PROTOCOL

Protocol Amendment 4.0

TITLE PAGE

Study Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Evaluate the Safety and Efficacy of CCX168 in Subjects with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis on Background Cyclophosphamide or Rituximab Treatment

Protocol Number: CL002_168

Investigational Product: Complement 5a Receptor Antagonist CCX168

Indication: ANCA-Associated Vasculitis

Sponsor: ChemoCentryx, Inc.

Development Phase: 2

EUDRACT number 2011-001222-15

Sponsor's Responsible Medical Officer: PPD
ChemoCentryx, Inc.
PPD

Sponsor Signatory: PPD

Approval Date: **31 March 2011—FINAL**
23 April 2012—Protocol Amendment 1.0
14 March 2013—Protocol Amendment 2.0
30 May 2014—Protocol Amendment 3.0
18 September 2015—Protocol Amendment 4.0

INVESTIGATOR SIGNATORY PAGE

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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 subjects, 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 Clinical 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

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Medical Officer

PPD

Chief Medical Officer

ChemoCentryx, Inc.

PPD

Clinical Operations Manager

PPD

Clinical Consultant

ChemoCentryx, Inc.

PPD

SPONSOR SIGNATURE FOR APPROVAL

Protocol Number: CL002_168

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PPD

Chief Medical Officer

25 SEP 2015

Date

PROTOCOL AMENDMENT 4.0: SUMMARY OF CHANGES

1. The statistical methodology section in the Synopsis and section 7.13.3 was revised to indicate that the difference in proportions of subjects achieving the categorical endpoints will be used instead of the odds ratio. The rationale for this change is to follow the precedence set by a prior clinical trial comparing rituximab with cyclophosphamide in AAV (Stone et al, 2010). A mixed model for repeated measures (MMRM) analysis for continuous variables was also added.
2. The Study Schema was corrected to indicate that the Step 3 enrollment target was 36 subjects, not 180.
3. The Synopsis, Time and Events table, and sections 1.2.3, 1.3, 5.9, 6.14, and 7.2.3 were revised to consolidate previous country-specific amendments.
4. Addition of a stopping criterion for CCX168/placebo dosing to Section 7.2.3 of the protocol regarding WBC and neutrophil counts: If a subject develops grade two or worse leukopenia (WBC $< 3 \times 10^9$/L) OR an absolute neutrophil count $< 1 \times 10^9$/L, dosing with CCX168 or placebo must be ceased in this subject. Study drug may be resumed only if WBC and absolute neutrophil count both exceed the lower limit of the respective normal range, the Investigator deems resumption to be appropriate, and the WBC and ANC are monitored closely thereafter. This recommendation was based on findings of leukopenia/neutropenia in two cases in another study in patients with ANCA-associated vasculitis (study CL003_168).

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STUDY SYNOPSIS

Name of Sponsor	**Name of Active Ingredient**	**Study number:**
ChemoCentryx, Inc.	CCX168	CL002_168

Title

A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Evaluate the Safety and Efficacy of CCX168 in Subjects with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis on Background Cyclophosphamide or Rituximab Treatment

Investigators

Several

Study centers

Multi-center

Study period	**Phase of development**
60 months	Phase 2

Aim

The aim of this trial is to optimize the treatment to induce remission for patients with anti-neutrophil cytoplasmic antibody vasculitis (AAV). The intent is to reduce the toxicity of induction therapy by reducing the overall exposure to or eliminating entirely the use of systemic corticosteroids during the induction period with an inhibitor of the complement C5a receptor plus cyclophosphamide or rituximab.

Objectives

The primary safety objective of this study is to evaluate the safety and tolerability of CCX168 in subjects with AAV on background cyclophosphamide or rituximab treatment.

The primary efficacy objective is to evaluate the efficacy of CCX168 based on the Birmingham Vasculitis Activity Score (BVAS) version 3.

The secondary objectives of this study include:

1. Evaluation of the efficacy of CCX168 compared to standard of care (SOC) based on changes in renal disease activity parameters:
   a. eGFR (MDRD serum creatinine equation);
   b. Hematuria (central laboratory microscopic count of urinary RBCs); and
   c. Albuminuria (first morning urinary albumin:creatinine ratio);
2. Assessment of changes in renal inflammatory activity based on urinary monocyte chemoattractant protein-1 (MCP-1):creatinine ratio and serum C-reactive protein concentration with CCX168 compared to SOC;

3. Assessment of the feasibility of reducing or eliminating the use of corticosteroids in the treatment of subjects with ANCA-associated vasculitis (AAV) without the need for rescue corticosteroid measures with CCX168 compared to SOC;
4. Assessment of health-related quality-of-life changes based on Short Form-36 version 2 (SF-36v2) and EuroQOL-5D-5L (EQ-5D-5L) with CCX168 compared to SOC;
5. Assessment of changes in Vasculitis Damage Index (VDI) with CCX168 compared to SOC;
6. Assessment of changes in ANCA (anti-PR3 and anti-MPO) with CCX168 compared to SOC;
7. Assessment of changes in pharmacodynamics markers in plasma and urine with CCX168 compared to SOC;
8. Evaluation of the pharmacokinetic profile of CCX168 in subjects with AAV.

Methodology

AAV standard therapy includes cyclophosphamide or rituximab and oral corticosteroids, tapered over a period of time. Severe disease warrants addition of IV corticosteroids and/or plasma exchange. Based on compelling results from preclinical studies in a mouse model of ANCA-associated renal vasculitis, CCX168 has the potential to be a corticosteroid sparing or corticosteroid replacement therapy for this disease. Hence, the clinical hypothesis of the trial is to test the feasibility of using CCX168 as a corticosteroid sparing or replacement therapy during induction of remission. This hypothesis will be tested in a three-step manner in this randomized, double-blind, placebo-controlled, Phase 2 clinical trial in up to approximately 60 subjects with new or relapsed AAV. An external data monitoring committee (DMC) will review safety data, including rescue IV or oral corticosteroid use over the course of the study and advise the Sponsor regarding progression from each step to the next in the study. Steps 1 and 2 of the study have been completed.

<u>STEP 1</u>

In Step 1 of the trial, up to approximately 12 subjects will be stratified to one of two strata, either newly diagnosed AARV or relapsed AARV, and then randomized to CCX168 or placebo (in a 2:1 ratio). A two-thirds reduced dose of oral corticosteroids will be given to subjects randomized to CCX168 and a full dose of oral corticosteroids to subjects randomized to placebo. All 12 subjects will receive IV cyclophosphamide treatment, which is part of standard therapy for AARV. If necessary, rescue IV methylprednisolone or oral rescue steroids after Day 1 should be given to subjects with worsening disease.

<u>STEP 2</u>

Step 2 will be opened for enrollment if both of the following criteria are met:

1. Not more than 1 SUSAR most likely related to CCX168, as assessed by the DMC, is observed in subjects receiving CCX168 in Step 1;
2. AARV disease activity is controlled in the majority of subjects (>50%) receiving CCX168 in Step 1, without the need for IV or oral rescue corticosteroid therapy, as assessed by the

DMC.

In Step 2 of the trial, up to approximately 12 subjects will be stratified to one of two strata, either newly diagnosed AARV or relapsed AARV, and then randomized to CCX168 or placebo (in a 2:1 ratio). Oral corticosteroids will not be given to subjects randomized to CCX168, but a full dose of oral corticosteroids will be given to subjects randomized to placebo. All 12 subjects will receive IV cyclophosphamide treatment. If necessary, rescue IV or oral methylprednisolone should be given to subjects with worsening disease.

STEP 3

In Step 3, approximately 36 subjects will be stratified prior to randomization based on the following stratification factors:

1. Either newly diagnosed AAV or relapsed AAV;
2. Either MPO or PR3 ANCA positivity;
3. Will receive either cyclophosphamide or rituximab as part of standard of care treatment.

Following stratification, subjects will be randomized 1:1:1 to one of three groups:

Group A: CCX168 plus cyclophosphamide/rituximab plus no oral corticosteroids;

Group B: Placebo plus cyclophosphamide/rituximab plus a full starting dose of oral corticosteroids;

Group C: CCX168 plus cyclophosphamide/rituximab plus a two-thirds reduced starting dose of oral corticosteroids;

If necessary, rescue IV methylprednisolone or oral rescue steroids should be given to subjects with worsening disease.

Step 3 will be opened for enrollment if both of the following criteria are met:

1. Not more than 1 SUSAR most likely related to CCX168, as assessed by the DMC, is observed in subjects receiving CCX168 in Step 2;
2. AAV disease activity is controlled in the majority of subjects (>50%) receiving CCX168 in Step 2, without the need for IV or oral rescue corticosteroid therapy.

The CCX168/placebo dosing period for all three steps of the study is 84 days, followed by an 84-day follow-up period.

In order to protect the blinding, a double-dummy design will be utilized:

STEP 1

In Step 1, the study drug and other medication for renal vasculitis will be taken as follows by study subjects:

- Group A (30 mg CCX168 twice daily):
  - Three 10-mg CCX168 capsules in the morning and 3 capsules in the evening,

approximately 12 hours after the morning dose, daily for 84 days.

- Prednisone 20 mg orally per day if the subject's body weight is ≥55 kg or 15 mg per day if the subject's body weight is <55 kg, starting on Day 1, with tapering according to the protocol-specified schedule.
- Prednisone matching placebo capsules equivalent to 40 mg orally per day if the subject's body weight is ≥55 kg or 30 mg per day if the subject's body weight is <55 kg, starting on Day 1, with tapering according to a protocol-specified schedule.
- Cyclophosphamide IV will be given on Day 1, and also on Days 15, 29, and 57; doses on Days 85, 113, 141, and 169 will be given at the discretion of the Principal Investigator.
- Rescue IV methylprednisolone or oral corticosteroids should be given to subjects with worsening disease.

- Group B (Placebo twice daily):
  - Three placebo CCX168 capsules in the morning and 3 capsules in the evening, approximately 12 hours after the morning dose, daily for 84 days.
  - Prednisone 60 mg orally per day if the subject's body weight is ≥55 kg or 45 mg per day if the subject's body weight is <55 kg, starting on Day 1 with tapering according to a protocol-specified schedule.
  - Cyclophosphamide IV will be given on Day 1 and also on Days 15, 29, and 57; doses on Days 85, 113, 141, and 169 will be given at the discretion of the Principal Investigator.
  - Rescue IV methylprednisolone or oral corticosteroids should be given to subjects with worsening disease.

<u>STEP 2</u>

In Step 2, study drug and other medication for vasculitis will be taken as follows by study subjects:

- Group A (30 mg CCX168 twice daily):
  - Three 10-mg CCX168 capsules in the morning and 3 in the evening, approximately 12 hours after the morning dose, daily for 84 days.
  - Prednisone matching placebo capsules equivalent to 60 mg orally per day if the subject's body weight is ≥55 kg or 45 mg per day if the subject's body weight is <55 kg, starting on Day 1 with tapering according to a protocol-specified schedule.
  - Cyclophosphamide IV will be given on Day 1 and also on Days 15, 29, and 57; doses on Days 85, 113, 141, and 169 will be given at the discretion of the Principal Investigator.

- Rescue IV methylprednisolone or oral corticosteroids should be given to subjects with worsening disease.

- Group B (Placebo twice daily):
  - Three placebo CCX168 capsules in the morning and 3 in the evening, approximately 12 hours after the morning dose, daily for 84 days.
  - Prednisone 60 mg orally per day if the subject's body weight is ≥55 kg or 45 mg per day if the subject's body weight is <55 kg, starting on Day 1 with tapering according to a protocol-specified schedule.
  - Cyclophosphamide IV will be given on Day 1 and also on Days 15, 29, and 57; doses on Days 85, 113, 141, and 169 will be given at the discretion of the Principal Investigator.
  - Rescue IV methylprednisolone or oral corticosteroids should be given according to subjects with worsening disease.

STEP 3

In Step 3, study drug and other medication for vasculitis will be taken as follows by study subjects:

- Group A (30 mg CCX168 twice daily with no corticosteroids):
  - Three 10-mg CCX168 capsules in the morning and 3 in the evening, approximately 12 hours after the morning dose, daily for 84 days.
  - Prednisone matching placebo capsules equivalent to 60 mg orally per day if the subject's body weight is ≥55 kg or 45 mg per day if the subject's body weight is <55 kg, starting on Day 1 with tapering according to a protocol-specified schedule.
  - If in the cyclophosphamide stratum, cyclophosphamide IV will be given on Day 1 and also on Days 15, 29, 57, and 85; starting on Day 99 through Day 168, all subjects will receive oral azathioprine at a target dose of 2 mg/kg/day.
  - If in the rituximab stratum, rituximab IV will be given on Days 1, 8, 15, and 22 (375 mg/m^2 at each timepoint).
  - Rescue IV methylprednisolone or oral steroids should be given to subjects with worsening disease.
- Group B (Placebo twice daily):
  - Three placebo CCX168 capsules in the morning and 3 in the evening, approximately 12 hours after the morning dose, daily for 84 days.
  - Prednisone 60 mg orally per day if the subject's body weight is ≥55 kg or 45 mg per day if the subject's body weight is <55 kg, starting on Day 1 with tapering according

to the protocol-specified schedule.

  - If in the cyclophosphamide stratum, cyclophosphamide IV will be given on Day 1 and also on Days 15, 29, 57, and 85; starting on Day 99 through Day 168, all subjects will receive oral azathioprine at a target dose of 2 mg/kg/day.
  - If in the rituximab stratum, rituximab IV will be given on Days 1, 8, 15, and 22 (375 mg/m^2 at each timepoint).
  - Rescue IV methylprednisolone or oral steroids should be given to subjects with worsening disease.

- Group C (30 mg CCX168 twice daily with reduced corticosteroids):
  - Three 10-mg CCX168 capsules in the morning and 3 capsules in the evening, approximately 12 hours after the morning dose, daily for 84 days.
  - Prednisone 20 mg orally per day if the subject's body weight is ≥55 kg or 15 mg per day if the subject's body weight is <55 kg, starting on Day 1, with tapering according to the protocol-specified schedule.
  - Prednisone matching placebo capsules equivalent to 40 mg orally per day if the subject's body weight is ≥55 kg or 30 mg per day if the subject's body weight is <55 kg, starting on Day 1, with tapering according to a protocol-specified schedule.
  - If in the cyclophosphamide stratum, cyclophosphamide IV will be given on Day 1, and also on Days 15, 29, 57, and 85; starting on Day 99 through Day 168, all subjects will receive oral azathioprine at a target dose of 2 mg/kg/day.
  - If in the rituximab stratum, rituximab IV will be given on Days 1, 8, 15, and 22 (375 mg/m^2 at each timepoint).
  - Rescue IV methylprednisolone or oral corticosteroids should be given to subjects with worsening disease.

Following the 84-day dosing period, there will be an 84-day follow-up period. All subjects will visit the study center during the screening period, and on Days 1, 2, 8, 15, 22, 29, 43, 57, 71, 85, 99, 113, 141, and 169. Subjects will not take study medication in the morning of the days of visits to the study center, and will be instructed to take the medication while at the study center. For the other study days, study medication will be taken at home in the morning within 1 hour after breakfast and in the evening within 1 hour after dinner.

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 demographics, medical history, medication history, physical examination and vital signs, serum chemistry, hematology, urinalysis (including hematuria, proteinuria [ACR]), ECG, chest X rays, viral screening, serology and complement measurements (if not done within the previous 12 months), estimated glomerular filtration rate (eGFR) assessment, ANCA measurement (indirect immunofluorescence test for P-ANCA and C-ANCA, as well as ELISA tests for anti-PR3 and anti-MPO), renal biopsy (if necessary for study eligibility), and BVAS assessment. To expedite

the screening process, blood and urine tests will 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. Eligible subjects must be ANCA-positive and must have at least one "major" item, or at least 3 non-major items, or at least two renal items on the BVAS version 3.

Eligible subjects will visit the study center on Day 1, after an overnight fast of at least 8 hours, for physical examination and vital signs, serum chemistry, hematology, urinalysis (including hematuria, proteinuria (ACR), and MCP-1:creatinine ratio assessment), eGFR, ANCA measurement (anti-PR3 and anti-MPO), a BVAS and VDI assessment, SF-36v2 and EQ-5D-5L assessment, hsCRP, baseline pharmacokinetics and pharmacodynamics (PK/PD) blood sample collection, and randomization. Medication will be administered (IV) and dispensed (for oral medications). The subjects will take the first dose of CCX168 or placebo, and prednisone or placebo while at the study center. The subjects will stay at the clinic for at least 6 hours after the first dose on Day 1 for safety observation and PK sample collection. A subject could be kept overnight in the hospital on Day 1, if necessary. 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 84 days. At post-Day 1 study visits, study medication will be administered according to the protocol schedule, blood and urine samples will be collected for safety and efficacy and PK/PD measurements. BVAS assessments will be made on Days 1, 29, 85, 113, and 169. VDI assessment will be made on Days 1, 85, and 169. SF-36v2 and EQ-5D-5L instruments will be completed on Days 1, 29, 85, and 169 in Step 3. Physical examinations, body system reviews, and vital sign assessments will be performed throughout the study. Concomitant medication and adverse event assessments will be made at every study visit.

Subjects will be discharged from the study when all the Study Day 169 visit procedures have been completed. The subject's condition will be evaluated by the Investigator at the end of the clinical trial (Day 169) and appropriate standard of care medical treatment will be provided to all subjects as needed.

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

Number of Subjects

Approximately 60 male or postmenopausal or surgically sterile female subjects with AAV will be randomized for this study. Subjects who drop out of the study prematurely will not be replaced. These subjects will be part of the intent-to-treat population. Subjects will not be allowed to participate in more than one Step of the study.

Main Criteria for Inclusion

1. Clinical diagnosis of granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis or renal limited vasculitis, consistent with Chapel-Hill consensus definitions (Jennette et al., 2013);
2. Male and postmenopausal (**lack of menses for** at least 2 years **without an alternative explanation**) or surgically sterile female subjects, aged at least 18 years, with new (within 4 weeks prior to screening) or relapsed AAV where treatment with cyclophosphamide or rituximab would be required; **If female under 50 years, the postmenopausal status should be confirmed by the relevant hormonal test.** Male subjects 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, and for at least the three months after study completion; Adequate contraception is defined as resulting in a failure rate of less than 1% per year; **acceptable methods include combined estrogen and progestogen (oral, intravaginal, or transdermal), or progestogen-only hormonal contraception (oral, injectable, or implantable), intra-uterine device, intrauterine hormone releasing system, bilateral tubal occlusion, vasectomized partner, or sexual abstinence;**
3. Positive indirect immunofluorescence (IIF) test for P-ANCA or C-ANCA, or positive ELISA test for anti-proteinase-3 (PR3) or anti-myeloperoxidase (MPO) at screening; If only the IIF assay is positive at screening, and none of the ELISA tests, there must be documentation in the study records of a positive ELISA assay in the past;
4. Have at least one "major" item, or at least 3 non-major items, or at least 2 renal items on the BVAS version 3;
5. Estimated glomerular filtration rate $\geq$ 20 mL per minute (MDRD);
6. Willing and able to give written Informed Consent and to comply with the requirements of the study protocol; and
7. Judged to be otherwise healthy by the Investigator, based on medical history, physical examination (including electrocardiogram [ECG]), and clinical laboratory assessments. Subjects 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 be of clinical significance, may be entered into the study.

Main Criteria for Exclusion

1. Severe disease as determined by rapidly progressive glomerulonephritis such that commencement of renal replacement therapy could be anticipated within 7 days, alveolar

hemorrhage leading to Grade 3 or higher hypoxia (i.e., decreased oxygen saturation at rest, e.g., pulse oximeter <88% or PaO_2 ≤55 mm Hg), hemoptysis, rapid-onset mononeuritis multiplex (Grade 3 or higher, leading to severe symptoms that limit self care activities of daily living or requiring an assistive device), or central nervous system involvement;

2. Any other multi-system autoimmune disease including eosinophilic granulomatosis with polyangiitis (Churg Strauss), systemic lupus erythematosus, IgA vasculitis (Henoch-Schönlein purpura), rheumatoid vasculitis, Sjögren's disease, anti-glomerular basement membrane disease, or cryoglobulinemia;
3. Medical history of coagulopathy or bleeding disorder;
4. Received cyclophosphamide within 12 weeks prior to screening; if on azathioprine, mycophenolate mofetil, or methotrexate at the time of screening, these drugs must be withdrawn prior to receiving the cyclophosphamide or rituximab dose on Day 1;
5. Received intravenous corticosteroids, >3000 mg methylprednisolone equivalent, within 12 weeks prior to screening;
6. Have been taking an oral daily dose of a corticosteroid of more than 10 mg prednisone-equivalent for more than 6 weeks continuously prior to the screening visit. If on an oral corticosteroid at a daily dose of more than 10 mg prednisone equivalent at the time of screening, the oral dose needs to be reduced to a daily dose not exceeding 10 mg prednisone-equivalent prior to Day 1;
7. 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 > 0.01×10^9/L); received anti-TNF treatment, abatacept, alemtuzumab, IVIg, belimumab, tocilizumab, or plasma exchange within 12 weeks prior to screening;
8. Symptomatic congestive heart failure requiring prescription medication, clinically evident peripheral edema of cardiac origin, poorly-controlled hypertension (systolic blood pressure >160 or diastolic blood pressure >100), history of unstable angina, myocardial infarction or stroke within 6 months prior to screening;
9. 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 cervical carcinoma *in situ* or breast carcinoma *in situ* that has been excised or resected completely and is without evidence of local recurrence or metastasis;
10. Evidence of tuberculosis based on chest X rays performed during screening as part of the BVAS assessment;
11. Positive HBV, HCV, or HIV viral screening test;
12. Any infection requiring antibiotic treatment within 4 weeks prior to screening (except for prophylactic treatment for *Pneumocystis carinii* pneumonia [PCP] or treatment for suspected infection that instead turns out to be a consequence of ANCA vasculitis, e.g., pneumonitis);

13. Received a live vaccine within 4 weeks prior to screening;
14. WBC count less than 4000/μL**,** or neutrophil count less than 2000/μL, or lymphocyte count less than 1000/μL;
15. Hemoglobin less than 9 g/dL (or 5.56 mmol/L) at screening;
16. Evidence of hepatic disease; AST, ALT, alkaline phosphatase, or bilirubin > 3 x the upper limit of normal;
17. Prothrombin time (PT) or partial thromboplastin time (PTT) above the normal reference limit;
18. Clinically significant abnormal ECG during screening, e.g., QTcF greater than 450 msec;
19. 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; and
20. History or presence of any medical condition or disease which, in the opinion of the Investigator, may place the subject at unacceptable risk for study participation.

Test Product

CCX168 will be administered via hard gelatin capsules containing 10 mg CCX168. The CCX168 capsules will be supplied to the study centers in plastic bottles containing 30 capsules.

Subjects in Group A in Steps 1 and 2, and Groups A and C in Step 3 (30 mg CCX168) will receive one kit containing 2 bottles of CCX168 capsules on Days 1, 8, 15, and 22. Subjects in Group A in Steps 1 and 2, and Groups A and C in Step 3 will receive two kits containing 2 bottles each of CCX168 capsules on Days 29, 43, 57, and 71. Subjects will be asked to take 3 capsules every morning and 3 capsules every evening, approximately 12 hours after the morning dose, as instructed. Study medication will be taken within 1 hour after breakfast in the morning and within 1 hour after dinner in the evening for 84 days continuously. Capsules will be taken with water, preferably with 50 mL, but not to exceed 100 mL. Placebo and CCX168 bottles and capsules will be identical in appearance.

Reference Therapy, Dose and Mode of Administration

Group B will be the placebo control group. Placebo capsules will be supplied to the study centers in plastic bottles containing 30 capsules.

Subjects in Group B (placebo) will receive 2 bottles of placebo capsules on Days 1, 8, 15, and 22. Subjects in Group B will receive 4 bottles of placebo capsules on Days 29, 43, 57, and 71. Subjects will be asked to take 3 capsules every morning and 3 capsules every evening, approximately 12 hours after the morning dose, as instructed. Study medication will be taken within 1 hour after breakfast in the morning and within 1 hour after dinner in the evening for 84 days continuously. Capsules will be taken with water, preferably with 50 mL, but not to exceed 100 mL.

Prednisone will be given as tablets, overencapsulated with hard gelatin capsules in order to maintain the blinding. Two dose strengths of prednisone will be provided, 20 mg and 5 mg. Placebo for prednisone will be given as matching hard gelatin capsules with inert filler.

Duration of Treatment and Observation

Subjects 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 84 days and all subjects will be followed for 84 days after the dosing period.

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

Safety Assessments

Safety assessments include adverse events, physical examination abnormalities, vital signs, and clinical laboratory tests (including blood chemistry, hematology, and urinalysis), and ECGs.

Efficacy Assessments

Efficacy assessments include:

1. BVAS version 3;
2. eGFR by Modification of Diet in Renal Disease (MDRD) formula;
3. Hematuria and proteinuria (ACR);
4. Corticosteroid IV or oral rescue use (dose and duration of dosing);
5. VDI;
6. ANCA (anti-PR3 and anti-MPO by ELISA);
7. Serum C-reactive protein concentration measured by high sensitivity CRP assay;
8. Urinary MCP-1:creatinine ratio, and
9. SF-36v2 and EQ-5D-5L measurements.

Pharmacokinetic Assessments

Concentrations of CCX168 and possible metabolites will be determined in plasma from blood samples collected in EDTA tubes on Days 1, 8, 15, 22, 29, 43, 57, 71, and 85. On Day 1, samples will be taken at pre-dose, 0.5, 1, 2, 3, 4, and 6 hours after dosing.

Urine will be collected on Day 1 starting after a complete void prior to dosing, and collection of all urine up to the 6-hour time point following dosing. Concentrations of CCX168 and possible metabolites will be measured in a representative sample from this 6-hour collection.

Pharmacodynamic Assessments

A plasma sample will be collected on Days 1, 29, 85, and 169 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

pharmacodynamics marker measurements.

Urine samples will also be collected on Days 1, 8, 15, 29, 57, 85, 113, and 169 for biomarker assessments including for example complement fragments, inflammatory chemokine and cytokine levels.

A saliva sample will be collected on Day 1 from subjects 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 subject baseline characteristics and demographic data (age, sex, race, ethnicity, weight, height, body mass index, smoking status, ECG, TB screen results, viral test results, ANCA, serology test results, vasculitis disease duration (from time of first induction treatment), BVAS, VDI, SF-36v2 score, EQ-5D-5L score, hsCRP, eGFR, hematuria, proteinuria (ACR), glomerular histopathology (if biopsy was taken), urinary MCP-1:creatinine ratio, physical examination abnormalities, medical history, previous (within 6 months of screening) and concomitant medications (including vasculitis medication use) at study entry will be listed by treatment group, study center, and subject number, and will also be summarized by treatment group and step of the study.

Safety Analysis

The primary safety endpoint is the subject incidence of adverse events.

Other safety endpoints include:

1. Subject incidence of events possibly associated with glucocorticoid use: serious infections, new-onset diabetes mellitus/hyperglycemia, bone fracture, peptic ulcer disease, cataracts, new onset/worsening hypertension, weight gain more than 10 kg, and psychiatric disorders;
2. Subject incidence of infections, serious infections, severe infections (i.e., Grade 3), and infections leading to subject withdrawal from the study;
3. Change from baseline in all safety laboratory parameters;
4. Change from baseline in vital signs;
5. Incidence of clinically significant ECG changes from baseline.

All subjects 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 subject, 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 compared across treatment groups. Serious adverse events and adverse events leading to withdrawal will be summarized and compared across treatment groups. Individual vital signs and change from baseline in vital signs will be listed by treatment group, subject, and study visit, and summarized descriptively. Laboratory data (actual values and

change from baseline) will be listed by treatment group, subject, and study visit. Abnormal laboratory values will be flagged. Laboratory data will also be summarized by treatment group and study visit. ECGs will be acquired at Baseline (Day 1) and Day 29. ECGs will be evaluated for any abnormalities, which will be assessed for clinical significance.

The incidence of adverse events and serious adverse events will be compared between CCX168 and standard of care control groups for all 3 steps.

Efficacy Analysis

The primary efficacy endpoint is the proportion of subjects achieving disease response at Day 85 defined as BVAS percent reduction from baseline of at least 50% plus no worsening in any body system component.

Other efficacy endpoints include:

1. In patients with hematuria and albuminuria at baseline, the proportion of subjects achieving renal response at Day 85; renal response is defined as an improvement in parameters of renal vasculitis:
    a. an increase from baseline to Day 85 in eGFR (MDRD serum creatinine equation), plus
    b. a decrease from baseline to Day 85 in hematuria (central laboratory microscopic count of urinary RBCs), plus
    c. a decrease from baseline to Day 85 in albuminuria (first morning urinary albumin:creatinine ratio).
2. Proportion of subjects achieving disease remission at Day 85 defined as BVAS of 0 or 1 plus no worsening in eGFR and urinary RBC count < 10/hpf;
3. Percent change from baseline to Day 85 in BVAS;
4. Change and percent change from baseline to Day 85 in eGFR;
5. In subjects with baseline hematuria > 5 RBCs/hpf, the proportion of subjects and time to first achieving urinary RBC count ≤ 5/hpf at any time during the 84-day treatment period;
6. In subjects with baseline hematuria ≥ 30 RBCs/hpf, the proportion of subjects and time to first achieving urinary RBC count < 30/hpf at any time during the 84-day treatment period;
7. In subjects with hematuria at baseline, the percent change from baseline to Day 85 in urinary RBC count;
8. In subjects with albuminuria at baseline, the percent change from baseline to Day 85 in urinary ACR;
9. Percent change from baseline to Day 85 in urinary MCP-1:creatinine ratio;
10. Proportion of subjects requiring rescue IV or oral glucocorticoid treatment;
11. Change from baseline to Day 85 in the Vasculitis Damage Index (VDI);
12. Change from baseline to Day 85 in health-related quality-of-life as measured by the Short Form-36 version 2.0 (SF-36v2) and EuroQOL-5D-5L (EQ-5D-5L);

Other endpoints include:

1. Total cumulative study-supplied prednisone dose and duration of dosing during the 84-day treatment period;
2. Total cumulative systemic corticosteroid dose (any use) and duration of dosing during the 84-day dosing period;
3. Total cumulative cyclophosphamide or rituximab dose and duration of dosing during the 84-day dosing period;
4. Percent change from baseline in hsCRP,
5. Percent change from baseline in ANCA (anti-PR3 and anti-MPO) at Day 85,
6. Proportion of patients becoming ANCA negative at Day 85, and
7. Change and percent change from baseline in plasma and urine biomarkers.

The 84-day follow-up period results for the endpoints listed above will also be summarized.

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, and standard deviations will be calculated. Geometric means will be calculated for urinary ACR, urinary RBC count, urinary MCP-1:creatinine, and hsCRP. Shift tables will be generated for urinary parameters such as hematuria and albuminuria. Results will be presented separately for each step, and combined for three groups: (1) the placebo subjects (standard of care group) across all three steps, (2) the CCX168 subjects receiving a low dose study-supplied prednisone dose from Steps 1 and 3, and (3) the CCX168 subjects receiving no study-supplied prednisone from Steps 2 and 3. Results will also be presented by stratum for each of the three stratification factors, newly diagnosed vs. relapsed patients, rituximab vs. cyclophosphamide use, and PR3 vs. MPO positive ANCA.

The main efficacy hypothesis in this study is that CCX168 treatment will induce treatment response while being corticosteroid-sparing, i.e., AAV disease activity will be controlled in the majority of subjects receiving CCX168 without the need for rescue IV or oral corticosteroids.

The primary efficacy endpoint is the proportion of subjects achieving disease response at Day 85 defined as BVAS percent reduction from baseline of at least 50% plus no worsening in any body system component. **The proportion of subjects achieving disease response** and the 1-sided 95% confidence interval **for the difference in proportion (CCX168 minus SOC)** will be estimated for the comparison between each CCX168 group and the SOC group. If the lower bound of the 95% confidence interval is greater than **-0.20**, the respective CCX168 group will be considered not inferior to the SOC group. If the lower bound of the confidence interval is greater than **0.0**, the respective CCX168 group will be considered superior to the SOC group in achieving the disease response.

Continuous variables will be analyzed using **mixed effects model for repeated measures (MMRM)** with treatment group**, visit, treatment-by-visit interaction,** and **randomization** strata (newly diagnosed AAV or relapsed AAV, rituximab or cyclophosphamide, PR3 or MPO

ANCA) **as factors**, **and baseline** as covariate. **Subjects will be considered as repeated measure units over visits.** Point estimates and corresponding 95% confidence intervals will be estimated for the difference between each CCX168 group and the placebo group **using simple contrast from the model**. **Additionally, analysis of covariance (ANCOVA) with the same factors and covariates will be applied for the between group comparison at each visit.** Continuous variables include change and/or percent change from baseline in BVAS, eGFR, hsCRP, urinary ACR, urinary MCP-1:creatinine ratio, VDI, SF-36v2 and EQ-5D-5L (total and subscores), pharmacodynamics markers, and ANCA (anti-PR3 and anti-MPO). Data that are not normally distributed, e.g., urinary ACR will be log-transformed before analysis.

Categorical variables will be analyzed using the CMH test. Other than the primary efficacy endpoint, these include the proportion of subjects achieving renal response at Day 85. Renal response is defined as an improvement from baseline in parameters of renal vasculitis, based on an increase in eGFR, a decrease from baseline in hematuria, and a decrease from baseline in urinary albuminuria. Other categorical parameters, i.e., proportion of subjects requiring rescue IV or oral steroids, achieving disease remission, urinary RBCs ≤5/hpf, and urinary RBCs <30/hpf will be analyzed similarly.

Subjects receiving rescue steroids after Day 1 but before Day 85 + 7 days (i.e. Day 92) will be considered as treatment failures.

All statistical testing will be one-sided and with the type I error rate at α=0.05. In the context of this being a Phase 2 trial, no adjustment for multiplicity will be made. If the two CCX168 groups showed a similar response, the two CCX168 groups may be combined for testing against the control group.

The main efficacy analysis will be in the intent-to-treat population. This includes all subjects who have signed informed consent to participate in the study, who were randomized in this study, have received at least one dose of study drug, and have at least one post baseline BVAS assessment.

A sample size of 12 subjects (8 active and 4 placebo) per step in the first 2 steps was chosen based on feasibility. A sample size of 36 subjects in Step 3, 12 in each of the CCX168 groups and 12 in the placebo, will provide a total of approximately 60 subjects across all three steps, and ~20 subjects in each of the treatment groups. Assuming a control group BVAS response of 44% at Day 85 and a CCX168 group response of 86%, a sample size of 20 in each group will provide approximately 90% power for the primary efficacy analysis.

Pharmacokinetic analysis

Plasma samples will be collected at Baseline (Day 1) and Days 8, 15, 22, 29, 43, 57, 71, and 85 to determine the PK profile of CCX168 (and potential metabolites). Individual plasma concentrations of CCX168 (and potential metabolites) will be listed, plotted, and summarized descriptively and graphically. The following parameters will be determined, where possible:

C_{max}	Maximum plasma concentration
T_{max}	Time of maximum plasma concentration
AUC_{0-6}	Area under the plasma concentration-time curve from Time 0 to Hour 6 on Day 1

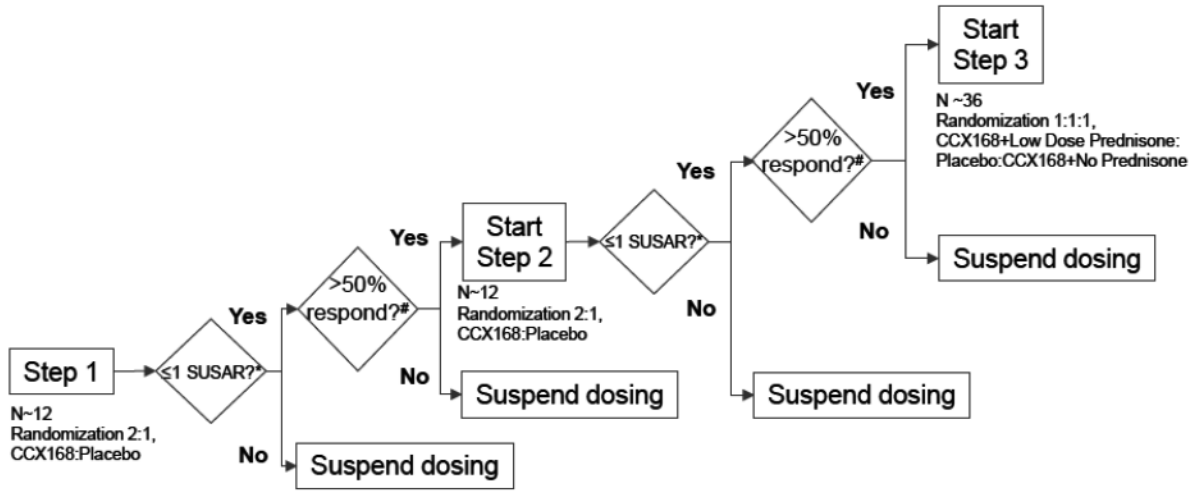
C_{min}	Trough level plasma concentrations at post-Day 1 visits

It is of interest to evaluate whether the PK profile of subjects with ANCA-associated vasculitis is similar to the profile in healthy volunteers. 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 BVAS, eGFR, urinary ACR, urinary MCP-1:creatinine ratio, serum hsCRP, hematuria, and other biomarkers may be used as PD markers.

Urinary concentrations of CCX168 and possible metabolites in a 6-hour urine sample collected on Day 1 will also be measured. Results will be listed and summarized descriptively.

Plasma concentrations of prednisolone, cyclophosphamide and its metabolites, and rituximab may also be measured in the PK plasma samples to evaluate potential drug-drug interaction.

STUDY SCHEMA



Step 1 = Partial corticosteroid withdrawal (67% reduced oral dose) (N~12 subjects)
Step 2 = Complete corticosteroid withdrawal (100% reduced oral dose) (N~12 subjects)
Step 3 = Include both partial corticosteroid withdrawal (67% reduced oral dose), and complete corticosteroid withdrawal (100% reduced oral dose) (N ~**36 subjects**)

* Not more than one suspected unexpected serious adverse reaction (SUSAR) most likely related to CCX168, observed in subjects receiving CCX168.
# >50% of subjects maintained on CCX168 without need for rescue IV steroids

TIME AND EVENTS TABLE

	Screening[1]	Study Day[2]													
	-14 to -1	**1[3]**	**2**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141**	**169**
Informed Consent	X														
Demographics, Medical History, Prior Medications	X														
Physical Examination[4]	X	X[5]			X		X		X		X		X		X
Body System Review			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
12-lead ECG	X						X								
Chest X rays[7]	X						(X)				(X)		(X)		(X)
HIV, HBV, HCV Testing	X														
ANA, anti-GBM antibodies, C3, C4, IgG, IgM, and IgA[8]	X														
PT and aPTT	X														
Serum Chemistry, Hematology	X	X[5]	X	X	X		X	X		X	X	X		X	X
WBC count (local lab)[9]		X[5]			X		X		X		X	X	**(X)**		
Serum Creatinine (when full Chemistry not done)									X				X		
Urinalysis[10]	X	X[5]	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine albumin, MCP-1 and creatinine assays		X[5]		X	X		X		X		X		X		X
ANCA measurement[11]	X	X[5]					X				X		X		X
Renal biopsy (optional procedure)	X										X[12]				
Randomization		X[5]													
CCX168 or Placebo Dispensing		X		X	X	X	X	X	X	X					

	Screening[1]	Study Day[2]													
	-14 to -1	**1[3]**	**2**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141**	**169**
CCX168 or Placebo Accountability				X	X	X	X	X	X	X	X				
Prednisone or Placebo Dispensing		X		X	X		X	X	X		X	X	X		
Prednisone or Placebo Accountability				X	X		X	X	X		X	X	X	X	(X)[13]
Cyclophosphamide IV dose[14]		X			X		X		X		X				
Azathioprine dosing[15]												X→	→	→	→
Rituximab IV dose[16]		X		X	X	X									
BVAS	X	X[5]					X				X		X		X
VDI		X[5]									X				X
SF-36v2 and EQ-5D-5L		X[5]					X				X				X
hsCRP		X[5]		X	X		X		X		X		X		X
PK Plasma Sample Collection		X[5,17]		X	X	X	X	X	X	X	X				
PD Plasma Sample Collection		X[5]					X				X				X
Saliva sample collection		X													
Urine sample collection for CCX168 analysis		X[18]													
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Instruct subjects who are on maintenance corticosteroids (≤ 10 mg prednisone equivalent) at screening regarding tapering over ≤ 6 weeks	X														
Adverse Event Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X

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

[2] Visit Days 1, 2, 8, and 15 must occur on the scheduled study days. Visit Days 22, 29, 43, 57, 71, and 85 may occur within a +/- 2-day window of the scheduled visit. Visit Days 99, 113, 141, and 169 may occur within a +/- 4-day window of the scheduled visit.

[3] A subject could be kept overnight in the hospital on Day 1, if necessary. This hospital stay would not be considered a serious adverse event, unless other SAE criteria are met.

[4] Physical examination will include body weight measurement; Height will only be measured at Screening.
[5] These procedures must be done BEFORE taking the first dose of study medication.
[6] Assessment of heart rate, body temperature, and blood pressure (supine, after at least 3 minutes of rest)
[7] Chest X rays will be acquired and examined at Screening to exclude the presence of TB and for baseline BVAS and VDI. Chest X rays at subsequent study visits will ONLY be acquired if in the clinical opinion of the Principal Investigator there is pulmonary disease involvement that needs to be assessed for safety, BVAS, or VDI.
[8] 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.
[9] For subjects 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 subjects receiving azathioprine, local WBC count will be done at the Day 113 visit.**
[10] Subjects will be asked to void their bladders completely, and a representative clean catch, midstream urine sample will be collected. During screening, the local laboratory will 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 pH, specific gravity, glucose, nitrite, ketones, bilirubin, urobilinogen, RBCs, and WBCs. Urinary ACR and MCP-1:creatinine will be measured by the central laboratory at study visits indicated in the table.
[11] At screening, an indirect immunofluorescence test for P-ANCA and C-ANCA, as well as ELISA tests for anti-proteinase-3 (PR3) and anti-myeloperoxidase (MPO) will be performed for study eligibility; for the rest of the study visits, only ELISA tests for anti- PR3 and anti-MPO will be performed.
[12] If possible, renal biopsy should be obtained from subjects with a pre-study biopsy.
[13] This accountability is only necessary for subjects who discontinue between Day 85 and 169, and come for an early termination visit.
[14] Applicable only to cyclophosphamide stratum. Cyclophosphamide doses given from Day 1 through 57 must be given according to directions provided in the protocol. The date and start and end time of the cyclophosphamide dose will be recorded.
[15] Azathioprine must be taken from Day 99 through Day 168 by all subjects in the cyclophosphamide but not the rituximab stratum.
[16] Applicable only to the rituximab stratum. A rituximab dosing regimen of 375 mg/m^2 IV on Days 1, 8, 15, and 22 should be used.
[17] PK blood sample will be collected prior to the morning dose on Day 1 and at 0.5, 1, 2, 3, 4, and 6 hours following dosing.
[18] Subjects will void prior to the morning dose of CCX168/placebo on this day, and then ALL urine will be collected over the first 6 hours following CCX168/placebo dosing. The 6-hour urine volume will be measured and a representative sample will be sent to measure CCX168 concentration in the urine.

LIST OF ABBREVIATIONS AND ACRONYMS

AAV	anti-neutrophil cytoplasmic antibody associated vasculitis
AARV	anti-neutrophil cytoplasmic antibody associated renal vasculitis
ACR	albumin:creatinine ratio
AE	adverse event
ALT	alanine aminotransferase (also called SGPT)
ANA	anti-nuclear antibodies
ANCA	anti-neutrophil cytoplasmic antibodies
API	active pharmaceutical ingredient
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase (also called SGOT)
AUC_{0-6}	area under the curve from hour 0 to 6
BLQ	below limit of quantification
BUN	blood urea nitrogen
BVAS	Birmingham Vasculitis Activity Score version 3
C3	complement 3
C4	complement 4
C3a	complement 3a
C4a	complement 4a
C5a	complement 5a
C5aR	complement 5a receptor
C5b9	complement 5b9
CA	competent authority
C-ANCA	cytoplasmic-anti-neutrophil cytoplasmic antibody
cGMP	current good clinical practice
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
DMC	data monitoring committee
EC	ethics committee
EC_{50}	50% effective concentration
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EQ-5D-5L	EuroQol-5D-5L
FACS	fluorescence activated cell sorting
FDA	Food and Drug Administration
FLIPR	Fluorometric Imaging Plate Reader
g	gram
GBM	glomerular basement membrane
GCP	good clinical practice
GGT	gamma-glutamyl transpeptidase
GPA	granulomatosis with polyangiitis (Wegener's)
GPCR	G protein-coupled receptor

HED	human equivalent dose
HEENT	head, eyes, ears, nose, throat
HIV	human immunodeficiency virus
hpf	high power field
IC_{50}	concentration to inhibit 50%
ICH	International Conference on Harmonisation
INR	International Normalized Ratio
IIF	Indirect immunofluorescence
IRB	Institutional Review Board
IVIg	intravenous immunoglobulin
K_3EDTA	tri-potassium ethylene diamine tetra-acetic acid
kg	kilogram
KIM-1	kidney injury molecule-1
LDH	lactate dehydrogenase
MAC	membrane attack complex
MCH	mean cell hemoglobin
MCHC	mean cell hemoglobin concentration
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
NOAEL	No observed adverse effect level
P-ANCA	perinuclear-anti-neutrophil cytoplasmic antibody
PCP	*Pneumocystis carinii* pneumonia
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PR3	proteinase 3
PT	prothrombin time
RBC	red blood cell
SAE	serious adverse event
SF-36v2	Short Form-36 version 2
SGPT	serum glutamic pyruvic transaminase (also called ALT)
SGOT	serum glutamic oxaloacetic transaminase (also called as AST)
SLE	systemic lupus erythematosus
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
T_{max}	time of maximum (plasma) concentration
TPMT	thiopurine S-methyltransferase
VDI	vasculitis damage index
WBC	white blood cell
WG	Wegener's granulomatosis

1. INTRODUCTION

1.1. Background

The activation of the complement pathway generates biologically active fragments of complement proteins, e.g. C3a, C4a and C5a anaphylatoxins and C5b-9 membrane attack complexes (MAC), 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 190 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 C5a receptor (C5aR), a G protein-coupled receptor (GPCR) expressed on human neutrophils, monocytes, basophils, eosinophils, renal glomerular tissues, and lung smooth muscle and endothelial cells.

Recently, several reports have shown that anti-neutrophil cytoplasmic antibody (ANCA)-induced glomerulonephritis in mice (a model that closely recapitulates the histological features of human pauci-immune necrotizing crescentic glomerulonephritis in granulomatosis with polyangiitis [GPA; Wegener's] and microscopic polyangiitis [MPA]) is dramatically ameliorated by genetic deletion of either C5 or C5aR (Schreiber et al., 2009). The development of systemic lupus erythematosus (SLE) is associated with the deposition of IgG-containing immune complexes in various tissues/organs, with the ensuing activation of the complement cascade and production of inflammatory stimuli such as C5a. Glomerular expression of C5aR mRNA and protein was shown to correlate positively with the degree of mesangial hypercellularity and level of serum creatinine in mesangial glomerulonephritis, including lupus nephritis (Abe et al., 2001). Recent studies showed that C5aR-deficient mice and mice treated with a small peptidic anti-C5aR antagonist are protected from tissue injury induced by immune complex formation. In addition, use of a C5 mAb in a spontaneous mouse model of lupus-like autoimmune disease resulted in significant amelioration of the course of glomerulonephritis and in markedly increased survival. A genetic version of the disease (MRLlpr mice) is also attenuated significantly when the C5aR receptor is deleted from that genetic background.

The therapeutic indication being pursued initially for CCX168, a potent and selective C5aR antagonist, is in the treatment of ANCA-associated vasculitis (AAV).

AAV currently is treated with glucocorticosteroids and cyclophosphamide, azathioprine, mycophenolate mofetil, rituximab, and plasma exchange in severe cases.

1.2. Study Drug Development

1.2.1. Non-Clinical Pharmacology

1.2.1.1. In-Vitro Efficacy and Selectivity for C5aR

CCX168 is a potent antagonist of the human C5a receptor (hC5aR). As measured *in vitro* with a myeloid human cell line, CCX168 functionally inhibits C5a-mediated chemotaxis with a potency (IC_{50}) of 0.92 nM. Additionally, CCX168 displaces ^{125}I-C5a from hC5aR with a potency (IC_{50}) of 0.65 nM. When tested on freshly isolated human neutrophils, CCX168 inhibits the C5a-mediated increase in cytoplasmic calcium levels with a potency (IC_{50}) of 0.2 nM.

CCX168 has been 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) was determined in human whole blood 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).

CCX168 displays greater than 10,000-fold selectivity for hC5aR relative to other chemotactic receptors, including CCR1, CCR2, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CCR12, CXCR1, CXCR2, CXCR3, CXCR4, CXCR6, CXCR7, C5L2, C3aR, ChemR23, GPR1 and FPRL1. CCX168 has been further evaluated against a panel of 55 unrelated receptors and membrane-associated proteins. Weak levels of activity (>1,000-fold selectivity relative to hC5aR) were noted against the site 2 sodium channel (59% inhibition with 10 µM CCX168).

1.2.1.2. Efficacy Models

CCX168 has been evaluated *in vivo* utilizing models that are relevant to the intended therapeutic use in humans. When C5a is generated locally in the bloodstream, C5aR-bearing leukocytes in the vicinity immediately upregulate adhesion molecules and adhere to the inner face of the blood vessel. If C5a is introduced systemically by intravenous injection, leukocyte adherence occurs immediately throughout the vasculature and, as a result, the number of leukocytes still flowing in the bloodstream drops transiently by a substantial amount. In general, evaluation of C5aR antagonists in animal models poses a challenge because C5aR antagonists that are potent for human C5aR, including CCX168, are less potent for C5aR orthologs in most other model species (such as mice, rats and rabbits). For this reason, CCX168 has been evaluated in C5a-induced leukopenia models using transgenic mice in which the mouse C5aR gene has been replaced with the human C5aR gene and non-human primates.

ChemoCentryx generated a human C5aR knock-in (hC5aR KI) mouse strain in which the mouse C5aR gene has been replaced with the human C5aR gene. The innate immune cells of these mice respond normally to C5a, in a manner highly sensitive to CCX168. *In vitro*, CCX168 blocks hC5a-mediated chemotaxis of leukocytes freshly isolated from these hC5aR KI mice with high potency (IC_{50} = 0.5 nM in 100% mouse plasma). This value is nearly identical to the potency (1.7 nM) exhibited by CCX168 in its inhibition of neutrophil migration to hC5a in whole human blood, indicating that the hC5aR KI mice are suitable for pharmacodynamic evaluation of CCX168. In the human C5aR knock-in mice, an intravenous dose of 20 µg/kg hC5a robustly

induces this leukopenia within one minute after injection. Pretreatment of the mice with an oral dose of 0.3 mg/kg CCX168, which resulted in a plasma concentration of approximately 75 nM at 60 min. post-dose, almost completely blocked the C5a-induced leukopenia. A dose of 0.03 mg/kg CCX168, producing a plasma concentration of 15 nM, resulted in a 50% reduction in the C5a-induced leukopenic response.

In cynomolgus monkeys, it was determined that an intravenous hC5a dose of 10 µg/kg robustly induces a drop in neutrophils (neutropenia) within one minute. Pre-treatment of the cynomolgus monkeys with a 30 mg/kg oral dose of CCX168 completely blocked the C5a-induced neutropenia. This dose of CCX168 resulted in a plasma concentration of approximately 230 nM at the time of hC5a administration. A dose of 3 mg/kg resulted in greater than 50% reduction of the hC5a response, an effect that was associated with a CCX168 plasma concentration of approximately 38 nM.

The efficacy of CCX168 in a mouse model of ANCA-associated glomerulonephritis was evaluated in order to assess the clinical potential of CCX168 in the treatment of ANCA-associated vasculitis. 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 (8.2% with vehicle, 1.1% with CCX168; $p<0.0001$) and crescent-containing glomeruli (29.3% with vehicle, 3.3% with CCX168; $p<0.0001$). These results were consistent with reduced protein, leukocytes and RBC levels in the urine and reduced serum BUN and creatinine in mice receiving CCX168. Some therapeutic benefit (30% reduction in the number of glomeruli with crescents) was noted at CCX168 doses as low as 0.1 mg/kg/day. Administration of 4 mg/kg CCX168 twice daily was identified as the lowest dosing regimen that produced a near-maximal therapeutic benefit. At this dose, plasma levels ranged from 35 ng/mL (C_{min}) to 200 ng/mL (C_{max}) throughout the day. The same blood biomarker of C5aR blockade used in the Phase 1 clinical trial was also used with the hC5aR KI mice; CCX168 had similar C5aR antagonist potency on human and hC5aR KI mouse neutrophils (inhibition of C5a-induced CD11b upregulation in blood, IC_{50} 4 nM). The extent of functional C5aR blockade on blood neutrophils associated with the plasma levels of 4 mg/kg CCX168 twice daily was determined to range from 99% (at C_{max}) to 95% (at C_{min}), with a time-averaged level of receptor blockade of 97%.

These mechanism-based pharmacology studies, taken together, support our estimate that maintaining human plasma CCX168 concentrations sufficiently high to provide ≥ 95% receptor coverage will provide significant clinical benefits in inflammatory conditions associated with C5aR activation.

1.2.2. Non-Clinical Safety and Toxicology

The toxicology program was designed to support this Phase 2 study to assess the safety, tolerability, pharmacokinetics, and efficacy of CCX168 in subjects with AAV. In this regard, a comprehensive toxicology program has been conducted in light of existing ICH nonclinical toxicology guidance (including M3 Nonclinical Safety Studies for the Conduct of Human Clinical trials for Pharmaceuticals; S2B Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals; and S7A Safety Pharmacology Studies for Human Pharmaceuticals).

The nonclinical toxicology program with CCX168 consisted of a series of acute (single-dose) and/or multiple-dose toxicology oral studies conducted in rats and cynomolgus monkeys. Oral repeat-dose range finding studies were subsequently followed by formal multiple-dose (28-day) studies utilizing the oral route of administration. The definitive 28-day and 13/20-week studies involved the administration of CCX168 at daily doses up to 100 mg/kg/day in rats and up to 50 mg/kg/day in cynomolgus monkeys and included comprehensive clinical evaluations and the microscopic assessment of a full list of tissues. The multiple-dose cynomolgus study included electrocardiographic measurements. Toxicokinetic data were also collected in the multiple-dose rat and cynomolgus studies. The highest doses used in the definitive 13/20-week studies (up to 100 and 30 mg/kg/day, in rats and cynomolgus monkeys, respectively) represented Human Equivalent Doses (HED's) of 15.6 and 11.1 mg/kg/day, respectively.

The effects of CCX168 upon the central nervous, respiratory, renal, and cardiovascular systems were also assessed in single-dose stand-alone safety pharmacology experiments in rats and cynomolgus monkeys. An *in vitro* study to assess the potential effects of CCX168 upon hERG channel ionic conductance was also conducted. With regard to genotoxicity, *in vitro* bacterial (reverse mutation in histidine-requiring strains of *S. typhimurium* and tryptophan-requiring strains of *E. coli*) and mammalian (mutation at the thymidine kinase locus of mouse lymphoma L5178Y cells) mutagenicity tests were performed. Additionally, an *in vivo* rat bone marrow micronucleus test was also performed.

All toxicology studies and safety pharmacology studies with the exception of dose analyses performed in support of the acute toxicology and hERG studies were conducted in accordance with GLP regulations. A summary of the nonclinical toxicology, genotoxicology, and safety pharmacology studies performed in support of CCX168 are described in Table 1 and Table 2.

Table 1: Overview of Toxicology Studies Performed with CCX168

Study Type	Method of Administration/Dosing Schedule	Species	Doses
Acute	Oral /Single-Dose	Rat	0, 5, 25, 100 mg/kg
Repeat Dose	Oral / 7-Day	Rat	0, 30, 100 mg/kg
	Oral / 4 / (2) -day	Cynomolgus monkey	3, 50, 65, (80), (120) mg/kg
	Oral/28-Day	Rat	0, 5, 25, 100 mg/kg
	Oral/28-Day	Cynomolgus monkey	0, 5, 15, 50 mg/kg
	Oral/13-Week	Rat	0, 3, 15, 100 mg/kg
	Oral/20-Week	Cynomolgus monkey	0, 5, 15, 30 mg/kg
Genotoxicity			
Ames	NA	*S. typhimurium* and tryptophan-requiring strains of *E. coli*	Up to 5000 µg/plate
Mouse Lymphoma	NA	Mouse lymphoma cells	Up to 500 µg/mL
Rat Bone Marrow Micronucleus	NA	Rat	0, 500, 1000 and 2000 mg/kg

Study Type	Method of Administration/Dosing Schedule	Species	Doses
Immunotoxicity	Oral/28-Day	Rat	0, 3, 15, 100 mg/kg

Table 2: Overview of Safety Pharmacology Studies Performed with CCX168

Study Type	Method of Administration/Dosing Schedule	Species	Doses
Central Nervous System	Oral/Single-Dose	Rat	0, 5, 25, 100 mg/kg
Cardiovascular – *In vivo*	Oral/Single-Dose	Cynomolgus monkey	0, 5, 15, 50 mg/kg
Cardiovascular – *In vitro* (hERG)	*In vitro*	Human cells transfected with human K-channel gene	0.6, 1.2, 2.3 and 6.9 µM
Respiratory	Oral /Single-Dose	Rat	0, 5, 25, 100 mg/kg
Renal	**Oral/Single-Dose**	**Rat**	**0, 5, 25, 100 mg/kg**

Based on *in vivo* safety pharmacology studies, which included a neuropharmacology study in rats, a pulmonary and renal safety study in rats, and a cardiovascular study in conscious telemetered cynomolgus monkeys, there was no evidence of toxicity of CCX168. In an *in vitro* cardiovascular safety study, the IC_{50} value for hERG inhibition was determined to be > 2.3 µM (the limit of solubility), further indicating CCX168 is unlikely to cause arrhythmias *in vivo*. 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), *in vitro* mammalian cell mutagenicity (mouse lymphoma) studies, and *in vivo* rat bone marrow micronucleus test were also conducted and did not identify any safety concerns or significant potential for drug-drug interactions. In an acute toxicology study, single doses of CCX168 up to 100 mg/kg in rats produced no remarkable effects. In a 28-day immunotoxicity study in rats, in which T-cell dependent antibody production was assessed, daily CCX168 doses up to 100 mg/kg were free of any effects.

CCX168 was well tolerated in 28-day studies up to doses of 100 mg/kg in rats and 50 mg/kg in cynomolgus monkeys. There were no significant toxicological findings of concern in these studies. At selected time points, minor but statistically significant differences existed in selected clinical pathology parameters between control and CCX168 treated rats. These included an increase in reticulocytes in 100 mg/kg/day recovery-phase females, an increase in prothrombin time in males given doses > 25 mg/kg/day and a minimal increase in ALT levels on Day 30 in females administered 100 mg/kg/day. These differences were not clearly test article-related and not considered to be of toxicological importance because of their small magnitude, mean and/or individual values falling within the range of normal variability and/or reversibility of the finding following a 2-week treatment-free period.

CCX168 was also well tolerated in a 13-week study in rats up to doses of 100 mg/kg/day and in a 20-week study in cynomolgus monkeys up to 30 mg/kg/day. There were no significant toxicological findings of concern in these studies. The only CCX168-related clinical observation in the rat study was infrequent salivation, which was noted in the mid and high dose groups. There were no CCX168 related changes in body weights, food consumption, ophthalmic examinations, hematology, coagulation, gross observations, organ weights, and microscopic evaluation. There were no CCX168-related effects on clinical chemistry at termination or recovery. Serum AST, ALT, and sorbitol dehydrogenase were mildly increased in two females at 100 mg/kg/day at termination. Given the magnitude and low incidence of these findings, they were considered incidental. In the monkey study, CCX168 was well tolerated at doses up to 30 mg/kg/day.

A metabolite of CCX168 (CCX168-M1) has been detected in human Phase 1 samples in significant amounts. This compound, which is also produced in significant amounts in the preclinical toxicology species, lacks strong inhibition of the hERG potassium channel (IC_{50} > 3 μM).

Given the lack of significant safety concerns in the toxicology studies and the Phase 1 study in healthy volunteers, and the safety results from this clinical trial so far, the risk for serious or unanticipated untoward events to occur in this clinical trial is considered low.

1.2.3. Non-Clinical ADME

The pharmacokinetic behavior of CCX168 has been assessed in female CD-1 mice, male Sprague-Dawley rats, male beagle dogs, and male cynomolgus monkeys through intravenous (i.v.) and/or oral (p.o.) dosing and the data are summarized in Table 3. Following intravenous dosing, the compound has a moderate to medium total body clearance in mice, rats, and dogs (30 - 50% of liver blood flow). The terminal elimination half-life is moderate to long, at ca. 2 h in mice and rats, and 14.2 h in dogs, while the volume of distribution is moderate (1.5, 2.5, and 4.7 L/kg for mice, rats, and dogs, respectively). Following oral dosing in mice and rats, CCX168 is readily absorbed, showing moderate bioavailability for the aqueous hydroxypropyl methylcellulose (HPMC) suspension and high bioavailability for the PEG-400/Solutol HS-15 solution.

Table 3: Pharmacokinetic Parameters of CCX168 in CD-1 Mice, Sprague-Dawley Rats, Beagle Dogs, and Cynomolgus Monkeys after Administration of a Single Oral Gavage or an Intravenous Dose of CCX168

a. Intravenous dosing

Parameter	Mouse	Rat	Dog
dose (mg/kg)	0.5	0.5	0.5
Formulation	Ethanol / *N,N*-dimethylacetamide / propylene glycol / 0.9% saline (10:10:30:75)	N,N-dimethylacetamide / ethanol / propylene glycol (31.6:36.8:31.6)	propylene glycol / *N,N*-dimethylacetamide / water (31.6/31.6/36.8)
N =	9 [a]	2	3
CL [mL/min/kg]	26.6	21.2	11.9
$t_{1/2}$ [h]	1.8	1.9	14.2
Vd_{ss} [L/kg]	1.5	1.8	4.7

[a] Non-serial blood sampling was used and a composite PK profile was obtained using the mean concentration at each time point

b. Oral dosing

Parameter	Mouse		Rat		Monkey
p.o. dose (mg/kg)	2	30	2	30	100
Formulation	1% HPMC (suspension)	PEG-400/solutol HS-15 (70:30) (solution)	1% HPMC (suspension)	PEG-400/Solutol HS-15 (70:30) (solution)	PEG-400 / solutol HS-15 (70:30) (solution)
N =	9 [a]	9 [a]	2	3	3
C_{max} [ng/mL]	75	4630	152	2530	3500
AUC [ng•h/mL]	240	18600	464	24600	33300
$t_{1/2}$ [h]		5.6	2.3	4.6	6.0
t_{max} [h]	1.0	1.0	1.0	1.5	4.0
F [%]	17	87	27	104	-

[a] Non-serial blood sampling was used and a composite PK profile was obtained using the mean concentration at each time point.
i.v. = intravenous
p.o. = oral
C_{max} = maximum concentration
CL = total body clearance
$t_{½}$ = terminal half-life
Vd_{ss} = volume of distribution at steady state
T_{max} = time of peak concentration
F = bioavailability
AUC = area under the concentration-vs.-time curve

CCX168 displays moderate *in vitro* metabolic turnover in cryo-preserved mouse, rat, and dog hepatocytes and low to moderate turnover in human hepatocytes. This result generally correlates well with the observed *in vivo* clearance in mice, rats and dogs and predicts a low to moderate clearance in humans. *In vitro* metabolism of CCX168 is primarily through monohydroxylation in monkey and human hepatocytes and through monohydroxylation, dealkylation and glucuronidation in rat and dog hepatocytes. A Phase I monohydroxylation metabolite, CCX168-

M1, was found to be a significant circulating metabolite in human volunteers in the Phase 1 study. Its exposure was adequately covered in rats and cynomolgus monkeys in the toxicology studies that support the current Phase 2 clinical trial.

The excretion pathways of CCX168 in animals were investigated in bile-duct cannulated Sprague-Dawley rats and intact cynomolgus monkeys. Neither CCX168 nor the metabolite CCX168-M1 is significantly excreted into urine or bile in rats or urine in cynomolgus monkeys.

The compound is very highly protein bound in mouse, rat, dog, and human plasma, at ca. 99% or higher, with corresponding unbound fractions at ca. 1% or lower. CCX168 has a low metabolism-mediated drug-drug interaction potential as a perpetrator, as its inhibition against major human cytochrome P450 isoforms is minimal (negligible for CYP1A2, 2C9, 2C19, and 2D6, and CYP3A4) and it shows no CYP3A4 and CYP2B6 induction potential at 10 μM in a human hepatocyte cytochrome P450 assay.

The ability of CCX168 or CCX168-M1 to inhibit the steroid-metabolizing enzymes 11β-HSD1 and 11β-HSD2 was evaluated using suitable *in vitro* systems and both compounds were found to be inactive against these enzymes. CCX168 was also found to have no impact on the unbound concentration of prednisone and prednisolone in human plasma. Furthermore, neither CCX168 nor CCX168-M1 interferes with the antiproliferative effects of cyclophosphamide, which is known to require CYP-mediated conversion to an active metabolite. Therefore, CCX168 has low potential for interfering with the biological effects of either cyclophosphamide or corticosteroids.

Preliminary results from mass balance studies in rats and healthy human subjects (CL004_168) with oral administration of [^{14}C]CCX168 showed that most of the radioactivity was recovered in feces, while renal elimination played a very minor role. Hepatic metabolism of CCX168 followed by biliary excretion of the metabolites appeared to be the major route of elimination for CCX168. Refer to the Investigator's Brochure for more details.

1.3. Prior Human Experience

A Phase 1 study in 48 healthy volunteers has been completed. This is a randomized, double-blind, placebo-controlled, two-period study in which subjects received either CCX168 or placebo (3:1 ratio) as a single dose in Period 1 and as multiple once daily or twice daily doses in Period 2. Single doses of 1, 3, 10, 30, and 100 mg CCX168 were studied, 6 subjects in each dose cohort received CCX168 and 2 received placebo, except in cohort 1 in which 5 subjects received CCX168 and 3 received placebo. 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 in this study. No serious adverse events or withdrawals due to adverse events have been observed. A summary of all the treatment-emergent adverse events observed in the single-dose period of the study is provided in Table 4.

Table 4: Summary of Treatment-emergent Adverse Events Observed in the Single-dose Period, CL001_168

	Period 1 (Single Dose)						
System Organ Class Preferred Term		CCX168 Dose					
	Placebo (N=11)	**1 mg (N=5)**	**3 mg (N=6)**	**10 mg (N=6)**	**30 mg (N=6)**	**100 mg (N=6)**	**All CCX168 (N=29)**
Number (%) of subjects with AEs	1 (9%)	3 (60%)	3 (50%)	1 (17%)	3 (50%)	2 (33%)	12 (41%)
Gastrointestinal Disorders	0 (0%)	0	1	1	1	0	3 (10%)
Abdominal pain	0 (0%)	0	0	1	1	0	2 (7%)
Diarrhoea	0 (0%)	0	1	1	0	0	2 (7%)
General Disorders and Administration Site Conditions	0 (0%)	1	1	0	1	0	3 (10%)
Catheter Site Pain	0 (0%)	0	0	0	1	0	1 (3%)
Fatigue	0 (0%)	1	0	0	0	0	1 (3%)
Injection Site Phlebitis	0 (0%)	0	1	0	0	0	1 (3%)
Vessel puncture site hematoma	0 (0%)	0	0	0	1	0	1 (3%)
Investigations	0 (0%)	1	0	0	2	1	4 (14%)
Lymphocyte percentage decreased	0 (0%)	0	0	0	1	0	1 (3%)
White blood cell count decreased	0 (0%)	1	0	0	1	1	3 (10%)
Menstruation and uterine bleeding NEC	0 (0%)	1	0	0	0	0	1 (3%)
Dysmenorrhoea	0 (0%)	1	0	0	0	0	1 (3%)
Nervous System Disorders	0 (0%)	0	2	0	1	1	4 (14%)
Dizziness	0 (0%)	0	0	0	0	1	1 (3%)
Headache	0 (0%)	0	2	0	1	0	3 (10%)
Respiratory, thoracic and mediastinal disorders	1 (9%)	0	0	0	2	0	2 (7%)
Nasopharyngitis	0 (0%)	0	0	0	1	0	1 (3%)
Rhinitis	0 (0%)	0	0	0	1	0	1 (3%)
Throat irritation	1 (9%)	0	0	0	0	0	0 (0%)

All adverse events were mild except for one AE of injection site phlebitis in the 3 mg CCX168 group and one of WBC count decrease in the 1 mg group that were considered moderate in intensity. The latter subject had a low WBC count at baseline, 3.09×10^9/L (lower limit of normal [LLN]: 4.23×10^9/L) and a medical history of low WBC count. The nadir was 2.04×10^9/L on Day 4. The other two subjects with low WBC had Grade 1 abnormalities; one subject, who had a low baseline WBC of 3.58×10^9/L (LLN: 3.98×10^9/L), received 30 mg CCX168 and had a nadir of 3.26×10^9/L on Day 2. The other subject, who also had a baseline WBC of 4.41×10^9/L (LLN: 4.23×10^9/L), received 100 mg CCX168 and reached a nadir of 3.83×10^9/L on Day 4. The other most common AE was headache, observed in three subjects, two receiving 3 mg and the third receiving 30 mg CCX168.

No clinically significant changes in laboratory parameters, vital signs, or ECG parameters were observed. Key pharmacokinetic results (mean, SD) from the single-dose period are summarized in Table 5.

Table 5: Summary of Key Pharmacokinetic Results from the Single-dose Period, CL001_168

	CCX168 Dose				
Parameter	**1 mg (N=5)**	**3 mg (N=6)**	**10 mg (N=6)**	**30 mg (N=6)**	**100 mg (N=6)**
C_{max} (ng/mL)	1.84 (0.889)	9.17 (1.98)	25.3 (5.71)	78.7 (35.6)	197 (157)
T_{max} (hr)	1.1 (0.22)	1.2 (0.26)	1.7 (0.26)	1.7 (0.41)	2.5 (1.8)
$t_{1/2}$ (hr)	2.03 (0.721)	1.92 (1.02)	22.9 (7.33)	71.8 (32.8)	64.0 (22.1)
CL/F (L/hr)	195 (79.7)	131 (38.5)	87.0 (40.8)	51.7 (14.9)	62.4 (34.0)
$AUC_{0\text{-}inf}$ (ng•hr/mL)	6.14 (3.25)	25.2 (9.58)	130 (39.4)	628 (199)	2030 (1070)

In general, CCX168 appears to have a biphasic profile, with a rapid distribution phase followed by a long terminal phase, and low apparent clearance in humans. Following oral administration, CCX168 was absorbed rapidly and reached peak plasma levels after 1 to 2 hours. Following a single dose of 1-100 mg, mean exposures as measured by $AUC_{0\text{-}inf}$ ranged from 6.14 to 2030 ng•hr/mL while C_{max} ranged from 1.84 to 197 ng/mL. The apparent mean terminal half-life ranged from 1.92 to 71.8 hr, while clearance ranged from 51.7 to 195 L/hr.

A summary of all the treatment-emergent adverse events observed in the multiple-dose period of the study is provided in Table 6.

Table 6: Summary of all the treatment-emergent adverse events observed in the multiple-dose period of the study, CL001_168

	Period 2 (Multi-Dose)						
System Organ Class Preferred Term		CCX168 Dose Group					
	Placebo (N=11)	**1 mg QD X 7d (N=5)**	**3 mg QD X 7d (N=6)**	**10 QD X 7d (N=6)**	**30 mg BID X 7d (N=6)**	**50 mg BID X 7d (N=6)**	**All CCX168 (N=29)**
Number (%) of subjects with AEs	4 (36%)	3 (60%)	2 (33%)	5 (83%)	4 (67%)	3 (50%)	17 (59%)
Eye disorders	1 (9%)	0	0	0	0	0	0 (0%)
Eyelid oedema	1 (9%)	0	0	0	0	0	0 (0%)
Gastrointestinal disorders	2 (18%)	0	0	2	0	2	4 (14%)
Abdominal pain lower	0 (0%)	0	0	1	0	1	2 (7%)
Abdominal pain upper	2 (18%)	0	0	0	0	1	1 (3%)
Constipation	0 (0%)	0	0	0	0	1	1 (3%)
Diarrhoea	1 (9%)	0	0	2	0	0	2 (7%)
Nausea	0 (0%)	0	0	1	0	1	2 (7%)
Vomiting	0 (0%)	0	0	1	0	0	1 (3%)
General disorders and administration site conditions	1 (9%)	1	1	0	0	0	2 (7%)
Fatigue	1 (9%)	0	0	0	0	0	0 (0%)

	Period 2 (Multi-Dose)						
System Organ Class Preferred Term		CCX168 Dose Group					
	Placebo (N=11)	**1 mg QD X 7d (N=5)**	**3 mg QD X 7d (N=6)**	**10 QD X 7d (N=6)**	**30 mg BID X 7d (N=6)**	**50 mg BID X 7d (N=6)**	**All CCX168 (N=29)**
Feeling of body temperature change	0 (0%)	1	0	0	0	0	1 (3%)
Injection site swelling	0 (0%)	0	1	0	0	0	1 (3%)
Infections and infestations	1 (9%)	0	0	1	0	0	1 (3%)
Cystitis	1 (9%)	0	0	0	0	0	0 (0%)
Sinusitis	0 (0%)	0	0	1	0	0	1 (3%)
Injury, poisoning and procedural complications	0 (0%)	0	0	1	0	0	1 (3%)
Tooth injury	0 (0%)	0	0	1	0	0	1 (3%)
Investigations	0 (0%)	1	0	1	0	0	2 (7%)
Aspartate aminotransferase increased	0 (0%)	0	0	1	0	0	1 (3%)
Blood creatine phosphokinase increased	0 (0%)	0	0	1	0	0	1 (3%)
White cell count decreased	0 (0%)	1	0	0	0	0	1 (3%)
Musculoskeletal and connective tissue disorders	0 (0%)	0	0	1	2	0	3 (10%)
Back pain	0 (0%)	0	0	1	0	0	1 (3%)
Muscular weakness	0 (0%)	0	0	0	1	0	1 (3%)
Neck pain	0 (0%)	0	0	0	1	0	1 (3%)
Nervous system disorders	2 (18%)	2	1	0	1	3	7 (24%)
Dizziness	0 (0%)	0	1	0	0	1	2 (7%)
Headache	2 (18%)	2	0	0	1	3	6 (21%)
Respiratory, thoracic and mediastinal disorders	1 (9%)	0	0	0	2	2	4 (14%)
Chest pain	0 (0%)	0	0	0	0	1	1 (3%)
Nasopharyngitis	0 (0%)	0	0	0	1	0	1 (3%)
Oropharyngeal pain	1 (9%)	0	0	0	1	1	2 (7%)
Skin and subcutaneous tissue disorders	0 (0%)	0	0	1	1	0	2 (7%)
Seborrhoeic dermatitis	0 (0%)	0	0	0	1	0	1 (3%)
Skin discomfort	0 (0%)	0	0	1	0	0	1 (3%)
Vascular disorders	0 (0%)	0	0	0	1	0	1 (3%)
Haematoma	0 (0%)	0	0	0	1	0	1 (3%)

The most common AE reported in subjects receiving CCX168 in the multi-dose period was headache, reported in 21% of subjects receiving CCX168 compared to 18% in the placebo group. Diarrhoea (7% vs. 9% in placebo), dizziness (7% vs. 0% in placebo), lower abdominal pain (7% vs. 0% in placebo), nausea (7% vs. 0% in placebo), and oropharyngeal pain (7% vs. 9% in placebo) were the other more commonly observed AEs. The one case of AST and CPK elevation was considered likely related to strenuous exercise and not considered related to CCX168. The one subject with low WBC count in the 1 mg CCX168 group was the same subject who had low WBC during the single-dose period of the study. The WBC count nadir was 2.22×10^9/L on Day 4. No clinically significant changes in laboratory parameters, vital signs, or ECG parameters were observed. In the multi-dose period of the study, a slight decrease in mean WBC and

neutrophil count was observed more frequently in subjects receiving CCX168 compared to placebo. These WBC and neutrophil counts most often remained within the reference range, decreases were observed within 1 to 2 days after start of dosing, appeared to be most pronounced in subjects with baseline WBC and neutrophil counts at the higher end of the normal range, and did not appear to progressively worsen over the 7-day dosing period. Only a few subjects had WBC or neutrophil counts below the lower limit of normal over the course of the study, and these cases were observed in both CCX168 and placebo groups. These slight changes in WBC and neutrophil counts may be related to the pharmacology of CCX168 as a C5aR blocker.

Pharmacokinetic results (mean, SD) from the multi-dose period, once daily dose groups are summarized in Table 7. CCX168 was given as a dosing solution to subjects in these three dose groups.

Table 7: Summary of Pharmacokinetic Results (mean, SD) from the Multi-dose Period, Once Daily Dose Groups, CL001_168

Parameter	1 mg once daily (N=5)		3 mg once daily (N=6)		10 mg once daily (N=6)	
	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
C_{max} (ng/mL)	2.59 (1.12)	2.86 (1.09)	9.94 (3.69)	13.5 (4.30)	19.2 (8.46)	31.4 (9.49)
T_{max} (hr)	1.5 (0.50)	1.0 (0.0)	1.3 (0.42)	1.2 (0.26)	1.8 (0.69)	1.9 (0.59)
$t_{1/2}$ (hr)	2.66 (0.840)	12.2 (13.7)	6.12 (3.15)	71.8 (40.2)	6.14 (1.53)	162 (74.7)
CL/F (L/hr)	134 (71.0)	86.3 (51.2)	96.9 (34.1)	34.1 (21.5)	102 (36.6)	17.3 (6.73)
$AUC_{0\text{-}tau}$ (ng•hr/mL)	8.72 (4.56)	11.2 (5.24)	34.4 (11.2)	49.1 (16.8)	104 (45.3)	178 (51.2)

Pharmacokinetic results (mean, SD) from the multi-dose period, twice daily dose groups are summarized in Table 8. CCX168 was given as capsules, similar to the capsules tested in the current study, to subjects in these two dose groups.

Table 8: Summary of Pharmacokinetic Results (mean, SD) from the Multi-dose Period, Twice Daily Dose Groups, CL001_168

Parameter	30 mg twice daily, Day 1 (N=6)		30 mg twice daily, Day 7 (N=6)		50 mg twice daily, Day 1 (N=6)		50 mg twice daily, Day 7 (N=6)	
	AM Dose	PM Dose	AM Dose	PM Dose	AM Dose	PM Dose	AM Dose	PM Dose
C_{max} (ng/mL)	97.2 (16.4)	274 (69.9)	161 (22.9)	191 (60.2)	202 (66.1)	423 (204)	425 (156)	359 (139)
T_{max} (hr)	1.8 (0.41)	2.0 (0.0)	2.3 (0.52)	2.2 (0.98)	2.0 (0.0)	2.3 (0.52)	2.3 (0.52)	2.8 (0.98)
$t_{1/2}$ (hr)	3.08 (0.761)	4.20 (1.01)	5.05 (1.33)	129 (30.7)	2.83 (0.582)	4.09 (0.666)	4.81 (1.35)	120 (19.5)
CL/F (L/hr)	78.4 (23.3)	41.4 (14.4)	28.7 (10.2)	5.86 (2.09)	62.5 (20.1)	37.3 (14.7)	19.4 (7.63)	4.05 (1.02)
$AUC_{0\text{-}tau}$ (ng•hr/mL)	380 (89.3)	695 (171)	880 (230)	966 (243)	820 (274)	1400 (728)	2340 (885)	2180 (811)

$AUC_{0\text{-}tau}$ is $AUC_{0\text{-}12}$ (Day 1) or $AUC_{12\text{-}24}$ (Day 7; shown as $AUC_{0\text{-}12}$ in WinNonlin data file after adjustment of start time).

Following administration at 1 to 10 mg CCX168 QD for 7 days, mean exposures as measured by $AUC_{0\text{-}tau}$ ranged from 8.72 to 104 ng•hr/mL on Day 1 and from 11.2 to 178 ng•hr/mL on Day 7, while C_{max} ranged from 2.59 to 19.2 ng/mL on Day 1 and 2.86 to 31.4 ng/mL on Day 7.

Following BID administration at 30 to 50 mg, mean exposures as measured by $AUC_{0\text{-}tau}$ ranged from 380 to 1400 ng•hr/mL on Day 1 and from 880 to 2340 ng•hr/mL on Day 7, while C_{max} ranged from 97.2 to 423 ng/mL on Day 1 and 161 to 425 ng/mL on Day 7.

CCX168 levels declined in a biphasic exponential manner, with a rapid distribution phase and an apparent mean plasma terminal $t_{1/2}$ ranging from 12.2 to 162 hr following once daily administration.

Repeat administration for seven days of CCX168 resulted in moderate accumulation (at 1 and 3 mg QD) or high accumulation (10 mg QD or 30 – 50 mg BID) of CCX168, consistent with the observed terminal half-life in these dosing groups. After QD dosing, the exposure of CCX168 as measured by C_{max} and AUC is approximately dose proportional in the 1 – 10 mg dose range. After BID dosing, the exposure increase of CCX168 statistically appears to be linearly proportional for 30 mg and 50 mg doses. Based on the measured trough concentrations, in general, CCX168 appeared to reach steady state after 3-4 days of dosing.

Food effect was also investigated by comparing the Day 7 0-12h (fasted) and 12-24h (fed) parameters. No significant effects were seen in either dose group.

CCX168-M1, a monohydroxylation metabolite of CCX168, was found to be a major circulating metabolite in humans. Following 7 days of oral administration of CCX168 at 30 mg and 50 mg BID, the $AUC_{0\text{-}24}$ for CCX168-M1 was 1600 and 2340 ng•hr/mL, respectively. These values represent 85% and 52%, respectively, of the levels of CCX168 measured at those doses. Its exposure was adequately covered in rats and cynomolgus monkeys in the toxicology studies that support this Phase 2 clinical trial.

Steps 1 and 2 of this study (CL002_168) have been completed. Results are summarized in the Investigator's Brochure. **The third step of this clinical trial CL002_168 is ongoing. One subject in Step 3 had a serious unexpected suspected adverse reaction of increased liver and pancreatic enzymes. The treatment assignment remains blinded, since Step 3 is still ongoing. An 80-year old man with a medical history of alcohol abuse, smoking, and elevated alkaline phosphatase and GGT at baseline, had an increase in hepatic transaminases, GGT, alkaline phosphatase, total and direct bilirubin, and pancreatic amylase starting approximately 3 weeks after starting study medication and IV cyclophosphamide, sulfamethoxazole plus trimethoprim, and pantoprazole. The subject experienced vomiting, fatigue, reduced appetite, and icterus since Day 23. No fever or eosinophilia was present. Abdominal ultrasonography showed hepatic steatosis and possible veno-occlusive disease. Study medication and cyclophosphamide were stopped on Day 26. There was no evidence of active viral hepatitis (including CMV). Abdominal CT done on Day 31 showed signs of minimal cholangitis, and no sign of cholestasis or pancreatitis. Liver biopsy on Day 34 showed a mixed pattern of injury with widely resolved hepatitis and persistent cholangitic/cholestatic components, consistent with drug-induced etiology. The patient's condition improved and he was discharged from hospital on Day 41.**

1.4. Rationale for the Study

AAV standard therapy includes cyclophosphamide (IV or oral, although IV is preferred because of a lower cumulative dose and lower toxicity), and oral corticosteroids, tapered over a period of time. Severe disease warrants addition of IV corticosteroids and/or plasma exchange. Results

from recent clinical trials (Jones et al., 2010 and Stone et al., 2010) that have attempted to eliminate cyclophosphamide use, indicated that the incidence of adverse events and the mortality rate remain high in subjects who did not receive cyclophosphamide but rituximab. High dose corticosteroid use likely contributes significantly to this high morbidity and mortality rates. Therefore, the medical need for alternative therapies remains high and it is important to find ways to reduce or eliminate corticosteroid use in the treatment of AAV.

Based on encouraging results from preclinical studies in a human C5aR knock-in mouse model of AARV (described in section 1.2.1.2, as well as the Investigator's Brochure), CCX168 has the potential to be a corticosteroid sparing or corticosteroid replacement therapy for this disease, with potential safety and tolerability advantages. Hence, the clinical hypothesis of the trial is to test the feasibility of using CCX168 as a corticosteroid sparing or replacement therapy during the period of induction of remission of AAV. Results from a Phase 1 clinical trial conducted in human volunteers indicated that CCX168 was well tolerated with a pharmacokinetic profile lending it to twice daily oral dosing, in order to provide sufficient C5aR plasma coverage. Therefore, the rationale for this Phase 2 study is to determine whether CCX168 is safe and well tolerated and shows evidence of efficacy, based on its potential to be corticosteroid-sparing, after oral administration of CCX168 for 84 consecutive days to subjects with AAV.

2. OBJECTIVES

2.1. Primary Objective

The primary safety objective of this study is to evaluate the safety and tolerability of CCX168 in subjects with AAV on background cyclophosphamide or rituximab treatment.

The primary efficacy objective is to evaluate the efficacy of CCX168 based on the Birmingham Vasculitis Activity Score (BVAS).

2.2. Secondary Objectives

The secondary objectives of the study include the following:

1. Evaluation of the efficacy of CCX168 compared to standard of care (SOC) based on changes in renal disease activity parameters:
   a. eGFR (MDRD serum creatinine equation);
   b. Hematuria (central laboratory microscopic count of urinary RBCs); and
   c. Albuminuria (first morning urinary albumin:creatinine ratio);
2. Assessment of changes in renal inflammatory activity based on urinary monocyte chemoattractant protein-1 (MCP 1):creatinine ratio and serum C-reactive protein concentration with CCX168 compared to SOC;
3. Assessment of the feasibility of reducing or eliminating the use of corticosteroids in the treatment of subjects with ANCA-associated vasculitis (AAV) without the need for rescue corticosteroid measures with CCX168 compared to SOC;
4. Assessment of health-related quality-of-life changes based on Short Form-36 version 2 (SF-36v2) and EuroQOL-5D-5L (EQ-5D-5L) with CCX168 compared to SOC;

5. Assessment of changes in Vasculitis Damage Index (VDI) with CCX168 compared to SOC;
6. Assessment of changes in ANCA (anti-PR3 and anti-MPO) with CCX168 compared to SOC;
7. Assessment of changes in pharmacodynamics markers in plasma and urine with CCX168 compared to SOC;
8. Evaluation of the pharmacokinetic profile of CCX168 in subjects with AAV.

3. STUDY DESIGN

AAV standard therapy includes cyclophosphamide or rituximab and oral corticosteroids, tapered over a period of time. Severe disease warrants addition of IV corticosteroids and/or plasma exchange. Based on numerous studies indicating the involvement of C5a in AAV, as well as compelling results with CCX168 in preclinical studies in a human C5aR knock-in mouse model of AARV, CCX168 has the potential to be a corticosteroid sparing or corticosteroid replacement therapy for this disease. Hence, the clinical hypothesis of the trial is to test the feasibility of using CCX168 as a corticosteroid sparing or replacement therapy during induction of remission of AAV. This hypothesis will be tested in a three-step manner in this randomized, double-blind, placebo-controlled, Phase 2 clinical trial in up to approximately 60 subjects with new or relapsed AAV. Refer to the Study Schema for the study flow.

Steps 1 and 2 of the study have been completed.

STEP 1

In Step 1 of the trial, up to approximately 12 subjects will be stratified to one of two strata, either newly diagnosed AARV or relapsed AARV, and then randomized to CCX168 or placebo (in a 2:1 ratio). A two-thirds reduced dose of oral corticosteroids will be given to subjects randomized to CCX168 and a full dose of oral corticosteroids to subjects randomized to placebo. All 12 subjects will receive IV cyclophosphamide treatment, which is part of standard therapy for AARV. If necessary, rescue IV methylprednisolone or oral rescue steroids after Day 1 should be given according to section 5.10 to subjects with worsening disease.

Progression to Step 2 is dependent upon the safety and efficacy of CCX168 observed in Step 1.

An external data monitoring committee (DMC) will review safety data, including rescue IV or oral corticosteroid use over the course of the study and advise the Sponsor regarding progression from each step to the next in the study (see section 7.6).

- If there are more than one suspected unexpected serious adverse reaction (SUSAR) most likely related to CCX168, as assessed by the DMC, in subjects receiving CCX168 in Step 1, further recruitment of subjects will be suspended.
- If AARV disease activity in the majority of subjects (>50%) on CCX168 in Step 1 is not controlled without the need for IV or oral rescue corticosteroid therapy, further recruitment of subjects will be suspended.
- If a clinically significant tolerability issue prevents further dosing of CCX168 at 30 mg twice daily, consideration will be given to testing a lower dose of CCX168. In this event, the protocol will be amended to specify the details.

- The PK profile of CCX168 30 mg twice daily will be assessed after at least 3 subjects have received at least one dose of CCX168 or placebo. The PK profile (C_{max}, AUC) on Day 1 will be compared to that observed in healthy volunteers. If on average CCX168 plasma exposure is more than twice that observed in healthy volunteers, consideration will be given to testing a lower dose of CCX168. In this event, the protocol will be amended to specify the details.

STEP 2

Step 2 will be opened for enrollment if both of the following criteria are met:

1. Not more than 1 SUSAR most likely related to CCX168, as assessed by the DMC, is observed in subjects receiving CCX168 in Step 1;
2. AARV disease activity is controlled in the majority of subjects (>50%) receiving CCX168 in Step 1, without the need for IV or oral rescue corticosteroid therapy, as assessed by the DMC.

In Step 2 of the trial, up to approximately 12 subjects will be stratified to one of two strata, either newly diagnosed AARV or relapsed AARV, and then randomized to CCX168 or placebo (in a 2:1 ratio). Oral corticosteroids will not be given to subjects randomized to CCX168, but a full dose of oral corticosteroids will be given to subjects randomized to placebo. All 12 subjects will receive IV cyclophosphamide treatment. If necessary, rescue IV methylprednisolone or oral rescue steroids should be given according to section 5.10 to subjects with worsening disease**.**

STEP 3

In Step 3, approximately 36 subjects will be stratified prior to randomization based on the following stratification factors:

1. Either newly diagnosed AAV or relapsed AAV;
2. Either MPO or PR3 ANCA positivity;
3. Will receive either cyclophosphamide or rituximab as part of standard of care treatment.

Following stratification, subjects will be randomized 1:1:1 to one of three groups:

Group A: CCX168 plus cyclophosphamide/rituximab with no oral corticosteroids;

Group B: Placebo plus cyclophosphamide/rituximab plus a full starting dose of oral corticosteroids;

Group C: CCX168 plus cyclophosphamide/rituximab plus a two-thirds reduced starting dose of oral corticosteroids.

If necessary, rescue IV methylprednisolone or oral rescue steroids should be given to subjects with worsening disease.

Step 3 will be opened for enrollment if both of the following criteria are met:

1. Not more than 1 SUSAR most likely related to CCX168, as assessed by the DMC, is observed in subjects receiving CCX168 in Step 2;

2. AAV disease activity is controlled in the majority of subjects (>50%) receiving CCX168 in Step 2, without the need for IV or oral rescue corticosteroid therapy.

In order to protect the blinding, a double-dummy design will be utilized. The study drug and other medication for renal vasculitis will be taken as described in sections 5.3, 5.9, 5.10, 11.5 and 11.6.

The dosing period is 84 days in all three steps of the study. Following the 84-day dosing period, there will be an 84-day follow-up period. All subjects will visit the study center during the screening period, and on Days 1, 2, 8, 15, 22, 29, 43, 57, 71, 85, 99, 113, 141, and 169. Subjects will not take study medication in the morning of the days of visits to the study center, and will be instructed to take the medication while at the study center after all study procedures for the day have been completed. For the other study days, study medication will be taken at home in the morning within 1 hour after breakfast and in the evening within 1 hour after dinner.

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 demographics, medical history, medication history, physical examination and vital signs, serum chemistry, hematology, PT, and aPTT, urinalysis (including hematuria and proteinuria [ACR] assessment), ECG, chest X rays, viral screening, serology and complement measurements (if not done within the previous 12 months), eGFR assessment, ANCA measurement (indirect immunofluorescence test for P-ANCA and C-ANCA, as well as ELISA tests for PR3 and MPO), renal biopsy (if necessary for study eligibility), and BVAS assessment. Laboratory results from the local laboratories obtained within 72 hours of screening are acceptable in order to avoid unnecessary blood draws. Eligible subjects must be ANCA-positive, must have at least one “major” item, or at least 3 non-major items, or at least two renal items on the BVAS version 3 (see section 11.3).

Eligible subjects will visit the study center on Day 1, after an overnight fast of at least 8 hours, for physical examination and vital signs, serum chemistry, hematology, urinalysis (including hematuria, proteinuria [ACR], MCP-1:creatinine ratio assessment), eGFR, ANCA (anti-PR3 and anti-MPO) measurement, a BVAS and VDI assessment, SF-36v2 and EQ-5D-5L assessment, baseline pharmacokinetics and pharmacodynamics (PK/PD) blood sample collection, and randomization. Medication will be administered (IV) and dispensed (for oral medications). The subjects will take the first dose of CCX168 or placebo, and prednisone or placebo while at the study center. The subjects will stay at the clinic for at least 6 hours after the first dose on Day 1 for safety observation and PK sample collection. A subject could be kept overnight in the hospital on Day 1, if necessary. 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 84 days. At post-Day 1 study visits, study medication will be administered according to the protocol schedule, blood and urine samples will be collected for safety and efficacy and PK/PD measurements. BVAS assessments will be made on Days 1, 29, 85, 113, and 169. VDI assessments will be made on Days 1, 85, and 169. SF-36v2 and EQ-5D-5L instruments will be completed on Days 1, 29, 85, and 169 in Step 3. Physical examinations, body system reviews, and vital sign assessments will be performed throughout the study. Concomitant medication and adverse event assessments will be made at every study visit.

Subjects will be terminated from the study when all the Study Day 169 visit procedures have been completed.

To the extent possible, any adverse events that are deemed study drug-related and are ongoing at discharge will be followed-up to resolution or until a determination is made that the unresolved event is stable. The subject’s condition will be evaluated by the Investigator at the end of the

clinical trial (Day 169) and appropriate standard of care medical treatment will be provided to all subjects as needed.

4. STUDY POPULATION

4.1. Size of the Population

The aim is to enroll up to approximately sixty (60) subjects for the study. Subjects who drop out of the study prematurely will not be replaced. These subjects will be part of the intent-to-treat population. Subjects will not be allowed to participate in more than one Step of the study.

4.2. Inclusion Criteria

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

1. Clinical diagnosis of granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis or renal limited vasculitis, consistent with Chapel-Hill consensus definitions (Jennette et al., 2013);
2. Male and postmenopausal (**lack of menses for** at least 2 years **without an alternative explanation**) or surgically sterile female subjects, aged at least 18 years, with new (within 4 weeks prior to screening) or relapsed AAV where treatment with cyclophosphamide or rituximab would be required; **If female under 50 years, the postmenopausal status should be confirmed by the relevant hormonal test.** Male subjects 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, and for at least the three months after study completion; Adequate contraception is defined as resulting in a failure rate of less than 1% per year; **Acceptable methods include combined estrogen and progestogen (oral, intravaginal, or transdermal), or progestogen-only hormonal contraception (oral, injectable, or implantable), intra-uterine device, intrauterine hormone releasing system, bilateral tubal occlusion, vasectomized partner, or sexual abstinence;**
3. Positive indirect immunofluorescence (IIF) test for P-ANCA or C-ANCA, or positive ELISA test for anti-proteinase-3 (PR3) or anti-myeloperoxidase (MPO) at screening; If only the IIF assay is positive at screening, and none of the ELISA tests, there must be documentation in the study records of a positive ELISA assay in the past;
4. Have at least one "major" item, or at least 3 non-major items, or at least 2 renal items on the BVAS version 3 (see section 11.3);
5. eGFR ≥20 mL per minute (MDRD);
6. Willing and able to give written Informed Consent and to comply with the requirements of the study protocol; and
7. Judged to be otherwise healthy by the Investigator, based on medical history, physical examination (including electrocardiogram [ECG]), and clinical laboratory assessments. Subjects 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 be of clinical significance, may be entered into the study.

4.3. Exclusion Criteria

1. Severe disease as determined by rapidly progressive glomerulonephritis such that commencement of renal replacement therapy could be anticipated within 7 days, alveolar hemorrhage leading to Grade 3 or higher hypoxia (i.e., decreased oxygen saturation at rest, e.g., pulse oximeter <88% or $P_aO_2 \leq 55$ mm Hg), hemoptysis, rapid-onset mononeuritis multiplex (Grade 3 or higher, leading to severe symptoms that limit self care activities of daily living or requiring an assistive device), or central nervous system involvement;
2. Any other multi-system autoimmune disease including eosinophilic granulomatosis with polyangiitis (Churg Strauss), systemic lupus erythematosus, IgA vasculitis (Henoch-Schönlein purpura), rheumatoid vasculitis, Sjögren's disease, anti-glomerular basement membrane disease, or cryoglobulinemia;
3. Medical history of coagulopathy or bleeding disorder;
4. Received cyclophosphamide within 12 weeks prior to screening; if on azathioprine, mycophenolate mofetil, or methotrexate at the time of screening, these drugs must be withdrawn prior to receiving the cyclophosphamide dose on Day 1;
5. Received intravenous corticosteroids, >3000 mg methylprednisolone equivalent, within 12 weeks prior to screening;
6. Have been taking an oral daily dose of a corticosteroid of more than 10 mg prednisone-equivalent for more than 6 weeks continuously prior to the screening visit. If on an oral corticosteroid at a daily dose of more than 10 mg prednisone equivalent at the time of screening, the oral dose needs to be reduced to a daily dose not exceeding 10 mg prednisone-equivalent prior to Day 1;
7. 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 > 0.01×10^9/L); received anti-TNF treatment, abatacept, alemtuzumab, IVIg, belimumab, tocilizumab, or plasma exchange within 12 weeks prior to screening;
8. Symptomatic congestive heart failure requiring prescription medication, clinically evident peripheral edema of cardiac origin, poorly-controlled hypertension (systolic blood pressure >160 or diastolic blood pressure >100), history of unstable angina, myocardial infarction or stroke within 6 months prior to screening;
9. 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 cervical carcinoma in situ or breast carcinoma in situ that has been excised or resected completely and is without evidence of local recurrence or metastasis;
10. Presence of tuberculosis based on chest X rays performed during screening as part of the BVAS assessment.
11. Positive HBV, HCV, or HIV viral screening test;
12. Any infection requiring antibiotic treatment within 4 weeks prior to screening (except for prophylactic treatment for *Pneumocystis carinii* pneumonia [PCP] or treatment for suspected infection that instead turns out to be a consequence of ANCA vasculitis, e.g., pneumonitis);

13. Received a live vaccine within 4 weeks prior to screening;
14. WBC count less than 4000/µL**,** or neutrophil count less than 2000/µL, or lymphocyte count less than 1000/µL;
15. Hemoglobin less than 9 g/dL (or 5.56 mmol/L) at screening;
16. Evidence of hepatic disease; AST, ALT, alkaline phosphatase, or bilirubin > 3 x the upper limit of normal;
17. Prothrombin time (PT) or partial thromboplastin time (PTT) above the normal reference limit;
18. Clinically significant abnormal ECG during screening, e.g., QTcF greater than 450 msec;
19. 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; and
20. History or presence of any medical condition or disease which, in the opinion of the Investigator, may place the subject at unacceptable risk for study participation.

4.4. Removal of Subjects from Therapy of Assessment

Subjects may be terminated early from the study for any of the following reasons:

1. Subject request: Subjects may withdraw their consent to participate in the study at any time without prejudice.
2. Investigator request: The Investigator may withdraw a subject if, in his/her clinical judgment, it is in the best interest of the subject or if the subject cannot comply with the protocol.
3. Sponsor request.

In the event of withdrawal from the study prior to the Day 85 visit, the tests and evaluations listed for Study Day 85 should be carried out as part of the Early Termination visit, whenever possible. For subjects who withdraw after Day 85, the Day 169 study procedures should be performed. The Sponsor should be notified of all study withdrawals in a timely manner.

In the event of treatment failure where rescue corticosteroid therapy is needed, the study drug (CCX168 or placebo) and blinded prednisone/placebo will be discontinued, and appropriate open-label standard of care measures will be taken. However, the subject will be asked to remain in the study and complete all remaining study visits. If this is not possible, an attempt will be made to complete all procedures scheduled for the Day 85 visit (if the rescue event occurred prior to the Day 85 visit) and Day 169 (if the rescue event occurred after the Day 85 visit).

5. STUDY MEDICATION/TREATMENT

5.1. Product Characteristics

CCX168 will be administered as hard gelatin capsules containing 10 mg CCX168. The capsules are manufactured under cGMP. All doses of study medication will be administered orally. The CCX168 capsules will be supplied to the study centers in plastic bottles containing 30 capsules.

5.2. Randomization and Method of Treatment Assignment

Eligible subjects will be enrolled, stratified in two strata: (1) newly diagnosed (within 4 weeks of screening) or (2) relapsed AAV for Steps 1 and 2, and the three stratification factors for Step 3 (i.e., newly diagnosed or relapsing disease, PR3 or MPO ANCA, and cyclophosphamide or rituximab use), and then randomized to one of the two treatment groups in a ratio of 2:1, CCX168:placebo for Steps 1 and 2, and one of three treatment groups in a ratio of 1:1:1, CCX168 plus no prednisone:Placebo:CCX168 plus reduced prednisone in Step 3. Randomization will be performed centrally via an interactive voice/web response system (IVRS/IWRS). In order to protect the blinding, the randomization schedule will not be accessible to study personnel directly involved in the study.

5.3. Doses and Regimens

There will be two groups in each of the first two steps of the study:

- Group A: CCX168 30 mg twice daily
- Group B: Placebo twice daily

There will be three groups in the third step of the study:

- Group A: CCX168 30 mg twice daily plus no prednisone
- Group B: Placebo twice daily
- Group C: CCX168 30 mg twice daily plus low dose prednisone

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.

STEP 1

In Step 1, the study drug and other medication for renal vasculitis will be taken as follows by study subjects:

- Group A (30 mg CCX168 twice daily):
  - Three 10-mg CCX168 capsules in the morning and 3 capsules in the evening, approximately 12 hours after the morning dose, daily for 84 days.
  - Prednisone 20 mg orally per day if the subject's body weight is ≥55 kg or 15 mg per day if the subject's body weight is <55 kg, starting on Day 1 with tapering according to the protocol-specified schedule (see section 11.5).
  - Prednisone matching placebo capsules equivalent to 40 mg orally per day if the subject's body weight is ≥55 kg or 30 mg per day if the subject's body weight is <55 kg, starting on Day 1 with tapering according to the protocol-specified schedule (see section 11.5).
  - Cyclophosphamide IV will be given on Day 1, and also on Days 15, 29, and 57; doses on Days 85, 113, 141, and 169 will be given at the discretion of the Principal Investigator (see section 11.6 for instructions).

  - Rescue IV methylprednisolone should be given according to section 5.10 to subjects with worsening disease.

- Group B (Placebo twice daily):
  - Three placebo CCX168 capsules in the morning and 3 capsules in the evening, approximately 12 hours after the morning dose, daily for 84 days.
  - Prednisone 60 mg orally per day if the subject's body weight is ≥55 kg or 45 mg per day if the subject's body weight is <55 kg, starting on Day 1 with tapering according to the protocol-specified schedule (see section 11.5).
  - Cyclophosphamide IV will be given on Day 1 and also on Days 15, 29, and 57; doses on Days 85, 113, 141, and 169 will be given at the discretion of the Principal Investigator (see section 11.6 for instructions).
  - Rescue IV methylprednisolone should be given according to section 5.10 to subjects with worsening disease.

STEP 2

In Step 2, study drug and other medication for vasculitis will be taken as follows by study subjects:

- Group A (30 mg CCX168 twice daily):
  - Three 10-mg CCX168 capsules in the morning and 3 in the evening, approximately 12 hours after the morning dose, daily for 84 days.
  - Prednisone matching placebo capsules equivalent to 60 mg orally per day if the subject's body weight is ≥55 kg or 45 mg per day if the subject's body weight is <55 kg, starting on Day 1 with tapering according to the protocol-specified schedule (see section 11.5).
  - Cyclophosphamide IV will be given on Day 1 and also on Days 15, 29, and 57; doses on Days 85, 113, 141, and 169 will be given at the discretion of the Principal Investigator (see section 11.6 for instructions).
  - Rescue IV methylprednisolone should be given according to section 5.10 to subjects with worsening disease.
- Group B (Placebo twice daily):
  - Three placebo CCX168 capsules in the morning and 3 in the evening, approximately 12 hours after the morning dose, daily for 84 days.
  - Prednisone 60 mg orally per day if the subject's body weight is ≥55 kg or 45 mg per day if the subject's body weight is <55 kg, starting on Day 1 with tapering according to the protocol-specified schedule (see section 11.5).
  - Cyclophosphamide IV will be given on Day 1 and also on Days 15, 29, and 57; doses on Days 85, 113, 141, and 169 will be given at the discretion of the Principal Investigator (see section 11.6 for instructions).

- Rescue IV methylprednisolone should be given according to section 5.10 to subjects with worsening disease.

STEP 3

In Step 3, study drug and other medication for vasculitis will be taken as follows by study subjects:

- Group A (30 mg CCX168 twice daily with no corticosteroids):
  - Three 10-mg CCX168 capsules in the morning and 3 in the evening, approximately 12 hours after the morning dose, daily for 84 days.
  - Prednisone matching placebo capsules equivalent to 60 mg orally per day if the subject's body weight is ≥55 kg or 45 mg per day if the subject's body weight is <55 kg, starting on Day 1 with tapering according to a protocol-specified schedule (see section 11.5).
  - If in the cyclophosphamide stratum, cyclophosphamide IV will be given on Day 1 and also on Days 15, 29, 57, and 85; starting on Day 99 through Day 168, all subjects will receive oral azathioprine at a target dose of 2 mg/kg/day (see section 11.6 for instructions).
  - If in the rituximab stratum, rituximab IV will be given on Days 1, 8, 15, and 22 (375 mg/m^2 at each timepoint; see section 11.7).
  - Rescue IV methylprednisolone or oral steroids should be given according to section 5.10 to subjects with worsening disease.
- Group B (Placebo twice daily):
  - Three placebo CCX168 capsules in the morning and 3 in the evening, approximately 12 hours after the morning dose, daily for 84 days.
  - Prednisone 60 mg orally per day if the subject's body weight is ≥55 kg or 45 mg per day if the subject's body weight is <55 kg, starting on Day 1 with tapering according to a protocol-specified schedule (see section 11.5).
  - If in the cyclophosphamide stratum, cyclophosphamide IV will be given on Day 1 and also on Days 15, 29, 57, and 85; starting on Day 99 through Day 168, all subjects will receive oral azathioprine at a target dose of 2 mg/kg/day (see section 11.6 for instructions).
  - If in the rituximab stratum, rituximab IV will be given on Days 1, 8, 15, and 22 (375 mg/m^2 at each timepoint; see section 11.7).
  - Rescue IV methylprednisolone or oral steroids should be given according to section 5.10 to subjects with worsening disease.
- Group C (30 mg CCX168 twice daily with reduced corticosteroids):
  - Three 10-mg CCX168 capsules in the morning and 3 capsules in the evening, approximately 12 hours after the morning dose, daily for 84 days.

- Prednisone 20 mg orally per day if the subject's body weight is ≥55 kg or 15 mg per day if the subject's body weight is <55 kg, starting on Day 1, with tapering according to the protocol-specified schedule (see section 11.5).
- Prednisone matching placebo capsules equivalent to 40 mg orally per day if the subject's body weight is ≥55 kg or 30 mg per day if the subject's body weight is <55 kg, starting on Day 1, with tapering according to a protocol-specified schedule.
- If in the cyclophosphamide stratum, cyclophosphamide IV will be given on Day 1 and also on Days 15, 29, 57, and 85; starting on Day 99 through Day 168, all subjects will receive oral azathioprine at a target dose of 2 mg/kg/day (see section 11.6 for instructions).
- If in the rituximab stratum, rituximab IV will be given on Days 1, 8, 15, and 22 (375 mg/m^2 at each timepoint; see section 11.7).
- Rescue IV methylprednisolone or oral corticosteroids should be given according to section 5.10 to subjects with worsening disease.

All subjects will take study medication as instructed on the days of visits to the study center. For the other study days, study medication will be taken at home as instructed. Following the 84-day dosing period, there will be an 84-day follow-up period.

Subjects in Group A in Steps 1 and 2, and Groups A and C in Step 3 (30 mg CCX168) will receive one kit containing two bottles of CCX168 capsules on Days 1, 8, 15, and 22. Subjects in Group A in Steps 1 and 2, and Groups A and C in Step 3 will receive two kits containing 2 bottles each of CCX168 capsules on Days 29, 43, 57, and 71. Subjects will be asked to take 3 capsules every morning and 3 capsules every evening as instructed. Subjects will be asked to bring all bottles, whether empty or not, to the study center at each study visit. Capsules will be taken within 1 hour after breakfast or dinner with water, preferably with 50 mL, but not to exceed 100 mL. Subjects in Group A will also take prednisone and/or matching placebo capsules once daily over the course of the study.

Subjects in Group B (placebo) will receive one kit containing two bottles of placebo CCX168 capsules on Days 1, 8, 15, and 22. Subjects in Group B will receive two kits containing 2 bottles each of placebo CCX168 capsules on Days 29, 43, 57, and 71. Subjects will be asked to take 3 capsules every morning and 3 capsules every evening as instructed. Subjects will be asked to bring all bottles, whether empty or not, to the study center at each study visit. Capsules will be taken within 1 hour after breakfast or dinner with water, preferably with 50 mL, but not to exceed 100 mL. Subjects in Group B will also take prednisone and/or matching placebo capsules once daily over the course of the study.

Prednisone will be given as tablets, overencapsulated with hard gelatin capsules in order to maintain the blinding. Two dose strengths of prednisone will be provided, 20 mg and 5 mg. Placebo prednisone will be given as matching hard gelatin capsules with inert filler. Each subject will receive 1 kit with 3 bottles containing prednisone or placebo prednisone on Study Days 1, 8, 15, 29, 43, 57, 85, 99, and 113. The 20 mg prednisone and matching placebo bottles will contain 10 capsules per bottle. The 5 mg prednisone and matching placebo bottles will contain 30 capsules per bottle. Subjects will be provided with detailed instructions regarding the number of

capsules to take each day from each bottle. The dose of corticosteroids will be tapered over the course of the study (see section 11.5 for the tapering schedule).

If a subject is already on a dose of oral corticosteroids of ≤ 10 mg prednisone-equivalent at the time of screening, an attempt will be made to taper this non-study corticosteroid use to zero over a period not to exceed 6 weeks, starting on Day 1 of the study. If tapering to zero is unsuccessful, the subject will be maintained on the lowest possible non-study maintenance corticosteroid dose, but not greater than 10 mg prednisone-equivalent.

Cyclophosphamide IV will be given on Day 1 and also on Days 15, 29, 57, and 85; starting on Day 99 through Day 168, all subjects will receive oral azathioprine at a target dose of 2 mg/kg/day (see section 11.6 for instructions).

Rituximab IV will be given on Days 1, 8, 15, and 22 (375 mg/m^2 at each time point; see section 11.7).

IV methylprednisolone or oral prednisone, only as rescue therapy, will be given according to section 5.10.

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 multiple once daily doses of 1, 3, and 10 mg CCX168 and multiple twice daily doses of 30 mg and 50 mg for up to 7 days were studied in the multiple dose period of the study. A dose of 30 mg CCX168 twice daily has been selected for this Phase 2 study in subjects with AAV, which is lower than the maximum dose of 50 mg twice daily studied in study CL001_168. All doses up to 100 mg (single dose) and 50 mg twice daily for 7 days were well tolerated with no significant safety concerns. It is anticipated that dose regimens of ≥ 30 mg CCX168 twice daily would provide at least 95% C5aR coverage 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 based on *in vitro* assays conducted in whole blood samples obtained from the Phase 1 clinical trial.

Based on the good safety profile observed in the toxicology studies, and the safety and tolerability results from the Phase 1 clinical trial and this clinical trial so far, 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 in kits (boxes) containing two bottles of CCX168 or placebo capsules. Each bottle will contain 30 capsules. All bottles will be labeled appropriately to indicate, at a minimum, protocol number, the bottle number, the study drug, the contents, storage conditions, cautionary statement to keep out of reach of children, and the expiry date. One kit will be dispensed to a subject on Study Days 1, 8, 15, and 22. Two kits will be dispensed to a subject on

Study Days 29, 43, 57, and 71. All kits will be labeled appropriately to indicate, at a minimum, protocol number, the study drug, the contents, storage conditions, cautionary statement to keep out of reach of children, and the expiry date.

Prednisone capsules containing either 20 mg or 5 mg prednisone 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. Each bottle of 20 mg or matching placebo capsules will contain 10 capsules. Each bottle of 5 mg or matching placebo capsules will contain 30 capsules. All bottles will be labeled appropriately to indicate, at a minimum, protocol number, the bottle letter, the study drug, the contents, storage conditions, cautionary statement to keep out of reach of children, and the expiry date. The prednisone and matching placebo bottles will be packaged in kits (boxes) containing three bottles of prednisone and/or placebo, depending on treatment group assignment. One kit will be dispensed to a subject on Study Days 1, 8, 15, 29, 43, 57, 85, 99, and 113. Detailed dosing instructions will be provided to all subjects. All kits will be labeled appropriately to indicate, at a minimum, protocol number, the study drug, the contents, storage conditions, cautionary statement to keep out of reach of children, and the expiry date.

5.5.2. Storage

CCX168 and CCX168 placebo capsules, as well as prednisone and prednisone 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; study site personnel, study subjects, 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 the study staff with direct contact with study sites during the study;
4. Efficacy data that would potentially be unblinding, i.e, anti-PR3 and anti-MPO antibodies, urinary MCP-1:creatinine ratio, urinary ACR, WBC and neutrophil count data within the normal range, and hsCRP data, will not be made available to study site personnel, study subjects, personnel responsible for study monitoring, and biostatisticians and data managers during the study unless for safety monitoring.

Treatment assignments for individual subjects will remain blinded to the study team, investigators, and subjects until after the study database has been cleaned and locked. Designated study staff will be provided with instructions regarding how to unblind individual subject

treatment assignment; individual subject treatment assignment may be unblinded only in the case of an adverse event that requires knowledge of the study medication received by the subject in order to provide appropriate treatment or management of the adverse event. The study monitor should be notified as soon as possible in the event that unblinding of an individual subject'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 (subject-by-subject 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 placebo capsules, and prednisone and prednisone placebo capsules, will be self-administered by participating study subjects. The morning doses of study drug on Day 1 will be taken in the presence of study site personnel. Subjects 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. Subjects 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 for any unused study drug, and a capsule count will be done of any remaining CCX168 and prednisone study medication. This information will be recorded in the CRF.

CCX168 plasma concentration measurements over the course of the study may also be used to assess subject 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 placebo, oral prednisone or prednisone placebo, IV cyclophosphamide or rituximab, or rescue IV or oral corticosteroids to treat AAV is prohibited over the course of the 84-day treatment period. This includes use of oral cyclophosphamide, azathioprine, mycophenolate mofetil, methotrexate, anti-TNF treatment, abatacept, alemtuzumab, IVIg, belimumab, tocilizumab, or other immunosuppressive agents. However, subjects in the cyclophosphamide stratum will take oral azathioprine at a target dose of 2 mg/kg/day from Day 99 through Day 168.

Prophylactic treatment for osteoporosis, gastroprotection, *Pneumocystis carinii* pneumonia (PCP), and anti-nausea medication (e.g., ondansetron), according to local practice, is allowed.

Subjects will also be encouraged to remain on stable doses of all other concomitant medication over the course of the study. If a subject is on a dose of oral corticosteroids of $\leq$ 10 mg

prednisone-equivalent at the time of screening, an attempt will be made to taper this corticosteroid use to zero over a period not to exceed 6 weeks starting at Day 1. If tapering to zero is unsuccessful, the subject will be maintained on the lowest possible maintenance corticosteroid dose, but not greater than 10 mg prednisone-equivalent.

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

Subjects will be receiving various background therapies in this trial, e.g., rituximab, cyclophosphamide, azathioprine, methotrexate, and/or mycophenolate mofetil. There are precautions listed in the prescribing information for each of these drugs. The local prescribing information for each background drug should be consulted prior to its use, so that these precautions can be taken into consideration.

5.10. Criteria for Rescue Corticosteroid Use

Use of rescue IV or high dose oral corticosteroids is deemed a treatment failure and should only be used under the following circumstances:

- Successive deterioration of eGFR over 3 days suggesting that, in the view of the principal investigator, if no extra intervention is taken, the renal function would continue to deteriorate;
- Worsening of renal function as judged by eGFR decrease of > 10 mL/min from baseline during the 84-day treatment period or during the 84-day follow-up period;
- Persistence or new occurrence of a major non-renal item as per BVAS, such as gangrene, sudden vision loss, retinal changes, sensorineural hearing loss, massive hemoptysis/alveolar hemorrhage, respiratory failure, cardiomyopathy, ischemic abdominal pain indicative of mesenteric ischemia, or nervous system disease; or
- If, based on the study site physician's assessment, it would be in the best interest of the subject.

The reason for rescue corticosteroid use will be captured on the CRF.

The standard IV rescue treatment will consist of 500 mg methylprednisolone given once daily for 3 days. This will be followed by oral corticosteroids according to the local standard of care. High dose oral prednisone rescue medication, e.g., 200 mg prednisone, with appropriate tapering, may also be used at the Investigator's discretion.

If rescue corticosteroid treatment is necessary, it would be considered a treatment failure and study drug (CCX168 or placebo) and blinded prednisone/placebo will be discontinued. The subject will receive appropriate open-label standard of care. Nevertheless, the subject will continue to be followed in the study (see section 4.4).

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 subjects to start treatment. Within a period not to exceed 14 days prior to randomization, subjects will undergo the following evaluations to determine their eligibility for study participation:

- Demographics, medical history, and prior and concomitant medication usage;
- In order to expedite the screening process, blood will be collected for testing at the local laboratory for the following:
  - Fasting blood chemistry, hematology, PTT and aPTT;
  - An estimated glomerular filtration rate will be calculated based on the following Modification of Diet in Renal Disease (MDRD) study equation:

    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)
  - ANCA measurement (indirect immunoflurescence test for P-ANCA and C-ANCA, as well as ELISA test for PR3 and MPO);
  - Virology assessments as detailed in section 7.2.2;
  - 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 eCRFs.
- BVAS assessment (see section 11.3); to be eligible for enrollment, a subject must have:
  - At least one "major" item (see items marked with "#" in section 11.3), or
  - At least three non-major items on the BVAS, or
  - At least two renal items due to vasculitis, i.e.:
    - Hypertension (diastolic BP >95 mmHg),
    - Proteinuria >1+ on urinalysis or >0.2 g/g creatinine,
    - Hematuria ('moderate" on urinalysis or ≥10 RBC per high power field, usually accompanied by RBC casts),
    - Serum creatinine ≥125 µmol/L, or
    - >30% rise in creatinine or >25% fall in creatinine clearance;
- Subjects will be asked to void their bladders completely, and a representative clean catch, midstream urine sample will be collected:
  - The local laboratory will perform a urinalysis for hematuria and proteinuria;

- A physical examination (excluding genitourinary, ophthalmic, and female breast assessments) will be performed; body weight, height, and body mass index will be determined;
- Vital signs (temperature, blood pressure, heart rate) will be measured supine after at least 3 minutes of rest;
- A 12-lead ECG will be recorded and assessed for any clinically significant abnormality;
- Chest X rays will be acquired for BVAS assessment and exclusion of TB;
- If a renal biopsy has been performed within 4 weeks prior to screening, the standard Histology Form will be completed; a copy of the biopsy results will be kept in the study records;
- After all screening procedures have been completed, and the subject satisfies all eligibility criteria, the study schedule will be discussed with the subject and the schedule will be provided to the subject to ensure compliance with the study visits;
- If the subject has been taking maintenance oral corticosteroids of 10 mg prednisone-equivalent or less at the time of screening, i.e., corticosteroids that are not considered part of the study medication, the subject will be provided with dose tapering instructions to a dose of zero over a period not to exceed 6 weeks from Day 1.

6.2. Study Day 1

If eligible for the study, the subject will visit the study center on Day 1, after an overnight fast of at least 8 hours, for the following procedures:

- A physical examination (excluding genitourinary, ophthalmic, and female breast assessments); body weight assessment will be performed;
- Vital signs (temperature, blood pressure, heart rate);
- Blood will be collected for shipment to the central laboratory for serum chemistry, hematology, hsCRP, ANCA (anti-PR3 and anti-MPO ELISA) measurement, and PK baseline measurements; the subjects may eat after the serum chemistry sample has been collected;
- 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 subjects who are in the cyclophosphamide stratum (see section 11.6);
- BVAS assessment (see section 11.3);
- VDI assessment (see section 11.4);
- Subjects will be asked to complete the SF36v2 and EQ-5D-5L questionnaires;
- Any pre-treatment adverse events (from time of the screening visit) will be recorded;
- The subject will be randomized;
- Study medication (1 kit of CCX168 or CCX168 placebo, and 1 kit of prednisone and/or prednisone placebo) will be provided to the subject with dosing instructions;

- Subjects will be asked to void their bladders completely, and a representative clean catch, midstream urine sample will be collected:
  - A urine sample will be sent to the central laboratory for urinalysis including pH, specific gravity, glucose, nitrite, ketones, bilirubin, urobilinogen, RBCs, and WBCs, as well as quantitative measurement of albumin and creatinine to calculate the ACR;
  - Two additional urine samples will be frozen and sent to the central laboratory for quantitative MCP-1 and creatinine measurements to calculate the MCP-1:creatinine ratio, and for exploratory urinary markers;
- The subject will be asked to take the first dose of study medication while at the study center; the CCX168 or CCX168 placebo capsules will be taken at least 30 minutes before the prednisone and/or prednisone capsules are taken;
- The time of the dosing of CCX168 or CCX168 placebo, as well as the time of dosing of prednisone or prednisone placebo, will be recorded;
- Blood samples will be collected at 0.5, 1, 2, 3, 4, and 6 hours following CCX168 or CCX168 placebo dosing for plasma CCX168 concentration measurements; the actual time of each blood sample collection will be recorded;
- All urine will be collected for a period of 6 hours following CCX168 or CCX168 placebo dosing; the total urine volume will be measured and recorded, and a representative urine sample will be obtained for CCX168 measurement;
- A blood sample will be collected for pharmacodynamic marker measurements;
- A saliva sample will be collected for genetic marker assessments;
- Cyclophosphamide IV dose will be given after receipt of the local WBC count (see section 11.6) to subjects in the cyclophosphamide stratum; The start and end times of the infusion will be recorded;
- Rituximab will be given to subjects in the rituximab stratum (see section 11.7); 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;
- Any post-dosing adverse events will be recorded;
- A subject could be kept overnight in the hospital on Day 1, 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 subject will be reminded to:
  - Come to the study center for the Day 2 study visit the next day, if not kept overnight;
  - Store the study medications in a cool and dry place according to label instructions for the duration of the study;
  - Take the CCX168 or CCX168 placebo medication in the evening approximately 12 hours after the morning dose;

- Not to take CCX168 and prednisone medication on the morning of Day 2, unless the visit is scheduled in the afternoon, in which case CCX168 and prednisone medication should be taken the morning of Day 2; and
- Continue taking all their other concomitant medications as usual.

6.3. Study Day 2

The Study Day 2 visit must occur on the scheduled date. The subjects must fast overnight for at least 8 hours before the study visit. During this visit, the following study procedures will be performed:

- Body system review to determine if there were any changes from Day 1;
- All treatment-emergent adverse events will be recorded;
- Vital signs (temperature, blood pressure, heart rate);
- Blood will be collected for shipment to the central laboratory for serum chemistry and hematology; the subjects may eat after the serum chemistry sample collection;
- Subjects will be asked to void their bladders completely, and a representative clean catch, midstream urine sample will be collected:
  - A urine sample will be sent to the central laboratory for urinalysis including pH, specific gravity, glucose, nitrite, ketones, bilirubin, urobilinogen, RBCs, and WBCs;
- The subject will be asked to take the morning doses of study medication while at the study center, unless already taken; the CCX168 or CCX168 placebo capsules will be taken at least 30 minutes before the prednisone and/or prednisone placebo capsules are taken;
- Any changes in concomitant medication use will be recorded; and
- After all study procedures have been completed, the subject will be reminded to:
  - Come to the study center for the Day 8 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 CCX168 placebo medication as instructed;
  - Take the prednisone or prednisone placebo dose as instructed;
  - Not to take CCX168 and prednisone medication on the morning of Day 8, unless the visit is scheduled in the afternoon, in which case CCX168 and prednisone medication should be taken the morning of Day 8; and
  - Continue taking all their other concomitant medications as usual.

6.4. Study Day 8

The Study Day 8 visit must occur on the scheduled date. The subjects must fast overnight for at least 8 hours before the study visit. During this visit, the following study procedures will be performed:

- Body system review to determine if there were any changes from Day 2;
- All treatment-emergent adverse events will be recorded;
- Vital signs (temperature, blood pressure, heart rate);
- Blood will be collected for shipment to the central laboratory for serum chemistry, hematology, and hsCRP measurements; the subjects may eat after the serum chemistry sample collection;
- The date and time of the last dose of CCX168 or CCX168 placebo will be recorded;
- A blood sample will be collected for CCX168 plasma concentration measurement, and the date and time of the sample collection will be recorded;
- Subjects will be asked to void their bladders completely, and a representative clean catch, midstream urine sample will be collected:
  - A urine sample will be sent to the central laboratory for urinalysis including pH, specific gravity, glucose, nitrite, ketones, bilirubin, urobilinogen, RBCs, and WBCs, as well as quantitative measurement of albumin and creatinine to calculate the ACR;
  - Two additional urine samples will be frozen and sent to the central laboratory for quantitative MCP-1 and creatinine measurements to calculate the MCP-1:creatinine ratio, and for exploratory urinary markers;
- Drug accountability of CCX168 or CCX168 placebo bottles;
- Drug accountability of prednisone or prednisone placebo bottles;
- Study medication (1 kit of CCX168 or CCX168 placebo, and 1 kit of prednisone and/or prednisone placebo) will be provided to the subject with dosing instructions; the subject will take the morning doses from these new kits while at the study site, unless the morning doses have already been taken by the subject;
- If a subject is on non-study oral maintenance corticosteroids, dose tapering to zero needs to be attempted, if feasible;
- Rituximab will be given to subjects in the rituximab stratum (see section 11.7); 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; and
- After all study procedures have been completed, the subject will be reminded to:
  - Come to the study center for the Day 15 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 CCX168 placebo medication as instructed;
- Take the prednisone or prednisone placebo dose as instructed;
- Not to take CCX168 and prednisone medication on the morning of Day 15, unless the visit is scheduled in the afternoon, in which case CCX168 and prednisone medication should be taken the morning of Day 15;
- Bring all study medication containers to the next study visit, whether empty or not, and
- Continue taking all their other concomitant medications as usual.

6.5. Study Day 15

The Study Day 15 visit must occur on the scheduled date. The subjects must fast overnight for at least 8 hours before the study visit. During this visit, the following study procedures will be performed:

- A physical examination (excluding genitourinary, ophthalmic, and female breast assessments) will be performed; body weight will also be measured;
- All treatment-emergent adverse events will be recorded;
- Vital signs (temperature, blood pressure, heart rate);
- Blood will be collected for shipment to the central laboratory for serum chemistry, hematology, and hsCRP measurements; the subjects may eat after the serum chemistry sample collection;
- 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 11.6) for subjects who are in the cyclophosphamide stratum;
- Subjects will be asked to void their bladders completely, and a representative clean catch, midstream urine sample will be collected:
  - A urine sample will be sent to the central laboratory for urinalysis including pH, specific gravity, glucose, nitrite, ketones, bilirubin, urobilinogen, RBCs, and WBCs, as well as quantitative measurement of albumin and creatinine to calculate the ACR;
  - Two additional urine samples will be frozen and sent to the central laboratory for quantitative MCP-1 and creatinine measurements to calculate the MCP-1:creatinine ratio, and for exploratory urinary markers;
- Drug accountability of CCX168 or CCX168 placebo bottles;
- Drug accountability of prednisone or prednisone placebo bottles;
- Study medication (1 kit of CCX168 or CCX168 placebo, and 1 kit of prednisone and/or prednisone placebo) will be provided to the subject with dosing instructions; the subject will take the morning doses from these kits while at the study site, unless the morning doses have already been taken by the subject;

- If a subject is still on non-study oral maintenance corticosteroids, dose tapering to zero needs to be attempted, if feasible;
- Cyclophosphamide IV dose will be given after receipt of the local WBC count (see section 11.6) to subjects in the cyclophosphamide stratum; The start and end times of the infusion will be recorded;
- Rituximab will be given to subjects in the rituximab stratum (see section 11.7); A dose of 375 mg/m^2 will be given; The start and end times of the infusion will be recorded;
- A blood sample will be collected for CCX168 plasma concentration measurement; the date and time of the last dose prior to sample collection will be recorded;
- Any changes in concomitant medication use will be recorded; and
- After all study procedures have been completed, the subject will be reminded to:
  - Come to the study center for the Day 22 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 CCX168 placebo medication as instructed;
  - Take the prednisone or prednisone placebo dose as instructed;
  - Not to take CCX168 and prednisone medication on the morning of Day 22, unless the visit is scheduled in the afternoon, in which case CCX168 and prednisone medication should be taken the morning of Day 22;
  - Bring all study medication containers to the next study visit, whether empty or not, and
  - Continue taking all their other concomitant medications as usual.

6.6. Study Day 22

The Study Day 22 visit must occur within a +/- 2-day window of the scheduled date. During this visit, the following study procedures will be performed:

- Body system review to determine if there were any changes from Day 15;
- All treatment-emergent adverse events will be recorded;
- Vital signs (temperature, blood pressure, heart rate);
- Subjects will be asked to void their bladders completely, and a representative clean catch, midstream urine sample will be collected:
  - A urine sample will be sent to the central laboratory for urinalysis including pH, specific gravity, glucose, nitrite, ketones, bilirubin, urobilinogen, RBCs, and WBCs;
- Drug accountability of CCX168 or CCX168 placebo bottles;

- Study medication (1 kit of CCX168 or CCX168 placebo) will be provided to the subject with dosing instructions; the subject will take the morning dose from this kit while at the study site, unless the morning dose has already been taken by the subject;
- If a subject is still on non-study oral maintenance corticosteroids, dose tapering to zero needs to be attempted, if feasible;
- A blood sample will be collected for CCX168 plasma concentration measurement; the date and time of the last dose prior to sample collection will be recorded;
- Rituximab will be given to subjects in the rituximab stratum (see section 11.7); 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; and
- After all study procedures have been completed, the subject will be reminded to:
  - Come to the study center for the Day 29 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 CCX168 placebo medication as instructed;
  - Take the prednisone or prednisone placebo dose as instructed;
  - Not to take CCX168 and prednisone medication on the morning of Day 29, unless the visit is scheduled in the afternoon, in which case CCX168 and prednisone medication should be taken the morning of Day 29;
  - Bring all study medication containers to the next study visit, whether empty or not, and
  - Continue taking all their other concomitant medications as usual.

6.7. Study Day 29

The Study Day 29 visit must occur within a +/- 2-day window of the scheduled date. The subjects must fast overnight for at least 8 hours before the study visit. During this visit, the following study procedures will be performed:

- A physical examination (excluding genitourinary, ophthalmic, and female breast assessments) will be performed; body weight will also be measured;
- All treatment-emergent adverse events will be recorded;
- Vital signs (temperature, blood pressure, heart rate);
- A 12-lead ECG will be recorded and assessed for any clinically significant abnormality;
- Blood will be collected for shipment to the central laboratory for serum chemistry, hematology, and hsCRP measurements; the subjects may eat after the serum chemistry sample collection;

- 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 11.6) for subjects who are in the cyclophosphamide stratum;
- A blood sample will be collected for pharmacodynamics marker measurements;
- Subjects will be asked to void their bladders completely, and a representative clean catch, midstream urine sample will be collected:
  - A urine sample will be sent to the central laboratory for urinalysis including pH, specific gravity, glucose, nitrite, ketones, bilirubin, urobilinogen, RBCs, and WBCs, as well as quantitative measurement of albumin and creatinine to calculate the ACR;
  - Two additional urine samples will be frozen and sent to the central laboratory for quantitative MCP-1 and creatinine measurements to calculate the MCP-1:creatinine ratio, and for exploratory urinary markers;
- ANCA (anti-PR3 and anti-MPO ELISA) measurement;
- BVAS assessment; chest X rays will only be acquired if deemed clinically necessary by the Principal Investigator (see section 11.3);
- Subjects will be asked to complete the SF36v2 and EQ-5D-5L questionnaires;
- Drug accountability of CCX168 or CCX168 placebo bottles;
- Study medication (2 kits of CCX168 or CCX168 placebo, and 1 kit of prednisone and/or prednisone placebo) will be provided to the subject with dosing instructions; the subject will take the morning doses from these kits while at the study site, unless the morning doses have already been taken by the subject;
- If a subject is still on non-study oral maintenance corticosteroids, dose tapering to zero needs to be attempted, if feasible.
- Drug accountability of prednisone or prednisone placebo bottles;
- Cyclophosphamide IV dose will be given after receipt of the local WBC count (see section 11.6) to subjects in the cyclophosphamide stratum; The start and end times of the infusion will be recorded;
- A blood sample will be collected for CCX168 plasma concentration measurement; the date and time of the last dose prior to sample collection will be recorded;
- Any changes in concomitant medication use will be recorded; and
- After all study procedures have been completed, the subject will be reminded to:
  - Come to the study center for the Day 43 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 CCX168 placebo medication as instructed;
  - Take the prednisone or prednisone placebo dose as instructed;

- Not to take CCX168 and prednisone medication on the morning of Day 43, unless the visit is scheduled in the afternoon, in which case CCX168 and prednisone medication should be taken the morning of Day 43;
- Bring all study medication containers to the next study visit, whether empty or not, and
- Continue taking all their other concomitant medications as usual.

6.8. Study Day 43

The Study Day 43 visit must occur within +/- 2 days of the scheduled date. The subjects must fast overnight for at least 8 hours before the study visit. During this visit, the following study procedures will be performed:

- Body system review to determine if there were any changes from Day 29;
- All treatment-emergent adverse events will be recorded;
- Vital signs (temperature, blood pressure, heart rate);
- Blood will be collected for shipment to the central laboratory for serum chemistry and hematology measurements; the subjects may eat after the serum chemistry sample collection;
- Subjects will be asked to void their bladders completely, and a representative clean catch, midstream urine sample will be collected:
  - A urine sample will be sent to the central laboratory for urinalysis including pH, specific gravity, glucose, nitrite, ketones, bilirubin, urobilinogen, RBCs, and WBCs;
- Drug accountability of CCX168 or CCX168 placebo bottles;
- Study medication (2 kits of CCX168 or CCX168 placebo, and 1 kit of prednisone and/or prednisone placebo) will be provided to the subject with dosing instructions; the subject will take the morning doses from these kits while at the study site, unless the morning doses have already been taken by the subject;
- Drug accountability of prednisone or prednisone placebo bottles;
- If a subject has been on non-study oral maintenance corticosteroids, dose tapering to zero needs to be completed by this visit, if feasible;
- A blood sample will be collected for CCX168 plasma concentration measurement; the date and time of the last dose prior to sample collection will be recorded;
- Any changes in concomitant medication use will be recorded; and
- After all study procedures have been completed, the subject will be reminded to:
  - Come to the study center for the Day 57 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 CCX168 placebo medication as instructed;

- Take the prednisone or prednisone placebo dose as instructed;
- Not to take CCX168 and prednisone medication on the morning of Day 57, unless the visit is scheduled in the afternoon, in which case CCX168 and prednisone medication should be taken the morning of Day 57;
- Bring all study medication containers to the next study visit, whether empty or not, and
- Continue taking all their other concomitant medications as usual.

6.9. Study Day 57

The Study Day 57 visit must occur within +/- 2 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination (excluding genitourinary, ophthalmic, and female breast assessments) will be performed; body weight will also be measured;
- All treatment-emergent adverse events will be recorded;
- Vital signs (temperature, blood pressure, heart rate);
- Blood will be collected for shipment to the central laboratory for serum creatinine and hsCRP measurement;
- 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 11.6) for subjects who are in the cyclophosphamide stratum;
- Subjects will be asked to void their bladders completely, and a representative clean catch, midstream urine sample will be collected:
  - A urine sample will be sent to the central laboratory for urinalysis including pH, specific gravity, glucose, nitrite, ketones, bilirubin, urobilinogen, RBCs, and WBCs, as well as quantitative measurement of albumin and creatinine to calculate the ACR;
  - Two additional urine samples will be frozen and sent to the central laboratory for quantitative MCP-1 and creatinine measurements to calculate the MCP-1:creatinine ratio, and for exploratory urinary markers;
- Drug accountability of CCX168 or CCX168 placebo bottles;
- Study medication (2 kits of CCX168 or CCX168 placebo, and 1 kit of prednisone and/or prednisone placebo) will be provided to the subject with dosing instructions; the subject will take the morning doses from these kits while at the study site, unless the morning doses have already been taken by the subject;
- Drug accountability of prednisone or prednisone placebo bottles;
- Cyclophosphamide IV dose will be given after receipt of the local WBC count (see section 11.6) to subjects in the cyclophosphamide stratum; The start and end times of the infusion will be recorded;

- A blood sample will be collected for CCX168 plasma concentration measurement; the date and time of the last dose prior to sample collection will be recorded;
- Any changes in concomitant medication use will be recorded; and
- After all study procedures have been completed, the subject will be reminded to:
  - Come to the study center for the Day 71 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 CCX168 placebo medication as instructed;
  - Take the prednisone or prednisone placebo dose as instructed;
  - Not to take CCX168 and prednisone medication on the morning of Day 71, unless the visit is scheduled in the afternoon, in which case CCX168 and prednisone medication should be taken the morning of Day 71;
  - Bring all study medication containers to the next study visit, whether empty or not, and
  - Continue taking all their other concomitant medications as usual.

6.10. Study Day 71

The Study Day 71 visit must occur within +/- 2 days of the scheduled date. The subjects must fast overnight for at least 8 hours before the study visit. During this visit, the following study procedures will be performed:

- Body system review to determine if there were any changes from Day 57;
- All treatment-emergent adverse events will be recorded;
- Vital signs (temperature, blood pressure, heart rate);
- Blood will be collected for shipment to the central laboratory for serum chemistry and hematology measurements; the subjects may eat after the serum chemistry sample collection;
- Subjects will be asked to void their bladders completely, and a representative clean catch, midstream urine sample will be collected:
  - A urine sample will be sent to the central laboratory for urinalysis including pH, specific gravity, glucose, nitrite, ketones, bilirubin, urobilinogen, RBCs, and WBCs;
- Drug accountability of CCX168 or CCX168 placebo bottles;
- Study medication (2 kits of CCX168 or CCX168 placebo) will be provided to the subject with dosing instructions; the subject will take the morning dose from one of these kits while at the study site, unless the morning dose has already been taken by the subject;
- A blood sample will be collected for CCX168 plasma concentration measurement; the date and time of the last dose prior to sample collection will be recorded;

- Any changes in concomitant medication use will be recorded; and
- After all study procedures have been completed, the subject will be reminded to:
  - Come to the study center for the Day 85 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 CCX168 placebo medication as instructed;
  - Take the prednisone or prednisone placebo dose as instructed;
  - Not to take CCX168 and prednisone medication on the morning of Day 85, but to take the prednisone medication at the study center on the day of the visit;
  - Bring all study medication containers to the next study visit, whether empty or not, and
  - Continue taking all their other concomitant medications as usual.

6.11. Study Day 85

The Study Day 85 visit must occur within +/- 2 days of the scheduled date. The subjects must fast overnight for at least 8 hours before the study visit. During this visit, the following study procedures will be performed:

- A physical examination (excluding genitourinary, ophthalmic, and female breast assessments) will be performed; body weight will also be measured;
- All treatment-emergent adverse events will be recorded;
- Vital signs (temperature, blood pressure, heart rate);
- Blood will be collected for shipment to the central laboratory for serum chemistry, hematology and hsCRP measurements; the subjects may eat after the serum chemistry sample collection;
- A blood sample will be collected for pharmacodynamics marker measurements;
- Cyclophosphamide IV dose will be given after receipt of the local WBC count (see section 11.6) to subjects in the cyclophosphamide stratum; The start and end times of the infusion will be recorded;
- Subjects will be asked to void their bladders completely, and a representative clean catch, midstream urine sample will be collected:
  - A urine sample will be sent to the central laboratory for urinalysis including pH, specific gravity, glucose, nitrite, ketones, bilirubin, urobilinogen, RBCs, and WBCs, as well as quantitative measurement of albumin and creatinine to calculate the ACR;
  - Two additional urine samples will be frozen and sent to the central laboratory for quantitative MCP-1 and creatinine measurements to calculate the MCP-1:creatinine ratio, and for exploratory urinary markers;
- ANCA (anti-PR3 and anti-MPO ELISA) measurement;

- BVAS assessment; chest X rays will only be acquired if deemed clinically necessary by the Principal Investigator (see section 11.3);
- VDI assessment (see section 11.4);
- Subjects will be asked to complete the SF36v2 and EQ-5D-5L questionnaires;
- Drug accountability of CCX168 or CCX168 placebo bottles;
- Drug accountability of prednisone or prednisone placebo bottles;
- Study medication (1 kit of prednisone and/or prednisone placebo) will be provided to the subject with dosing instructions; the subject will take the morning dose from this kit while at the study site, unless the morning dose has already been taken by the subject;
- A blood sample will be collected for CCX168 plasma concentration measurement; the date and time of the last dose prior to sample collection will be recorded;
- If a renal biopsy has been performed prior to Day 1 for renal disease assessment, if possible, a renal biopsy will be taken at/within 1 week after the Day 85 visit and the Histology Form completed;
- Any changes in concomitant medication use will be recorded; and
- After all study procedures have been completed, the subject will be reminded to:
  - Come to the study center for the Day 99 study visit;
  - Store the study medications in a cool and dry place according to label instructions for the duration of the study;
  - Take the prednisone or prednisone placebo dose as instructed;
  - Not to take the prednisone medication on the morning of Day 99, unless the visit is scheduled in the afternoon, in which case prednisone medication should be taken the morning of Day 99;
  - Bring all study medication containers to the next study visit, whether empty or not, and
  - Continue taking all their other concomitant medications as usual.

6.12. Study Day 99

The Study Day 99 visit must occur within +/- 4 days of the scheduled date. The subjects must fast overnight for at least 8 hours before the study visit. During this visit, the following study procedures will be performed:

- Body system review to determine if there were any changes from Day 85;
- All treatment-emergent adverse events will be recorded;
- Vital signs (temperature, blood pressure, heart rate);

- Blood will be collected for shipment to the central laboratory for serum chemistry and hematology measurements; the subjects may eat after the serum chemistry sample collection;
- Subjects will be asked to void their bladders completely, and a representative clean catch, midstream urine sample will be collected:
  - A urine sample will be sent to the central laboratory for urinalysis including pH, specific gravity, glucose, nitrite, ketones, bilirubin, urobilinogen, RBCs, and WBCs;
- Drug accountability of prednisone or prednisone placebo bottles;
- Study medication (1 kit of prednisone and/or prednisone placebo) will be provided to the subject with dosing instructions; the subject will take the morning dose from this kit while at the study site, unless the morning dose has already been taken by the subject;
- Subjects in the cyclophosphamide stratum will start oral azathioprine after the WBC count from the local laboratory has been received, and will continue taking it through Day 168 (see section 11.6 for dosing instructions);
- Any changes in concomitant medication use will be recorded; and
- After all study procedures have been completed, the subject will be reminded to:
  - Come to the study center for the Day 113 study visit;
  - Store the study medication in a cool and dry place according to label instructions for the duration of the study;
  - Take the prednisone or prednisone placebo dose as instructed;
  - Not to take the prednisone medication on the morning of Day 113, unless the visit is scheduled in the afternoon, in which case prednisone medication should be taken the morning of Day 113;
  - Bring all study medication containers to the next study visit, whether empty or not, and
  - Continue taking all their other concomitant medications as usual.

6.13. Study Day 113

The Study Day 113 visit must occur within +/- 4 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination (excluding genitourinary, ophthalmic, and female breast assessments) will be performed; body weight will also be measured;
- All treatment-emergent adverse events will be recorded;
- Vital signs (temperature, blood pressure, heart rate);
- Blood will be collected for shipment to the central laboratory for serum creatinine and hsCRP measurement;

- BVAS assessment; chest X rays will only be acquired if deemed clinically necessary by the Principal Investigator (see section 11.3);
- Subjects will be asked to void their bladders completely, and a representative clean catch, midstream urine sample will be collected:
  - A urine sample will be sent to the central laboratory for urinalysis including pH, specific gravity, glucose, nitrite, ketones, bilirubin, urobilinogen, RBCs, and WBCs, as well as quantitative measurement of albumin and creatinine to calculate the ACR;
  - Two additional urine samples will be frozen and sent to the central laboratory for quantitative MCP-1 and creatinine measurements to calculate the MCP-1:creatinine ratio, and for exploratory urinary markers;
- Drug accountability of prednisone or prednisone placebo bottles;
- Study medication (1 kit of prednisone and/or prednisone placebo) will be provided to the subject with dosing instructions; the subject will take the morning dose from this kit while at the study site, unless the morning dose has already been taken by the subject;
- Subjects in the cyclophosphamide stratum will be given oral azathioprine at a target dose of 2 mg/kg/day (see section 11.6 for dosing instructions);
- ANCA (anti-PR3 and anti-MPO ELISA) measurement;
- Any changes in concomitant medication use will be recorded; and
- After all study procedures have been completed, the subject will be reminded to:
  - Come to the study center for the Day 141 study visit;
  - Store the study medication in a cool and dry place according to label instructions for the duration of the study;
  - Take the prednisone or prednisone placebo dose as instructed;
  - Not to take the prednisone medication on the morning of Day 141; and
  - Continue taking all their other concomitant medications as usual.

6.14. Study Day 141

The Study Day 141 visit must occur within +/- 4 days of the scheduled date. The subjects must fast overnight for at least 8 hours before the study visit. During this visit, the following study procedures will be performed:

- Body system review to determine if there were any changes from Day 113;
- All treatment-emergent adverse events will be recorded;
- Vital signs (temperature, blood pressure, heart rate);
- Blood will be collected for shipment to the central laboratory for serum chemistry and hematology measurements; the subjects may eat after the serum chemistry sample collection;

- Subjects will be asked to void their bladders completely, and a representative clean catch, midstream urine sample will be collected:
  - A urine sample will be sent to the central laboratory for urinalysis including pH, specific gravity, glucose, nitrite, ketones, bilirubin, urobilinogen, RBCs, and WBCs;
- Subjects in the cyclophosphamide stratum will be given oral azathioprine at a target dose of 2 mg/kg/day (see section 11.6 for dosing instructions); **a local laboratory WBC count will be done in these subjects;**
- Drug accountability of prednisone or prednisone placebo bottles;
- Any changes in concomitant medication use will be recorded; and
- After all study procedures have been completed, the subject will be reminded to:
  - Come to the study center for the Day 169 study visit; and
  - Continue taking all their other concomitant medications as usual.

6.15. Study Day 169

The Study Day 169 visit must occur within +/- 4 days of the scheduled date. The subjects must fast overnight for at least 8 hours before the study visit. During this visit, the following study procedures will be performed:

- A physical examination (excluding genitourinary, ophthalmic, and female breast assessments) will be performed; body weight will also be measured;
- All treatment-emergent adverse events will be recorded;
- Vital signs (temperature, blood pressure, heart rate);
- Blood will be collected for shipment to the central laboratory for serum chemistry, hematology, and hsCRP measurements; the subjects may eat after the serum chemistry sample collection;
- A blood sample will be collected for pharmacodynamics marker measurements;
- Subjects will be asked to void their bladders completely, and a representative clean catch, midstream urine sample will be collected:
  - A urine sample will be sent to the central laboratory for urinalysis including pH, specific gravity, glucose, nitrite, ketones, bilirubin, urobilinogen, RBCs, and WBCs, as well as quantitative measurement of albumin and creatinine to calculate the ACR;
  - Two additional urine samples will be frozen and sent to the central laboratory for quantitative MCP-1 and creatinine measurements to calculate the MCP-1:creatinine ratio, and for exploratory urinary markers;
- ANCA (anti-PR3 and anti-MPO ELISA) measurement;
- BVAS assessment; chest X rays will only be acquired if deemed clinically necessary by the Principal Investigator (see section 11.3);
- VDI assessment (see section 11.4);

- Subjects will be asked to complete the SF36v2 and EQ-5D-5L questionnaires;
- Drug accountability of prednisone or prednisone placebo bottles, only if this is an early termination visit;
- Any changes in concomitant medication use will be recorded; and
- After all study procedures have been completed, the subject will be discharged from the study. The subject's condition will be evaluated by the Investigator at the end of the clinical trial (Day 169) and appropriate standard of care medical treatment will be provided to all subjects as needed.

7. STUDY ASSESSMENTS

7.1. Efficacy Assessments

7.1.1. Corticosteroid Rescue Use

If rescue IV or high dose oral corticosteroids are needed, it is deemed a treatment failure for purposes of data analysis (see section 5.10). Methylprednisolone IV rescue use (total dose and duration of dosing) and oral rescue corticosteroid use must be recorded for all subjects and will be compared **among** treatment groups.

7.1.2. Estimated Glomerular Filtration Rate

Estimated glomerular filtration rate (eGFR) will be calculated at all applicable study visits using the following MDRD equation:

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)

Cystatin C measurements may be used to calculate eGFR 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)

7.1.3. Urinary Assessments

Urine samples collected at all study visits will be analyzed for hematuria, RBC casts, and proteinuria (ACR). A clean catch midstream urine sample needs to be collected according to instructions provided separately. The urine samples will be sent to the central laboratory for analysis. Microscopic review is triggered if a urinary dipstick test is positive for WBC, RBC, 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. For the purpose of analyzing the change from baseline in urinary RBCs, the following values will be assigned for each category:

None = 0.1, Occ = 0.5, 1 - 2 = 1, 3 - 5 = 3, 6 - 9 = 6, 10 - 15 = 10, 16 - 29 = 16, 30 - 49 = 30; 50 - 75 = 50, >75 = 75.

Proteinuria will be assessed by measuring the albumin and creatinine concentrations and calculating the urinary ACR. Results will be expressed as mg albumin/g creatinine. This will be done by the central laboratory.

7.1.4. Birmingham Vasculitis Activity Score (BVAS)

The BVAS (version 3) will be calculated based on responses in 10 domains: general, cutaneous, mucous membranes and eyes, ear/nose/throat (ENT), chest, cardiovascular, abdominal, renal, nervous system, and other. Section 11.3 provides a list of items that need to be assessed. BVAS data will be adjudicated before finalization.

7.1.5. Vasculitis Damage Index (VDI)

The VDI (according to Luqmani and Hall, 2004) will be calculated based on responses in 11 organ systems as provided in section 11.4. VDI data will be adjudicated before finalization.

7.1.6. Anti-Neutrophil Cytoplasmic Antibody (ANCA) Assessments

ANCA assessments will include indirect immunofluorescence test for P-ANCA and C-ANCA as well as ELISA tests for anti-PR3 and anti-MPO at Screening and only ELISA tests for anti-PR3 and anti-MPO on Days 1 (prior to dosing), 29, 85, 113, and 169. ELISA assays will be performed by a central laboratory.

7.1.7. Serum C-Reactive Protein (CRP)

Serum CRP will be measured by the central laboratory on Days 1 (prior to dosing), 8, 15, 29, 57, 85, 113, and 169 by high sensitivity CRP assay.

7.1.8. Urinary MCP-1 Assessments

Urine MCP-1 will be measured by the central laboratory in urine samples collected on Study Days 1 (prior to dosing), 8, 15, 29, 57, 85, 113, and 169 by specific ELISA. Urine creatinine will be measured in the same urine samples and MCP-1 levels will be standardized to urine creatinine and expressed as pg MCP-1/mg creatinine. Additional urine samples will be stored at -70°C and may also be used to measure other cytokine, inflammatory and complement markers.

7.1.9. Health-Related Quality of Life Assessments

The SF-36v2 and EQ-5D-5L health-related quality of life questionnaires will be completed by study subjects at the Day 1 (pre-dose), 29, 85, and 169 study visits to measure changes from baseline in health-related quality of life. Proven translations will be used for non-English speaking subjects. An administrator will facilitate completion of the questionnaires by the subjects. The administrator will establish a rapport with the subject, emphasize the importance of completing the form, and serve to answer questions and address concerns. The questionnaires should be completed by subjects before seeing the Investigator.

7.1.10. Histology

A standard Histology Form will be provided to investigators to document histologic findings in a standard manner for all subjects from whom renal biopsies are taken. This will be completed for available baseline and Day 85 renal biopsies. To the extent possible, changes from baseline in

typical histologic findings, e.g., percentage of glomeruli with crescents or sclerosis will be analyzed.

7.2. Safety Assessments

7.2.1. Physical Examinations and Vital Signs

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 assessment will be performed at Screening and Study Days 1, 15, 29, 57, 85, 113, and 169. Physical examinations during screening and on Study Days 1, 29, 85, 113, and 169 must be sufficiently comprehensive to include ALL components of the BVAS (see section 11.3). Findings must be recorded in the source documents. Systematic body system reviews will be done at Study Days 2, 8, 22, 43, 71, 99, and 141.

Any new or worsening findings upon physical examination or body system review need to be recorded as adverse events.

Body weight will be measured at Screening and Days 1, 15, 29, 57, 85, 113, and 169.

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 assessments will be performed while the subject is in the supine position and after the subject has rested for at least three minutes.

Twelve-lead ECGs will be acquired during Screening and on Day 29 and will be assessed for any clinically significant abnormalities.

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, red blood cell (RBC) count, white blood cell (WBC) count with differential, platelet count, mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), mean corpuscular volume.
- Serum Chemistry: liver panel (bilirubin, lactate dehydrogenase [LDH], SGOT/AST, SGPT/ALT), renal panel (BUN, creatinine), creatine phosphokinase (CPK), albumin, sodium, potassium, bicarbonate, chloride, calcium, inorganic phosphorus, glucose, total proteins, alkaline phosphatase, cholesterol, uric acid.
- Coagulation (measured only at Screening at the local laboratory): prothrombin time (PT), and activated partial thromboplastin time (aPTT)
- Urinalysis: At the central laboratory, pH, specific gravity, glucose, nitrite, ketones, bilirubin, urobilinogen, RBC, and WBC tests, as well as quantification of albumin and creatinine for ACR calculation will be performed. A second sample will be analyzed quantitatively for MCP-1 and creatinine at visits specified in the Time and Events Table. Analysis at the local laboratory will include hematuria and albuminuria assessments at screening.

- Virology (measured only at Screening at the local laboratory): hepatitis B surface antigen, hepatitis C antibodies, HIV 1 and 2 antibodies.
- Serology and Complement (measured only at Screening 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 eCRFs.
- TB screen: Chest X rays, done as part of BVAS, will be performed at screening to rule out TB. Chest X rays at subsequent visits will only be performed if deemed clinically necessary by the Principal Investigator.

7.2.3. Reporting of Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a subject participating in a clinical trial who is administered an investigational product, at any dose; the adverse event does not necessarily have to have a causal relationship with this product. 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 an investigational product, whether or not considered related to the investigational product. 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 Clinical Investigator's Brochure, or that is of greater severity than expected based on the information in the Clinical Investigator's Brochure.

All adverse events occurring in subjects who have been randomized to treatment will be recorded on the CRF 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 AE 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 whether continued follow-up of the adverse event is warranted.

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)

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: CCX168/placebo administration and the adverse event occurrence were reasonably related in time, and the AE was explained equally well by causes other than CCX168/placebo or was more likely explained by exposure to CCX168/placebo than by other causes.

The relationship of corticosteroid use, cyclophosphamide, rituximab, or azathioprine 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 corticosteroid, cyclophosphamide, rituximab, or azathioprine use.
- Possibly Related: the corticosteroid, cyclophosphamide, rituximab, or azathioprine administration and the adverse event occurrence were reasonably related in time, and the AE was explained equally well by causes other than corticosteroid, cyclophosphamide, rituximab, or azathioprine use or was more likely explained by exposure to corticosteroid, cyclophosphamide, rituximab, or azathioprine use than by other causes.

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. Malignancies and infections requiring antibiotics are considered serious.

Elective surgery, already known during screening to occur in course of the study and elective hospitalizations for convenience of the subject which are clearly unrelated to any medical condition, and agreed between the investigator and the subject prior to randomization, will not have to be reported as SAEs.

A suspected unexpected serious adverse reaction (SUSAR) is defined as an SAE that is considered at least possibly related to study drug (CCX168/placebo) and that is unexpected, i.e., not described in terms of nature, severity, or frequency in the current Investigator's Brochure.

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 and the Investigator will be advised to follow patients with notably high liver functions tests closely and to take appropriate steps, such as potentially discontinuing study medication, in case the abnormalities persist. Additionally, if a subject develops grade two or worse leukopenia (WBC < 3 x 10^9/L) OR an absolute neutrophil count < 1 x 10^9/L, dosing with CCX168 or placebo must be ceased in this subject. Study drug may be resumed only if WBC and absolute neutrophil count both exceed the lower limit of the respective

normal range, the Investigator deems resumption to be appropriate, and the WBC and ANC are monitored closely thereafter.

The DMC will review all SUSARs unblinded and determine, based on a careful consideration of the events whether the SUSAR is most likely related to CCX168. This review will take all aspects into account, including onset of the SUSAR relative to dosing with CCX168, course of adverse event in relation to de-challenge and possible re-challenge with study medication, actual treatment (i.e. CCX168 or placebo) received, other potential causes for the SUSAR such as concomitant medication including corticosteroid use, cyclophosphamide use, rituximab use, azathioprine use, other comorbidities and underlying conditions, and other previous adverse events observed over the course of the study. Only SUSARs that were assessed by the DMC as most likely related to CCX168 will be taken into account for the decision to proceed with the next step of the trial.

Any pregnancies that occur in female subjects or partners of male study subjects must be reported within 24 hours of awareness as indicated in section 7.2.4. All pregnancies must be followed up until conclusion and the outcome of the pregnancy reported within 24 hours of awareness as indicated in section 7.2.4.

The therapies used to treat patients with AAV, i.e., cyclophosphamide, rituximab, and corticosteroids, are often associated with adverse events. A list of reported adverse events observed with cyclophosphamide use is provided in section 11.8, with corticosteroid use in section 11.9, with rituximab use in section 11.10, and with azathioprine use in section 11.11. In assessing potential causality of adverse events to CCX168/placebo, the known association between cyclophosphamide, corticosteroids, rituximab, and azathioprine to these adverse events will be taken into account.

7.2.4. Reporting of Serious Adverse Events

Any serious adverse event, 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 electronically in the Electronic Data Capture (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]:
PPD

Any medication or other therapeutic measures used to treat the event will be recorded on the appropriate CRF page(s) in addition to the outcome of the adverse event. The sponsor 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. Events related to the underlying disease where IV or oral corticosteroid rescue medication are given, will not be considered as SUSARs, unless there is a reasonable possibility that CCX168 use was associated with the event. These events will be included in the annual safety reports.

7.3. Pharmacokinetic Assessments

Concentrations of CCX168 (and potential metabolites) will be determined in plasma from 6-mL blood samples collected in K_3EDTA tubes on Days 1, 8, 15, 22, 29, 43, 57, 71, and 85. The samples on Day 1 will be collected just prior to the morning dose on that day, and at 0.5, 1, 2, 3, 4, and 6 hours following the morning dose. The date and time of the last dose prior to the sample collections on Days 8, 15, 22, 29, 43, 57, 71, and 85 will be recorded in the eCRF. The blood samples will be mixed gently and kept on wet ice until centrifuged (within 30 minutes after collection) at approximately 2000 x g, for approximately 10 minutes. Resultant plasma needs to be split into three ~1-mL aliquots and transferred to three appropriately labeled polypropylene tubes and stored at approximately -70°C or below until analysis. If the site does not have access to a -70°C freezer, the samples must be put on dry ice and shipped to the central laboratory as expeditiously as possible, or stored at -20°C and shipped to the central laboratory according to instructions provided.

Total plasma concentrations of CCX168 (and potential metabolites) will be determined using validated analytical methods. In addition, plasma concentrations of co-medications and relevant active metabolites, such as cyclophosphamide, 4-hydroxycyclophosphamide or other metabolites, rituximab, prednisone, and prednisolone may be measured in these samples. These plasma samples may also be used to measure cytokines, complement fragments, or other markers associated with ANCA vasculitis.

A representative urine sample from a 6-hour urinary collection following the morning dose on Day 1 will be used to determine the CCX168 urine concentration. After the 6-hour collection, the urine volume will be measured and recorded, and a representative urine sample (20 mL) will also be stored at -70°C or below until analysis. If the site does not have access to a -70°C freezer, the samples must be put on dry ice and shipped to the central laboratory as expeditiously as possible, or stored at -20°C and shipped to the central laboratory according to instructions provided.

7.4. Pharmacodynamic Assessments

A plasma sample will be collected on Days 1, 29, 85, and 169 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.

Urine samples will also be collected on Days 1, 8, 15, 29, 57, 85, 113, and 169 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]), complement fragments, inflammatory chemokine and cytokine levels.

A saliva sample will be collected on Day 1 from subjects who have provided informed consent for assessment of genetic markers of ANCA disease as well as the complement pathway. Potential markers include *HLA DPB1*0401*, *SERPINA1*, *PRTN3*, and *HLA-DQ*. C5aR polymorphism may also be investigated.

7.5. Study Completion and Withdrawal

Day 169 will be the last Study Day for all subjects. Procedures for this day will be completed per the Time and Events Table. The subject'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 subjects as needed. For early withdrawals (prior to Day 85), the procedures scheduled for Study Day 85 will be performed and recorded as an Early Termination visit. For withdrawals after Day 85, procedures for Day 169 will be performed.

7.6. Data Monitoring Committee

In addition to ongoing safety monitoring by the Medical Monitor and Clinical staff, an external Data Monitoring Committee (DMC) will monitor the safety of subjects, including rescue corticosteroid use, over the course of the study. The DMC will consist of two independent physicians and one biostatistician. A DMC charter will be developed before start of the study and the DMC will function according to the charter. The following will be triggers for a formal DMC data review:

Study Step 1

1. More than 1 subject have a SUSAR, or
2. More than 3 subjects require rescue IV steroids, or
3. 10 subjects complete Day 85 without a SUSAR and at least 7 of these subjects did not require rescue corticosteroid treatment, or
4. When 12 subjects in Step 1 have reached at least the Day 29 visit.

Study Step 2

1. More than 1 subject have a SUSAR, or
2. More than 3 subjects require rescue IV steroids, or
3. 10 subjects complete Day 85 without a SUSAR and at least 7 of these subjects did not require rescue corticosteroid treatment, or
4. When 12 subjects in Step 2 have reached at least the Day 29 visit.

Study Step 3

1. Once every 3 to 6 months, depending on the enrollment rate, or
2. If any unanticipated safety issues occur.

It is anticipated that there will be at least 6 DMC meetings: a kick-off meeting and five meetings over the course of the study. 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.

The DMC will review all SUSARs and determine, based on a careful consideration of the events whether the SUSAR is most likely related to CCX168. This review will take all aspects into account, including onset of the SUSAR relative to dosing with CCX168, course of adverse event in relation to de-challenge and possible re-challenge with study medication, actual treatment (i.e. CCX168 or placebo) received, other potential causes for the SUSAR such as concomitant medication including corticosteroid use, cyclophosphamide use, rituximab use, other comorbidities and underlying conditions, and other previous adverse events observed over the course of the study.

7.7. Statistical Methods

Statistical analysis of efficacy data will be performed using SAS® (SAS Institute, Cary, NC) software, based on a predefined Statistical Analysis Plan. Data analysis and writing of an Integrated Clinical and Statistical Report (ICSR) for all study data will be performed by the designated CRO in accordance with its SOPs. Data analysis of pharmacokinetic data, using WinNonlin software, and writing of a pharmacokinetic appendix to the ICSR will be performed by a designated pharmacokinetic team in accordance with its SOPs.

Unless specified otherwise, all statistical testing will be one-sided and with the type I error rate at α=0.05. In the context of this being a Phase 2 trial, no adjustment for multiplicity will be made. No missing data will be imputed.

7.8. Subject Populations

For the purposes of data analysis, the ITT Population will include all subjects who are randomized, have received at least one dose of study drug, and have at least one post baseline BVAS assessment. The safety population will include all subjects who are randomized and have received at least one dose of study drug. A per protocol (PP) population may also be defined if there are major protocol deviations that could affect study outcome.

7.9. Safety Endpoints

The primary safety endpoint is the subject incidence of adverse events.

Other safety endpoints include:

1. Subject incidence of events possibly associated with glucocorticoid use: serious infections, new-onset diabetes mellitus/hyperglycemia, bone fracture, peptic ulcer disease, cataracts, new onset/worsening hypertension, weight gain more than 10 kg, and psychiatric disorders;
2. Subject incidence of infections, serious infections, severe infections (i.e., Grade 3), and infections leading to subject withdrawal from the study;
3. Change from baseline in all safety laboratory parameters;
4. Change from baseline in vital signs;
5. Incidence of clinically significant ECG changes from baseline.

7.10. Efficacy Endpoints

The primary efficacy endpoint is the proportion of subjects achieving disease response at Day 85 defined as BVAS percent reduction from baseline of at least 50% plus no worsening in any body system component.

Other efficacy endpoints include:

1. In patients with hematuria and albuminuria at baseline, the proportion of subjects achieving renal response at Day 85; renal response is defined as an improvement in parameters of renal vasculitis:
    a. an increase from baseline to Day 85 in eGFR (MDRD serum creatinine equation), plus

b. a decrease from baseline to Day 85 in hematuria (central laboratory microscopic count of urinary RBCs), plus
c. a decrease from baseline to Day 85 in albuminuria (first morning urinary albumin:creatinine ratio).

2. Proportion of subjects achieving disease remission at Day 85 defined as BVAS of 0 or 1 plus no worsening in eGFR and urinary RBC count < 10/hpf;
3. Percent change from baseline to Day 85 in BVAS;
4. Change and percent change from baseline to Day 85 in eGFR;
5. In subjects with baseline hematuria > 5 RBCs/hpf, the proportion of subjects and time to first achieving urinary RBC count ≤ 5/hpf at any time during the 84-day treatment period;
6. In subjects with baseline hematuria ≥ 30 RBCs/hpf, the proportion of subjects and time to first achieving urinary RBC count < 30/hpf at any time during the 84-day treatment period;
7. In subjects with hematuria at baseline, the percent change from baseline to Day 85 in urinary RBC count;
8. In subjects with albuminuria at baseline, the percent change from baseline to Day 85 in urinary ACR;
9. Percent change from baseline to Day 85 in urinary MCP-1:creatinine ratio;
10. Proportion of subjects requiring rescue IV or oral glucocorticoid treatment;
11. Change from baseline to Day 85 in the Vasculitis Damage Index (VDI);
12. Change from baseline to Day 85 in health-related quality-of-life as measured by the Short Form-36 version 2.0 (SF-36v2) and EuroQOL-5D-5L (EQ-5D-5L);

Other endpoints include:

1. Total cumulative study-supplied prednisone dose and duration of dosing during the 84-day treatment period;
2. Total cumulative systemic corticosteroid dose (any use) and duration of dosing during the 84-day dosing period;
3. Total cumulative cyclophosphamide or rituximab dose and duration of dosing during the 84-day dosing period;
4. Percent change from baseline in hsCRP;
5. Percent change from baseline in ANCA (anti-PR3 and anti-MPO) at Day 85,
6. Proportion of patients becoming ANCA negative at Day 85; and
7. Change and percent change from baseline in plasma and urine biomarkers.

The 84-day follow-up period results for the endpoints listed above will also be summarized.

7.11. Pharmacokinetic Endpoints

Plasma samples will be collected on Days 1, 8, 15, 22, 29, 43, 57, 71, and 85 to determine the PK profile of CCX168 and potential metabolites. The following parameters will be determined on Day 1, where possible:

C_{max} Maximum plasma concentration

T_{max} Time of maximum plasma concentration

AUC_{0-6} Area under the plasma concentration-time curve from Time 0 to Hour 6 on Day 1

C_{min} Trough level plasma concentrations at post-Day 1 visits

7.12. Pharmacodynamic Endpoints

Plasma samples will be collected on Days 1, 29, 85, and 169 to measure potential change and percent change from baseline in 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)

Urine samples will be collected on Days 1, 8, 15, 29, 57, 85, 113, and 169 to measure potential change and percent change from baseline in biomarkers such as renal injury and inflammation markers (e.g., KIM-1 and NGAL), complement fragments, inflammatory chemokine and cytokine levels.

A saliva sample will be collected on Day 1 to evaluate the effect of genetic markers on treatment response to CCX168 treatment. Potential markers include *HLA DPB1*0401*, *SERPINA1*, *PRTN3*, and *HLA-DQ*. C5aR polymorphism may also be investigated.

7.13. Statistical Analysis Methodology

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

7.13.1. Baseline Characteristics

All subject baseline characteristics and demographic data (age, sex, race, ethnicity, weight, height, body mass index, smoking status, ECG, TB screen results, viral test results, ANCA, vasculitis disease duration (from time of first induction treatment), BVAS, VDI, SF-36v2, EQ-5D-5L, hsCRP, eGFR, hematuria, urine RBC casts, proteinuria (ACR), glomerular histopathology (if biopsy was taken), urinary MCP-1:creatinine ratio, physical examination abnormalities, medical history, previous (within 6 months of screening) and concomitant medications (including vasculitis medication use) at study entry will be listed by treatment group, study center, and subject number, and will also be summarized by treatment group and step of the study. Data for CCX168 treated subjects receiving a reduced starting prednisone dose from Steps 1 and 3, and data for CCX168 treated subjects receiving a no study-supplied prednisone from Steps 2 and 3 will be combined for summary and analyses purposes. Data for

placebo treated subjects from Steps 1, 2, and 3 will be combined for summary and analyses purposes. Data will also be presented separately for the cyclophosphamide and rituximab strata.

The number of patients randomized, completed, or discontinued from the study, along with the reason for discontinuation, will be presented overall and by treatment group. Patient count by analysis population will also be tabulated.

7.13.2. Safety Analyses

Safety analyses will be performed on the Safety Population. The **two** CCX168 treatment group**s** will be compared to the standard of care placebo group in terms of the subject incidence of adverse events.

All safety data will be summarized descriptively by treatment group.

Adverse events will be coded using MedDRA and listed, including all available information of interest such as onset and resolution dates, study day of onset relative to first dosing day, severity, seriousness, causal relationship to study medication, corticosteroid, cyclophosphamide, or rituximab use, action taken, and outcome. Adverse events will be considered as "pre-treatment" if these occur prior to the time of administration of the first dose of study medication. All other adverse events will be considered "treatment-emergent". Pre-treatment adverse events will be listed separately from treatment-emergent adverse events. Symptoms or signs of vasculitis will be considered adverse events if these increase in severity or frequency while a subject is on-study. Adverse events will be listed by subject, and treatment group. AEs will be summarized by treatment group and tabulated separately for maximum severity, relationship to study drug, and relationship to systemic corticosteroid, cyclophosphamide, or rituximab use. AEs leading to withdrawal and SAEs will be tabulated separately.

Safety laboratory data will be listed by treatment group and subject number, and will be summarized by treatment group. Actual laboratory values and change from baseline in laboratory values will be listed and summarized. Laboratory values outside the reference ranges will be flagged in the listings. Laboratory shift tables from baseline to subsequent study visits will also be generated for all safety laboratory parameters. Vital signs data will be summarized similarly. Incidence of clinically significant ECG changes from baseline will be summarized by treatment group.

No inferential statistical analysis will be performed on adverse event or other safety data.

7.13.3. Efficacy Analyses

The primary efficacy endpoint is the proportion of subjects achieving disease response at Day 85 defined as BVAS percent reduction from baseline of at least 50% plus no worsening in any body system component.

The proportion of subjects achieving disease response will be calculated for the comparison between each CCX168 group against the SOC group. If the lower bound of the 1-sided 95% confidence interval for the **difference (CCX168 minus control group)** is greater than **-0.20, the respective CCX168 group will be considered not inferior to the SOC group. If the lower bound is greater than 0.0**, the respective CCX168 group will be considered superior to the SOC group in achieving the disease response. Continuous variables will be analyzed using **mixed effects model for repeated measures (MMRM)** with treatment group**, visit, treatment-by-visit**

interaction, and randomization strata (newly diagnosed AAV or relapsed AAV, rituximab or cyclophosphamide, PR3 or MPO ANCA) as **factors, and baseline as** covariate. **Subjects will be considered as repeated measure units over visits. The MMRM model will be constructed for the treatment period as well as for the entire study period.** Point estimates and corresponding 95% confidence intervals will be computed for the difference between each CCX168 group and the placebo group **using simple contrast from the model. Additionally, analysis of covariance (ANCOVA) with the same factors and covariates will be applied for the between group comparison at each visit**. Data that are not normally distributed, e.g., urinary ACR will be log-transformed before analysis.

Categorical variables will be analyzed using the CMH test. Subjects receiving rescue steroids after Day 1 but before Day 85 + 7 days (i.e. Day 92) will be considered as treatment failures.

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, and standard deviations will be calculated. Geometric means will be calculated for urinary ACR, urinary RBC count, urinary MCP-1:creatinine, and hsCRP. Shift tables will be generated for urinary parameters such as hematuria and albuminuria. Results will be presented separately for each Step of the study, and also combined for three groups: (1) the placebo subjects (standard of care group) across all three steps, (2) the CCX168 subjects receiving a low dose study-supplied prednisone dose from Steps 1 and 3, and (3) the CCX168 subjects receiving no study-supplied prednisone from Steps 2 and 3. Results will also be presented by stratum for each of the three stratification factors, newly diagnosed vs. relapsed patients, rituximab vs. cyclophosphamide use, and PR3 vs. MPO positive ANCA. If the two CCX168 groups showed a similar response, the two CCX168 groups may be combined for testing against the control group.

The main efficacy analysis will be in the ITT population. Sensitivity analyses may also be done in the PP population

Baseline is defined as the last value prior to start of dosing with study medication (typically the Day 1 pre-dose value).

7.13.4. Covariates

The effect of the following baseline parameters (in addition to the defined strata, i.e., newly diagnosed AAV or relapsed AAV, rituximab or cyclophosphamide background treatment, and PR3 vs. MPO ANCA) on study outcome may be assessed:

- Gender
- BMI
- Age at diagnosis of AAV
- Smoking
- Subject's age and ethnicity (if plausible)
- Baseline eGFR
- Baseline hematuria

- Baseline urinary ACR
- Baseline BVAS
- Baseline VDI
- Baseline hsCRP
- Baseline urinary MCP-1:creatinine ratio

7.13.5. Pharmacokinetic Analysis

Individual plasma concentrations of CCX168 and relevant metabolites, as well as co-medications and active metabolites such as cyclophosphamide, 4-hydroxycyclophosphamide, prednisone, and prednisolone, and rituximab (if measured) will be listed, plotted, and summarized descriptively and graphically. Pharmacokinetic parameters will be calculated based on plasma CCX168 concentrations at the time of sample collection in relation to time of administration of the most recent dose of study medication. Plasma levels of significant metabolites may also be determined and PK parameters calculated.

It is of interest to evaluate whether the PK profile of subjects with ANCA-associated vasculitis is similar to the profile in healthy volunteers. 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, BVAS, VDI, serum hsCRP, ANCA (anti-PR3 and anti-MPO), ACR, hematuria, urinary MCP-1:creatinine ratio, or other biomarkers may be used as PD markers.

7.14. Sample Size Justification

Step 1 and 2

Steps 1 and 2 are designed to provide an initial evaluation on the safety and feasibility using CCX168 as a corticosteroid sparing or replacement therapy during induction of remission. The study will progress to the next step (Step 3) if AAV disease activity in the majority of subjects on CCX168 (>50%) is maintained without the need for rescue corticosteroid therapy. A sample size of 12 subjects (8 active and 4 placebo) per step for the first two steps of the study was chosen based on feasibility. Table 9 provides the probabilities of continuing to the next step for a range of true percentages of patients requiring rescue therapy.

Table 9: Percent Probability of Continuation to Next Step

True Percentage of subjects requiring rescue therapy	Probability of continuing to next step *
10%	100%
20%	94%
30%	81%
40%	60%
50%	36%
60%	17%
70%	6%
80%	1%

True Percentage of subjects requiring rescue therapy	Probability of continuing to next step *
90%	0%

* Probability that at least 5 of the 8 subjects on CCX168 did not require rescue therapy.

The table is read as follows: if the true percentage of subjects requiring rescue therapy is 80%, then there is a 1% chance that the study would continue to the next step.

Step 3

A sample size of 36 subjects in Step 3, 12 in each of the CCX168 groups and 12 in the placebo, will provide a total of approximately 60 subjects across all three steps, and ~20 subjects in each of the treatment groups. Assuming a control group BVAS response of 44% at Day 85 and a CCX168 group response of 86%, a sample size of 20 in each group will provide approximately 90% power for the primary efficacy analysis.

7.15. Interim Analysis

Efficacy and 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 the analyses.

Data from Step 1 and 2 will be summarized before proceeding to Step 3. No inferential statistical analysis will be performed before completion of Step 3. Therefore, no alpha penalty will be taken. When all subjects have completed the 84-day treatment period, data may be analyzed to make decisions regarding future clinical development plans.

7.16. 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 subjects and/or study visits with significant protocol deviations.

8. STUDY COMPLETION AND TERMINATION

8.1. Study Completion

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

8.2. Study Termination

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

9. REGULATORY AND ADMINISTRATIVE REQUIREMENTS

9.1. Investigator Responsibilities

Prior to trial initiation, the Investigator will provide the Sponsor with a fully executed and signed FDA Form 1572 and a Financial Disclosure Form. 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 subjects 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 subjects will be respected; and each subject will give his/her informed consent before any protocol-specific tests or evaluations are performed.

9.2. 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.

9.3. 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 Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 46, Subpart A), will be signed by each subject prior to entering the trial. Either the investigator or the investigator's designee will obtain the consent of the study subject. The subject 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 subject and by the person who conducted the informed consent discussion. The Investigator will provide a copy of the signed Informed Consent Form to each subject and will maintain a copy in the subject's record file.

9.4. Protocol Modifications

Only the Sponsor may modify the protocol. Amendments to the protocol will be made only after consultation and agreement between the Sponsor and the Principal Investigator. The only exception is when the Investigator considers that a subject'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 subject 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 subjects 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 competent authorities of the Member State or Member States 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)".

9.5. 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 at least 10 years according to national Swedish and EU regulations (LVFS 2003:3).

9.6. Subject Identification Register

The Investigator agrees to complete a subject 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 assigned number only.

9.7. 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. The FDA requires retention of records for two years following the date a marketing application is approved, or for two years after the FDA is notified that the IND is discontinued if there is no marketing application. Records must be retained for a period at least as long as that specified by FDA regulations. Clinical trial related documents will be archived for at least 10 years according to national Swedish and EU regulations (LVFS 2003:3).

9.8. Case Report Form Completion

Electronic Case Report Forms (CRFs) will be generated for each subject. The electronic system must 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 subjects' records. The Investigator must therefore agree to allow access to subjects' records, and source data must be made available for all study data. The subjects (or their legal representatives) must also allow access to the subjects' 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.

9.9. Monitoring

At intervals during the study, as well as after the completion of subject enrollment, the study center will be monitored by a CRA for compliance, which will include ensuring that accurate and complete data are recorded on CRFs, 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.

9.10. On-site 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.

9.11. 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 may elect to publish some or all of 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.

10. REFERENCES

Abe K, Miyazaki M, Koji T, et al. 2001 Enhanced espression of complement C5a receptor mRNA in human diseased kidney assessed by in situ hybridization. Kidney Int 60:137-146.

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11. APPENDICES

11.1. 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 prestudy 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 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 subject, 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 subjects 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 subject, (e) correspondence between the EC and the Investigator (Informed Consent Form changes, protocol amendments, etc.).

B. Informed Consent of Human Subjects.

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 subject 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 subject and a study center representative sign the Informed Consent Form and the subject 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 subject.
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 completed, accurately reflect the medical records on each subject.
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 subject.
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 subject.
c. Inventory records.

The FDA requires retention of records for two years following the date a marketing application is approved, or for two years after the FDA is notified that the IND is discontinued if there is no marketing application. Records must be retained for a period at least as long as that specified by FDA regulations. Clinical trial related documents will be archived for at least 10 years according to national Swedish and EU regulations (LVFS 2003:3).

11.2. Informed Consent Form

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

1. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject'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 subject.
3. A description of any benefits to the subject 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 subject.
5. A statement describing the extent, if any, to which confidentiality of records identifying the subject 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 whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research related injury to the subject.
8. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

ADDITIONAL ELEMENTS OF INFORMED CONSENT

1. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus if the subject is or may become pregnant) which are currently unforeseeable.
2. Anticipated circumstances under which the subject’s participation may be terminated by the Investigator without regard to the subject’s consent.
3. Any additional costs to the subject that may result from participation in the research.
4. The consequences of a subject’s decision to withdraw from the research and procedures for orderly termination of participation by the subject.
5. A statement that significant new findings developed during the course of the research which may relate to the subject’s willingness to continue participation will be provided to the subject.
6. The approximate number of subjects involved in the study.

11.3. Birmingham Vasculitis Activity Score (BVAS) Version 3

Patient ID: **Date of birth:** **Total score:**

Assessor: **Date of assessment:**

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

Is this the patient's first assessment? **Yes** ☐ **No** ☐

	None	Active Disease		None	Active Disease
1. General	☐		**6. Cardiovascular**	☐	
Myalgia		☐	Loss of pulses		☐
Arthralgia / arthritis		☐	Valvular heart disease		☐
Fever ≥38 °C		☐	Pericarditis		☐
Weight loss ≥2 kg		☐	*Ischaemic cardiac pain #*		☐
2. Cutaneous	☐		*Cardiomyopathy #*		☐
Infarct		☐	*Congestive cardiac failure #*		☐
Purpura		☐	**7. Abdominal**	☐	
Ulcer		☐	Peritonitis		☐
Gangrene #		☐	Bloody diarrhoea		☐
Other skin vasculitis		☐	*Ischaemic abdominal pain #*		☐
3. Mucous membranes / eyes	☐		**8. Renal**	☐	
Mouth ulcers		☐	Hypertension		☐
Genital ulcers		☐	Proteinuria >1+		☐
Adnexal inflammation		☐	*Haematuria ≥10 RBCs/hpf #*		☐
Significant proptosis		☐	Serum creatinine 125-249 µmol/L*		☐
Scleritis / Episcleritis		☐	Serum creatinine 250-499 µmol/L*		☐
Conjunctivitis / Blepharitis / Keratitis		☐	*Serum creatinine ≥500 µmol/L* #*		☐
Blurred vision		☐	*Rise in serum creatinine >30% or fall in creatinine clearance >25% #*		☐
Sudden visual loss		☐	***Can only be scored on the first assessment**		
Uveitis		☐	**9. Nervous system**	☐	
Retinal changes (vasculitis / thrombosis / exudate / haemorrhage) #		☐	Headache		☐
4. ENT	☐		Meningitis		☐
Bloody nasal discharge / crusts / ulcers / granulomata		☐	Seizures (not hypertensive)		☐
Paranasal sinus involvement		☐	*Cerebrovascular accident #*		☐
Subglottic stenosis		☐	Organic confusion		☐
Conductive hearing loss		☐	*Spinal cord lesion #*		☐
Sensorineural hearing loss #		☐	*Cranial nerve palsy #*		☐
5. Chest	☐		Sensory peripheral neuropathy		☐
Wheeze		☐	*Mononeuritis multiplex #*		☐
Nodules or cavities		☐	**10. Other**	☐	
Pleural effusion / pleurisy		☐	a.		☐
Infiltrate		☐	b.		☐
Endobronchial involvement		☐	c.		☐

Massive haemoptysis / alveolar haemorrhage #		□	d.		□
Respiratory failure #		□	**PERSISTENT DISEASE ONLY:** (Tick here if **all** the abnormalities are due to persistent disease)		□

 # Major items

References: Version 1: Luqmani, RA, et al. (1994). "Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis." QJM 87(11):671-8. Version 2: Luqmani, RA, et al. (1997). "Disease assessment and management of the vasculitides." Baillieres Clin Rheumatol 11(2): 423-46. Version 3: Mukhtyar C, et al (2009). "Modification and validation of the Birmingham Vasculitis Activity Score (version 3)" Ann Rheum Dis. 68:1827-1832

11.4. Vasculitis Damage Index

The Vasculitis Damage Index (VDI) is used to record cumulative organ damage since the onset of vasculitis, regardless of whether it is attributed to vasculitis. It does not give an indication of current disease activity; the BVAS is used to record the latter. The VDI score can only remain the same or get worse over time. Newly diagnosed patients (i.e., within the previous 3 months) typically will have a VDI of zero. In patients with vasculitis diagnosed more than 3 months ago, the score could be non-zero.

The VDI will be scored according to the guidance provided by R. A. Luqmani and C. Hall for The Lothian University Hospitals NHS Trust (2004). The VDI captures damage in the following organ systems: Musculoskeletal, Skin/Mucous membranes, Ocular, ENT, Pulmonary, Cardiovascular, Peripheral vascular disease, Gastrointestinal, Renal, Neuropsychiatric, and Other. One point will be scored for each positive item and the VDI is the sum of all scores. Items scored at a particular visit will be carried forward to subsequent visits.

11.5. Prednisone Dose Schedule

Steps 1 and 3 (for CCX168 group with reduced prednisone)

Subjects with a body weight of ≥55 kg, who are randomized to the CCX168 group, will start at an oral prednisone dose of 20 mg per day on Day 1 and will taper the dose down to zero by the end of the 168-day study period. Subjects with a body weight less than 55 kg will start at an oral prednisone dose of 15 mg per day and will taper the dose down to zero by the end of the 168-day study period.

Subjects with a body weight of ≥55 kg, who are randomized to the placebo group, will start at an oral prednisone dose of 60 mg per day on Day 1 and will taper the dose down to zero by the end of the 168-day study period. Subjects 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 by the end of the 168-day study period.

The tapering schedule for subjects with body weight of ≥55 kg is provided in the table below:

Study Days	CCX168 Group	Placebo Group
	Daily Prednisone Dose	
1 to 7	20 mg	60 mg
8 to 14	15 mg	45 mg
15 to 21	10 mg	30 mg
22 to 28	10 mg	25 mg
29 to 35	10 mg	25 mg
36 to 42	10 mg	25 mg
43 to 49	5 mg	20 mg
50 to 56	5 mg	20 mg
57 to 63	5 mg	15 mg
64 to 70	5 mg	15 mg
71 to 77	5 mg	10 mg
78 to 84	5 mg	10 mg
85 to 98	5 mg	10 mg
99 to 140	0	5 mg
141 to 168	0	0

The tapering schedule for subjects with body weight less than 55 kg is provided in the table below:

Study Days	CCX168 Group	Placebo Group
	Daily Prednisone Dose	
1 to 7	15 mg	45 mg
8 to 14	15 mg	45 mg
15 to 21	10 mg	30 mg
22 to 28	10 mg	25 mg
29 to 35	10 mg	25 mg
36 to 42	10 mg	25 mg
43 to 49	5 mg	20 mg
50 to 56	5 mg	20 mg
57 to 63	5 mg	15 mg
64 to 70	5 mg	15 mg
71 to 77	5 mg	10 mg
78 to 84	5 mg	10 mg
85 to 98	5 mg	10 mg

Study Days	CCX168 Group	Placebo Group
	Daily Prednisone Dose	
99 to 140	0	5 mg
141 to 168	0	0

Steps 2 and 3 (for CCX168 group with no prednisone)

Subjects who are randomized to the CCX168 group will not receive any oral prednisone over the course of the study.

Subjects with a body weight of ≥55 kg, who are randomized to the placebo group, will start at an oral prednisone dose of 60 mg per day and will taper the dose down to zero by the end of the 168-day study period. Subjects 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 by the end of the 168-day study period.

The tapering schedule for subjects with body weight of ≥55 kg is provided in the table below:

Study Days	CCX168 Group	Placebo Group
	Daily Prednisone Dose	
1 to 7	0	60 mg
8 to 14	0	45 mg
15 to 21	0	30 mg
22 to 28	0	25 mg
29 to 35	0	25 mg
36 to 42	0	25 mg
43 to 49	0	20 mg
50 to 56	0	20 mg
57 to 63	0	15 mg
64 to 70	0	15 mg
71 to 77	0	10 mg
78 to 84	0	10 mg
85 to 98	0	10 mg
99 to 140	0	5 mg
141 to 168	0	0

The tapering schedule for subjects with body weight less than 55 kg is provided in the table below:

Study Days	CCX168 Group	Placebo Group
	Daily Prednisone Dose	
1 to 7	0	45 mg
8 to 14	0	45 mg
15 to 21	0	30 mg
22 to 28	0	25 mg
29 to 35	0	25 mg
36 to 42	0	25 mg
43 to 49	0	20 mg
50 to 56	0	20 mg
57 to 63	0	15 mg
64 to 70	0	15 mg
71 to 77	0	10 mg
78 to 84	0	10 mg
85 to 98	0	10 mg
99 to 140	0	5 mg

Study Days	CCX168 Group	Placebo Group
	Daily Prednisone Dose	
141 to 168	0	0

Note that all subjects will take prednisone or matching placebo capsules in order to maintain the study blinding. Detailed dosing instructions will be provided to all subjects.

11.6. Cyclophosphamide and Azathioprine Dosing

- Cyclophosphamide doses given from Day 1 through 85 must be given according to directions provided below.
- A dose of 15 mg/kg cyclophosphamide will be given IV to all subjects, unless a lower dose is required per instructions below. The maximum permitted dose is 1.2 g.
- Mesna and antiemetic treatment need to be given according to local practice. Ondansetron 8 mg is recommended.
- Cyclophosphamide needs to be administered over a 1-hour period.
- Cyclophosphamide dose will be determined by four factors: subject age, eGFR, WBC at the study visit, and WBC nadir in between dose pulses (where applicable).
- Age:
  - If <60 years, a full dose will be given (unless influenced by the other three factors);
  - If 60 to 70 years, the dose will be reduced by 2.5 mg/kg;
  - If > 70 years, the dose will be reduced by 5 mg/kg.
- eGFR:
  - If ≥30 mL/min, a full dose will be given (unless influenced by the other three factors);
  - If <30 mL/min, the dose will be reduced by 2.5 mg/kg.
- WBC count at the time of cyclophosphamide dose (local lab WBC counts):
  - If ≥4 x 10^9/L, a full dose will be given (unless influenced by the other three factors);
  - If 2 to 3.9 x 10^9/L, the dose will be reduced by 25%;
  - If <2 x 10^9/L, the dose will be withheld until the WBC count increases to above 3 x 10^9/L.
- WBC count nadir in between cyclophosphamide doses:
  - If >3 x 10^9/L, a full dose will be given (unless influenced by the other three factors);
  - If 2 to 3 x 10^9/L, the dose will be reduced by 20%;
  - If 1 to 1.9 x 10^9/L, the dose will be reduced by 40%;
  - If <1 x 10^9/L, the next dose will be withheld and further dosing would only be given if the WBC is >3 x 10^9/L.
- Note that the cyclophosphamide dose adjustment is cumulative, e.g., a subject >70 years, with an eGFR <30 mL/min, and a WBC at time of dosing of 3 x 10^9/L, will receive a dose of 5.6 mg/kg (15 mg/kg minus 5 mg/kg for age, minus 2.5 mg/kg for eGFR, and reduced 25% for WBC).
- Oral azathioprine will be started on Day 99 and continue through Day 168. Typically the dose will be increased gradually until the target dose of 2 mg/kg/day is reached after 2

weeks. Doses will be rounded down to the nearest 25 mg increment, e.g., a subject weighing 60 kg will have a target dose of 100 mg azathioprine per day. Testing for thiopurine S-methyltransferase (TPMT) 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 2×10^9/L. In case azathioprine is not tolerated, methotrexate or mycophenolate mofetil could be used instead.

11.7. Rituximab Dosing

- The following dosing regimen of rituximab will be given:
  - 375 mg/m^2 given as an IV infusion on Study Days 1, 8, 15, and 22.
- 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 recommended.
- For the first IV infusion, initiate the infusion at a rate of 50 mg/hr. In the absence of infusion toxicity, increase infusion rate by 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.
- For subsequent infusions, initiate the infusion at a rate of 100 mg/hr. In the absence of infusion toxicity, increase rate by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr.

11.8. 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. Note that only post-menopausal women will be eligible for this study. Men treated with cyclophosphamide may develop oligospermia, azoospermia, impaired sexual potency or libido, 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

11.9. Adverse Events Reported with Corticosteroid 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-greatest potential 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

11.10. Adverse Events Reported with Rituximab Use

The following adverse events were reported at an incidence of ≥ 10% in subjects 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. Infections including upper respiratory tract infections, urinary tract infections, and herpes zoster have been reported. Hypogammaglobulinemia was also reported.

11.11. 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.