allowed to have received oral glucocorticoids at any dose in the 6-week period prior to screening.

Patients will not be eligible for screening if they have received continuous treatment with moderate or high dose glucocorticoids continuously for more than 6 weeks; moderate to high dose is defined as greater than 10 mg prednisone-equivalent per day.

12.6.2.2. During the Screening Period

During the screening period of the study (which is not to exceed 14 days), IV glucocorticoids will be allowed for patients with severe AAV, as long as the cumulative dose for the 4-week period prior to screening plus the IV dose(s) given during the screening period does not exceed 3 g methylprednisolone equivalent.

During the screening period of the study (which is not to exceed 14 days), oral glucocorticoids will be allowed for patients with severe AAV. If a patient receives oral glucocorticoids during the screening period, the dose needs to be tapered to a dose that does not exceed 20 mg prednisone equivalent on Day 1 of the study.

12.6.2.3. During the Treatment Period

If a patient is still taking a dose of ≤20 mg non-study supplied oral prednisone on Day 1 of the study, this dose of non-study supplied oral glucocorticoids must be tapered to zero over a 4-week period after Day 1. If glucocorticoids cannot be tapered to a dose of zero due to adrenal insufficiency, the adverse event of adrenal insufficiency and treatment administered must be recorded, along the evidence supporting the diagnosis. Replacement glucocorticoids for adrenal insufficiency should not exceed 10 mg prednisone equivalent per day; taper should be re-initiated as soon as possible, and condition should be monitored consistent with Investigator judgment and local standards. The adverse event of adrenal insufficiency, and treatment for the event, must be recorded and updated as treatment is tapered.

Patients who experience a *relapse* of their AAV during the study may be treated with IV glucocorticoids (typically 0.5 to 1 g methylprednisolone per day for 3 days) and/or oral glucocorticoids, tapered according to the patient's condition. A relapse is defined as worsening of disease, after having previously achieved remission (BVAS = 0) at Week 26, that involves:

- one or more major item in the BVAS, or
- three or more minor items in the BVAS, or
- one or two minor items in the BVAS recorded at two consecutive study visits.

These patients may continue study drug treatment and should continue in the study.

Patients who experience worsening of disease during the study that involves a major item in the BVAS may be treated with IV glucocorticoids (typically 0.5 to 1 g methylprednisolone per day for 3 days) and/or oral glucocorticoids, tapered according to the patient's condition. Worsening not involving a major item in the BVAS may be treated with a short burst (i.e., not more than 2

weeks) of oral glucocorticoids, at a maximum dose of 20 mg prednisone equivalent. Patients experiencing worsening of disease may continue study drug treatment and should continue in the study.

Patients experiencing a relapse or worsening of disease may continue study drug treatment and should continue in the study. In patients experiencing a relapse, the study-supplied prednisone/matching placebo will be temporarily halted during the IV and/or oral course of glucocorticoids, and if the patient's condition stabilizes, the study-supplied prednisone/matching placebo may be restarted according to the original study visit schedule. The CCX168/matching placebo may also continue during and following the treatment for the relapse, at the discretion of the investigator.

Patients who have one or more major items in the BVAS before study entry, and who do not show an improvement or stabilization of these major items within the first 4 weeks of the study, may receive additional IV or oral glucocorticoids, tapered according to the patient's condition. If the Investigator considers giving other medications, such as additional rituximab or cyclophosphamide treatment, these should be discussed with the Medical Monitor. These patients may continue study drug treatment and should continue in the study.

In patients with early resistant disease, the study-supplied prednisone/matching placebo will be temporarily halted during the IV and/or oral course of glucocorticoids, and if the patient's condition improves, the study-supplied prednisone/matching placebo may be resumed according to the original visit schedule. The CCX168/matching placebo may also continue during the treatment for early resistance, at the discretion of the investigator.

12.7. Cyclophosphamide and Azathioprine Dosing

12.7.1. Cyclophosphamide Dosing

- For patients in the cyclophosphamide strata, cyclophosphamide doses must be given according to directions provided below.
- A dose of 15 mg/kg cyclophosphamide will be given IV to all patients in the IV cyclophosphamide stratum, unless a lower dose is required per instructions below. The maximum permitted IV dose is 1.2 g.
- A dose of 2 mg/kg/day cyclophosphamide will be given orally to all patients in the oral cyclophosphamide stratum, unless a lower dose is required per instructions below. The maximum daily oral dose permitted is 200 mg. Cyclophosphamide doses will be rounded down to the nearest 25 mg (or 50 mg, if 25 mg dose units are not available).
- Mesna and antiemetic treatment need to be given according to local practice.
- IV cyclophosphamide needs to be administered over a one-hour period. The start and end time of the IV infusion needs to be recorded.
- The cyclophosphamide dose will be determined by four factors: patient age, eGFR, WBC at the study visit, and WBC nadir in between dose pulses (where applicable). The dose for oral and IV cyclophosphamide, based on age and eGFR, is provided in Table 8.

Table 8: Dose (mg/kg) for Oral or IV Cyclophosphamide Based on Age and eGFR

Age (years)	Oral Cyclophosphamide Dose (mg/kg/day)		IV Cyclophosphamide Dose (mg/kg)	
	eGFR (mL/min/1.73 m^2)		eGFR (mL/min/1.73 m^2)	
	>30	≤30	>30	≤30
<60	2	1.5	15	12.5
60-70	1.5	1.25	12.5	10
>70	1.25	1	10	7.5

For those receiving IV cyclophosphamide, the dose should be reduced further based on the WBC count as follows:

- WBC count assessed just prior to the IV dose:
  - If ≥ 3.5 x 10^9/L, dosing according to Table 8 will be given;
  - If < 3.5 x 10^9/L, the dose will be postponed until the WBC count is ≥ 3.5 x 10^9/L and then the dose from Table 8 will be reduced by another 25%;
- WBC count nadir in between IV cyclophosphamide doses:
  - If > 3 x 10^9/L, dosing according to Table 8 will be given;
  - If 2 to 3 x 10^9/L, the dose from Table 8 will be reduced by 20%;
  - If 1 to 1.9 x 10^9/L, the dose from Table 8 will be reduced by 40%;
  - If < 1 x 10^9/L, the next dose will be withheld and further dosing will only be given if the WBC is > 3 x 10^9/L.

For those receiving oral cyclophosphamide, the dose should be reduced further based on the WBC count as follows:

- If WBC count is < 3.5 x 10^9/L, withhold dosing. When WBC count returns to ≥3.5 x 10^9/L for two consecutive tests, or ≥ 5 x 10^9/L on a single test, restart oral cyclophosphamide at 25 mg less than dose from Table 8. Monitor WBC count weekly after this episode. If only 50 mg dose units are available, restart oral cyclophosphamide at 50 mg less than dose from Table 8.
- If WBC count is < 1 x 10^9/L, or < 3.5 x 10^9/L for more than 2 weeks, withhold dosing. When WBC count returns to ≥ 3.5 x 10^9/L for two consecutive tests or ≥ 5 x 10^9/L on a single test, restart oral cyclophosphamide at 50 mg less than dose from Table 8. Monitor WBC count weekly after this episode. Consider giving granulocyte colony stimulating factor (G-CSF), fungal prophylaxis, or other precautions.
- If WBC count decreases markedly without overt leukopenia, e.g., WBC count < 6 x 10^9/L and at least 2 x 10^9/L lower than before, weekly WBC count monitoring should be done and the oral cyclophosphamide dose from Table 8 reduced by 25 mg (or 50 mg if 25 mg dose units are not available) if the WBC count continues to decrease.

The last IV cyclophosphamide dose will be given at the Week 13 visit. The last oral cyclophosphamide dose will be given the day prior to Week 15.

12.7.2. Azathioprine and Mycophenolate Dosing

- Oral azathioprine will be started at Week 15 for those patients in the IV and oral cyclophosphamide strata and continue through the end of the study.
- The azathioprine dose will be started at 1 mg/kg/day for the first week, and increased to a target dose of 2 mg/kg/day by 2 weeks.
- Doses will be rounded down to the nearest 25 mg increment, e.g., a patient weighing 60 kg will have a target dose of 100 mg azathioprine per day.
- Testing for thiopurine S-methyltransferase polymorphism and dose adjustment should be implemented according to the local institution policy.
- Azathioprine will not be initiated if the WBC count is $< 2 \times 10^9$/L. In this case, treatment initiation will be delayed until the WBC has increased to above 3×10^9/L.
- In case azathioprine is not tolerated due to gastrointestinal intolerance/bleeding, hematologic abnormalities, hepatotoxicity, or other major side effects, mycophenolate mofetil (target dose of 2 g/day) may be used instead. In this case, the starting dose is 500 mg twice daily for the first week, and increased to 1000 mg twice daily in the second week according to patient tolerance. If mycophenolate mofetil is not tolerated or not available, enteric coated mycophenolate sodium may be given at a target dose of 1440 mg/day. The starting dose is 720 mg/day.

12.8. Rituximab Dosing

- The following dosing regimen of rituximab will be given:
  - 375 mg/m^2 given as an IV infusion on Study Day 1, and Weeks 1, 2, and 3.
- It is recommended to pre-medicate before each infusion with acetaminophen and an anti-histamine. For the first rituximab infusion, 100 mg methylprednisolone, or equivalent is given. Glucocorticoid pre-medication for the second, third, and fourth rituximab infusions is allowed.
- For the first IV infusion, it is recommended to initiate the infusion at a rate of 50 mg/hr. In the absence of infusion toxicity, it is recommended to increase the infusion rate by 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.
- For subsequent infusions, it is recommended to initiate the infusion at a rate of 100 mg/hr. In the absence of infusion toxicity, it is recommended to increase the rate by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr.
- The start and end times of the IV rituximab infusions need to be recorded.

12.9. Adverse Events Reported with Cyclophosphamide

Carcinogenesis

Increased risk of cancer; most frequently, these have been urinary bladder, myeloproliferative, or lymphoproliferative malignancies.

Cardiac System

Congestive heart failure, hemorrhagic myocarditis, hemopericardium, myocardial necrosis, pericarditis

Digestive System

Nausea, vomiting, anorexia, abdominal discomfort, abdominal pain, diarrhea, hemorrhagic colitis, oral mucosal ulceration, jaundice

Hematopoietic System

Leukopenia, neutropenia, fever in neutropenic patients, thrombocytopenia, anemia

Infections

Viral, bacterial, fungal, protozoan, or helminthic infections

Reproductive System

Cyclophosphamide interferes with oogenesis and spermatogenesis. It may cause sterility in both sexes. Men treated with cyclophosphamide may develop oligospermia, azoospermia, impaired sexual potency or libido, and testicular atrophy

Respiratory System

Interstitial pneumonitis, interstitial pulmonary fibrosis

Skin and Its Structures

Alopecia, skin rash, skin pigmentation, nail disorders, Stevens-Johnson syndrome, toxic epidermal necrolysis

Urinary System

Cystitis, urinary bladder fibrosis, hemorrhagic ureteritis, renal tubular necrosis

Other

Anaphylactic reactions; death associated with anaphylactic reactions, SIADH (syndrome of inappropriate ADH secretion), malaise, asthenia

12.10. Adverse Events Reported with Glucocorticoid Use

Allergic Reactions

Anaphylactoid or hypersensitivity reactions, anaphylaxis, angioedema

Cardiovascular System

Bradycardia, cardiac arrest, cardiac arrhythmias, cardiac enlargement, circulatory collapse, congestive heart failure, ECG changes caused by potassium deficiency, edema, fat embolism, hypertension or aggravation of hypertension, myocardial rupture following recent myocardial infarction, necrotizing angiitis, pulmonary edema, syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis

Dermatologic

Acne, acneiform eruptions, allergic dermatitis, alopecia, angioedema, angioneurotic edema, atrophy and thinning of skin, dry scaly skin, ecchymoses and petechiae (bruising), erythema, facial edema, hirsutism, impaired wound healing, increased sweating, Karposi's sarcoma, lupus erythematosus-like lesions, perineal irritation, purpura, rash, striae, subcutaneous fat atrophy,

suppression of reactions to skin tests, striae, telangiectasis, thin fragile skin, thinning scalp hair, urticaria

Endocrine

Adrenal insufficiency-typically caused by high potency glucocorticoids with long duration of action (associated symptoms include; arthralgias, buffalo hump, dizziness, life-threatening hypotension, nausea, severe tiredness or weakness), amenorrhea, postmenopausal bleeding or other menstrual irregularities, decreased carbohydrate and glucose tolerance, development of cushingoid state, diabetes mellitus (new onset or manifestations of latent), glycosuria, hyperglycemia, hypertrichosis, hyperthyroidism, hypothyroidism, increased requirements for insulin or oral hypoglycemic agents in diabetics, lipids abnormal, moon face, negative nitrogen balance caused by protein catabolism, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery or illness)

Fluid and Electrolyte Disturbances

Congestive heart failure in susceptible patients, fluid retention, hypokalemia, hypokalemic alkalosis, metabolic alkalosis, hypotension or shock-like reaction, potassium loss, sodium retention with resulting edema.

Gastrointestinal

Abdominal distention, abdominal pain, anorexia which may result in weight loss, constipation, diarrhea, elevation in serum liver enzyme levels (usually reversible upon discontinuation), gastric irritation, hepatomegaly, increased appetite and weight gain, nausea, oropharyngeal candidiasis, pancreatitis, peptic ulcer with possible perforation and hemorrhage, perforation of the small and large intestine (particularly in patients with inflammatory bowel disease), ulcerative esophagitis, vomiting

Hematologic

Anemia, neutropenia (including febrile neutropenia)

Metabolic

Negative nitrogen balance due to protein catabolism

Musculoskeletal

Arthralgias, aseptic necrosis of femoral and humeral heads, increase risk of fracture, loss of muscle mass, muscle weakness, myalgias, osteopenia, osteoporosis, pathologic fracture of long bones, steroid myopathy, tendon rupture (particularly of the Achilles tendon), vertebral compression fractures

Neurological/Psychiatric

Amnesia, anxiety, benign intracranial hypertension, convulsions, delirium, dementia (characterized by deficits in memory retention, attention, concentration, mental speed and efficiency, and occupational performance), depression, dizziness, EEG abnormalities, emotional instability and irritability, euphoria, hallucinations, headache, impaired cognition, incidence of severe psychiatric symptoms, increased intracranial pressure with papilledema (pseudotumor cerebri) usually following discontinuation of treatment, increased motor activity, insomnia, ischemic neuropathy, long-term memory loss, mania, mood swings, neuritis, neuropathy,

paresthesia, personality changes, psychiatric disorders including steroid psychoses or aggravation of pre-existing psychiatric conditions, restlessness, schizophrenia, verbal memory loss, vertigo, withdrawn behavior

Ophthalmic

Blurred vision, cataracts (including posterior subcapsular cataracts), central serous chorioretinopathy, establishment of secondary bacterial, fungal and viral infections, exophthalmos, glaucoma, increased intraocular pressure, optic nerve damage, papilledema

Other

Abnormal fat deposits, aggravation/masking of infections, decreased resistance to infection, hiccups, immunosuppresion, increased or decreased motility and number of spermatozoa, malaise, insomnia, moon face, pyrexia

12.11. Adverse Events Reported with Rituximab Use

The following adverse events were reported at an incidence of ≥ 10% in patients receiving rituximab in patients with GPA or MPA: nausea, diarrhea, headache, muscle spasms, anemia, peripheral edema, insomnia, arthralgia, cough, fatigue, increased ALT, hypertension, epistaxis, dyspnea, leukopenia, and rash. Infusion reactions included cytokine release syndrome, flushing, throat irritation, and tremor. Progressive multifocal leukoencephalopathy resulting in death has been reported. Hepatitis B reactivation with fulminant hepatitis, sometimes fatal, has been reported. Other infections including upper respiratory tract infections, urinary tract infections, and herpes zoster have been reported. Cardiac arrhythmias and angina can occur and can be life-threatening. Bowel obstruction and perforation have been observed. Hypogammaglobulinemia was also reported.

12.12. Adverse Events Reported with Azathioprine Use

Azathioprine use has been associated with an increased risk of certain types of cancers including skin cancer and lymphoma. Azathioprine may also cause serious (rarely fatal) blood disorders (decreased bone marrow function leading to anemia, low WBC and platelet count). Its use is also associated with increased risk of infection. Gastrointestinal side effects, including nausea and vomiting, diarrhea, fever, malaise, myalgias, pancreatitis, hepatotoxicity, and other side effects including hypersensitivity reactions, hepatic veno-occlusive disease, skin rashes, alopecia, fever, arthralgias, steatorrhea, negative nitrogen balance, reversible pneumonitis, and Sweet's syndrome (acute febrile neutrophilic dermatosis) have been reported.

12.13. Adverse Events Reported with Mycophenolate Mofetil Use

Immunosuppression leading to increased risk for infection, allergic reactions, increased risk of developing lymphomas and other malignancies, particularly skin malignancies, progressive multifocal encephalopathy, neutropenia, pure red cell aplasia, gastrointestinal bleeding and perforations, diarrhea, leukopenia, sepsis, vomiting, and pulmonary edema have been reported.

12.14. Benefit-Risk Assessment

12.14.1. Nonclinical Evaluation

Single-dose and repeat-dose toxicology, safety pharmacology, and genotoxicity studies have been conducted with CCX168. General toxicity studies of up to 26-week duration in rats and 44-week duration in cynomolgus monkeys have been conducted at CCX168 doses up to 200 and 45 mg/kg/day, respectively, significantly higher than the highest human daily dose of 30 mg b.i.d. being tested in patients with AAV and other indications.

Based on in vivo safety pharmacology studies, which included neuropharmacology, pulmonary, and renal safety studies in rats, and a cardiovascular safety study in conscious telemetered cynomolgus monkeys, there was no evidence of toxicity of CCX168. No evidence of electrocardiographic alterations was seen in the monkey 4-week, 20-week, or 44-week studies or in in vitro cardiovascular safety studies (IC_{50} values for hERG inhibition was determined to be >2.3 μM for CCX168 and >3.0 μM for its metabolite CCX168-M1, the limit of solubility for both compounds). A safety margin for CCX168 and metabolite CCX168-M1 of at least 3,500-fold relative to expected steady state human unbound maximum plasma is projected.

Protein binding, red blood cell partitioning, hepatocyte metabolism, cytochrome P450 inhibition and induction, Caco-2 permeability and genotoxicity studies, including in vitro bacterial mutagenicity (Ames test) and in vitro mammalian cell mutagenicity (mouse lymphoma) studies, in vivo bone marrow rat micronucleus and in silico mutagenicity evaluation of starting materials, intermediates and chemical impurities utilized and formed during the synthesis of CCX168) were also conducted and did not identify any safety concerns or significant potential for drug-drug interactions. In an acute toxicity study, single doses of CCX168 up to 100 mg/kg in rats produced no remarkable effects. No effects on IgG and IgM antibody production in rats or monkeys were noted following immunization with keyhole limpet hemocyanin (KLH) antigen. Immunophenotypic analyses performed in the 44-week monkey study did not reveal any CCX168-related effects. No phototoxicity potential was observed for CCX168 in the in vitro 3T3 assay.

CCX168 was well tolerated in studies up to 26 and 44 weeks in rats and cynomolgus monkeys, respectively, up to the highest doses tested (200 mg/kg/day in rats and 45 mg/kg/day in cynomolgus monkeys). There were no significant toxicological findings of concern in these chronic studies or the preceding sub-chronic studies. Metabolite CCX168-M1 (which has been identified in humans) was present in samples collected in the rat 13- and 26-week and the monkey 20- and 44-week studies at relatively high levels indicating that this metabolite has been qualified.

No CCX168-related effects were observed upon pregnancy or embryo-fetal development in studies at doses up to 1000 mg/kg and 200 mg/kg in hamsters and rabbits, respectively. No evidence of histopathological alterations to the male or female reproductive system was seen in rats or monkeys in toxicity studies.

In summary, no safety findings in toxicology studies in rats, cynomolgus monkeys, rabbits and hamsters have been observed that would preclude dosing to humans at the 30 mg b.i.d. dose in this clinical trial.

12.14.2. Clinical Evaluation

Four Phase 1 clinical trials have been conducted with CCX168 in 102 healthy volunteers. CCX168 doses up to 100 mg twice daily for up to 7 days have been tested in these studies. CCX168 generally has been well tolerated by subjects in these trials. No serious adverse events have been observed in the Phase 1 trials.

The most frequently reported adverse events in subjects receiving CCX168 in Phase 1 clinical studies were headache (14.6% vs. 14.3% for placebo), diarrhea (6.7% vs. 7.1% for placebo), dizziness (4.5% vs. 0% for placebo), upper respiratory tract infection (4.5% vs. 0% for placebo), nausea (3.4% vs. 0% for placebo), oropharyngeal pain (3.4% vs. 7.1% for placebo), and WBC count decreased (3.4% vs. 0% for placebo). All other adverse events occurred at an incidence less than 3%.

Two Phase 2 clinical trials (CL002_168 and CL003_168) have been conducted in 109 patients with AAV; 73 of these were randomized to receive CCX168 in these trials. A total of 60 patients received 30 mg CCX168 twice daily and 13 patients received 10 mg CCX168 twice daily for 12 weeks.

No deaths were observed in the Phase 2 AAV studies. As anticipated, since all patients received rituximab or cyclophosphamide, and most also received glucocorticoids, serious infections were the most common serious adverse event. The incidence of serious infections was similar in patients receiving CCX168 compared to the control group. Vasculitis or renal vasculitis (worsening) was also reported at a similar incidence in the two groups.

The most commonly reported treatment-emergent adverse events in patients with AAV receiving CCX168 in studies CL002_168 and CL003_168 combined were hypertension (17.8% vs. 16.7% in the control group), nausea (17.8% vs. 19.4% in the control group), vomiting (13.7% vs. 0.0% in the control group), headache (11.0% vs. 11.1% in the control group), nasopharyngitis (11.0% vs. 8.3% in the control group), peripheral edema (9.6% vs. 11.1% in the control group), arthralgia (8.2% vs. 2.8% in the control group), and diarrhea (8.2% vs. 2.8% in the control group). Grade 3 lymphopenia has been observed in more patients receiving CCX168 plus cyclophosphamide or rituximab compared to cyclophosphamide or rituximab alone. This lymphopenia occurred within the first 2 weeks of treatment, and was not progressive with continued treatment.

CCX168 did not show evidence of pro-arrhythmic potential in an intensive ECG study (CL007_168).

Caution should be exercised when CCX168 is given with potent CYP3A4 inhibitors such as itraconazole, since the CCX168 plasma exposure may increase.

CCX168 has shown evidence of efficacy in Phase 2 study CL002_168 based on BVAS, quality of life measurements, renal response, urinary albuminuria, and urinary MCP-1:creatinine results. This efficacy was demonstrated across a number of relevant immunological and clinical subgroups, i.e., patients with MPO ANCA-positive disease vs. PR3 ANCA-positive disease, newly diagnosed vs. relapsing patients, patients on cyclophosphamide vs. those on rituximab. CCX168 was able to safely replace the oral prednisone use, with the same or greater efficacy based on results from this study.

It is of note that CCX168 as a selective C5aR blocker does not appear to affect the formation of C5b and the membrane attack complex (MAC) or terminal complement complex (TCC) which is needed to protect against *Neisseria* infections. Nevertheless, all local and national vaccination protocols should be followed and investigators should be vigilant in reporting all infections occurring during clinical trials and should attempt to identify the organisms involved in all infections.

Based on DMC review of unblinded safety data in the present study, the Investigator Brochure has been updated to state that general gastrointestinal adverse events (e.g. nausea, diarrhea) observed in Phase 2 studies have also been observed in the ongoing Phase 3 study at approximately the same frequency and severity. The Investigator Brochure has also been updated to state that adverse events of urticaria with angioedema, and adverse events of hepatic transaminase elevation with or without elevation of bilirubin have been observed in the ongoing Phase 3 study; suspension of study drug was associated with improvement of the observed events. The frequency of monitoring hepatic transaminases, alkaline phosphatase and bilirubin has been increased to monthly.

Based on DMC review of unblinded safety data from all completed and ongoing studies of CCX168, the frequency of monitoring of hematology has been increased to monthly and rules for pausing administration of blinded study drug have been modified. [redacted] In all reported cases, subjects were receiving multiple immunosuppressants (e.g. cyclophosphamide, rituximab, mycophenolate mofetil, others) in addition to study medication. Therefore a causal relationship with study medication is not clear.

12.14.3. Pediatric Testing

There is currently no approved therapy for ANCA-associated vasculitis in juveniles.

CCX168 appears to be generally well tolerated and safe in adults with ANCA-associated vasculitis who have been included in clinical trials. There are no data currently available on the efficacy and safety of CCX168 in patients younger than 18 years of age. However, CCX168 has been well tolerated at supra-therapeutic doses in young animals (rats and cynomolgus monkeys) in long term toxicology studies, and at doses up to 100 mg twice daily in adults. Therefore, it is reasonable to postulate that CCX168 may be well tolerated in younger patients.

The current therapies that are used to treat ANCA-associated vasculitis in children have significant safety concerns. Glucocorticoids increase the risk of infection, new onset diabetes and hypertension, acne and Cushingoid changes, psychiatric disorders, glaucoma, cataracts, and peptic ulceration. It may negatively impact growth, immunity, and adrenal function. Cyclophosphamide use leads to a high incidence of infertility and increases the risk of developing cancer in later years. Rituximab use is associated with increased risk of infection, progressive multifocal leukoencephalopathy, and hypogammaglobulinemia with chronic use. Other immunosuppressive drugs also increase the risk of infection.

CCX168 is a highly selective inhibitor of the terminal effector of the complement cascade, C5a, by blocking the binding of C5a to its receptor, C5aR. It does not appear to block other parts of the complement pathway, e.g., formation of the terminal complement complex, C5b-9, C3a, C3b,

or other parts of the immune system. It is not known at this time whether the efficacy and safety profile of CCX168 would be different in children compared to adults. However, it is anticipated that the mechanism of action of CCX168 would also apply to ANCA-associated vasculitis in children. There is also no evidence from the animal toxicology studies in young growing animals that CCX168 affects growth and organ maturation.

CCX168 is orally administered, which makes it more suitable for use in children compared to drugs such as rituximab that need to be given intravenously.

CCX168 has shown evidence of efficacy in adults in Phase 2 studies in adults with AAV (CL002_168 and CL003_168) based on the Birmingham Vasculitis Activity Score (BVAS), quality of life, and other markers such as albuminuria.

The PK profile of CCX168 in children is not known. However, since CCX168 is cleared from the body primarily through hepatic metabolism mediated by CYP3A4, which is known to mature in children well before the age of 12 (Johnson et al, 2006), it can be scientifically justified to adjust the CCX168 dose for 12-17 year old patients based on body weight. This methodology is proposed in this clinical trial. In a recent study of 126 unique products with pediatric studies by FDA scientists (Momper et al, 2013), allometric scaling using body weight was found to predict adolescent drug clearance well, with an overall mean absolute percentage error of 17.0%. By taking this approach, a 40 kg adolescent would need a 2/3 dose relative to a 70 kg adult to produce similar drug exposure. In this study (CL010_168), a conservative approach is followed with an adolescent <40 kg, with a starting dose that is 1/3 of the adult dose (i.e., 10 mg instead of 30 mg CCX168 b.i.d.), and the dose is further adjusted based on the Day 1 CCX168 plasma concentrations. Linear pharmacokinetics is assumed for this approach based on the approximate dose linearity in AUC observed between 10 mg and 30 mg in adult AAV patients in Study CL003_168 (153 ± 86.7 and 525 ± 276 ng•hr/mL for 10 mg and 30 mg CCX168, respectively).

The level of discomfort and the risk threshold for adolescents participation in this study have been carefully considered, and measures taken to monitor patients closely during the study:

- Based on all available data, there is no evidence of a negative effect of CCX168 on growth and maturation of all relevant organ systems.
- All patients will be monitored closely over the course of the study by the study center personnel, study monitors, as well as an external data monitoring committee for any untoward effects.
- The protocol provides clear guidance regarding management of patients with severe AAV, those experiencing disease relapses, as well as those who have early resistant disease during the trial (see Section 12.6.2.3).
- The protocol provides stopping rules for significant laboratory abnormalities, such as hepatic enzyme elevations, WBC, neutrophil, and lymphocyte count decreases, and CPK increases (Section 7.1.6 and Section 7.2.4.6).
- Patients will be seen frequently over the course of the study, with a particularly high frequency in the first 4 weeks of treatment.
- Adolescents will be kept for at least 6 hours at the clinic, and in severe cases, overnight. During this time, plasma samples will be taken to measure the levels of CCX168, and to adjust the dose of CCX168 if the plasma levels are too high or low (Section 3.3).

In summary, the potential benefits of testing CCX168 in adolescent patients with AAV in this study, i.e., no currently approved medications for AAV in juveniles, complement biology involvement in AAV, potential safety and efficacy advantages compared to other non-approved therapies such as glucocorticoids, orally administered selective inhibition of C5aR, outweigh the potential risk, i.e., lack of data with CCX168 in adolescents.

Summary Benefit-Risk Statement

Based on the nonclinical and clinical study results, the potential benefits of testing CCX168 in subjects with AAV outweigh the potential risks.

Subjects participating in clinical trials must be closely monitored for any adverse events, and laboratory, physical examination, vital signs, or ECG abnormalities. Hepatic enzyme levels, CPK levels, WBC, neutrophil, and lymphocyte counts must be monitored over the course of the studies.

As with all investigational compounds, the potential exists for unanticipated serious or life-threatening toxicities or adverse events not predicted by the animal toxicology or clinical studies conducted to date. Investigators should exercise vigilance in the monitoring of subjects involved in this clinical trial with CCX168.

For additional details, please refer to the current version of the Investigator's Brochure.