PROTOCOL

Protocol Amendment 4.0

TITLE PAGE

Study Title:	A Randomized, Double-Blind, Placebo-Controlled, Dose Assessment Phase 2 Study to Evaluate the Safety and Efficacy of CCX168 in Subjects with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis
Protocol Number:	CL003_168
Investigational Product:	Complement 5a Receptor Antagonist CCX168
Indication:	ANCA-Associated Vasculitis
Sponsor:	ChemoCentryx, Inc.
Development Phase:	2
IND number	120784
Sponsor's Responsible Medical Officer:	PPD ChemoCentryx, Inc. PPD
Sponsor Signatory:	PPD
Approval Date:	31 May 2014—FINAL **13 August 2014—Protocol Amendment 1.0** **3 November 2014—Protocol Amendment 1.1 (Canada)** **12 May 2015—Protocol Amendment 2.0** **19 August 2015—Protocol Amendment 3.0** **19 February 2016—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

Protocol Number: CL003_168

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Dose Assessment Phase 2 Study to Evaluate the Safety and Efficacy of CCX168 in Subjects with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis

Medical Officer

PPD

Chief Medical Officer

ChemoCentryx, Inc.

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SPONSOR SIGNATURE FOR APPROVAL

Protocol Number: CL003_168

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PPD

25 FEB 2016

Date

Chief Medical Officer

PROTOCOL AMENDMENT 4.0: SUMMARY OF CHANGES

1. **Because of the relatively small sample size of the study, analysis of the primary efficacy endpoint was modified. Results will be summarized and no inferential statistical analysis will be performed. Modifications have been made to the Study Synopsis and Section 7.13.3 to indicate this change.**
2. **Since the continuous variables are typically measured at multiple time points over the course of the study, the main analysis methodology of continuous variables was changed from analysis of covariance (ANCOVA) to mixed model for repeated measures (MMRM). Modifications have been made to the Study Synopsis and Section 7.13.3 to reflect this change.**
3. **An efficacy endpoint of early remission, based on BVAS of 0 at Day 29 AND Day 85, was added to evaluate the ability of CCX168 to induce early remission; the definition of remission was modified to BVAS of 0, since patients in this trial do not necessarily have renal disease involvement; the threshold endpoints regarding hematuria were removed for the same reason. Modifications have been made to the Study Synopsis and Section 7.10 to reflect these changes.**
4. **Because of the relatively small sample size of the study, the justification for the sample size was modified to indicate that it was based on practical and not statistical considerations. Modifications were made to the Study Synopsis and Section 7.14 to reflect this change.**

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STUDY SYNOPSIS

Name of Sponsor	**Name of Active Ingredient**	**Study number:**
ChemoCentryx, Inc.	CCX168	CL003_168

Title

A Randomized, Double-Blind, Placebo-Controlled, Dose Assessment Phase 2 Study to Evaluate the Safety and Efficacy of CCX168 in Subjects with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis

Investigators

Several

Study centers

Multi-center

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

Aim

The aim of this trial is to test the safety and efficacy of two dose regimens of the complement C5a receptor CCX168 in patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV).

Objectives

The primary safety objective of this study is to evaluate the safety and tolerability of CCX168 in subjects with AAV on background standard of care (SOC) cyclophosphamide or rituximab plus corticosteroid treatment.

The primary efficacy objective is to evaluate the efficacy of CCX168 based on the Birmingham Vasculitis Activity Score (BVAS) in subjects with AAV on SOC cyclophosphamide or rituximab plus corticosteroid treatment.

The secondary objectives of this study include:

1. Evaluation of the efficacy of CCX168 compared to 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 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;
4. Assessment of changes in Vasculitis Damage Index (VDI) with CCX168 compared to SOC;
5. Assessment of changes in ANCA (anti-PR3 and anti-MPO) with CCX168 compared to SOC;
6. Assessment of changes in pharmacodynamic markers in plasma and urine with CCX168 compared to SOC;
7. 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-induced glomerulonephritis, as well as early results from another clinical trial in patients with AAV (CL002_168), CCX168 has potential in the treatment of patients with AAV. A CCX168 dose regimen of 30 mg twice daily has been tested in study CL002_168. No other dose has been tested previously in AAV. Hence, the clinical hypothesis of the trial is to test whether a lower dose of CCX168, i.e., 10 mg twice daily in addition to the 30 mg twice daily regimen is safe and efficacious in patients with AAV receiving SOC cyclophosphamide or rituximab plus corticosteroids. This hypothesis will be tested in this randomized, double-blind, placebo-controlled, Phase 2 clinical trial in up to approximately 45 subjects with new or relapsed AAV. An external data monitoring committee (DMC) will review safety data, including rescue corticosteroid use over the course of the study and advise the Sponsor regarding the study.

Up to approximately 45 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 SOC treatment.

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

Group A: CCX168 10 mg twice daily plus cyclophosphamide/rituximab plus corticosteroids;
Group B: CCX168 30 mg twice daily plus cyclophosphamide/rituximab plus corticosteroids;
Group C: Placebo twice daily plus cyclophosphamide/rituximab plus corticosteroids.
If necessary, rescue corticosteroids should be given to subjects with worsening disease.

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

- Group A (10 mg CCX168 twice daily):
  - One 10-mg CCX168 capsule in the morning and 1 in the evening, approximately 12

hours after the morning dose, daily for 84 days.

- Two matching placebo capsules in the morning and 2 in the evening, approximately 12 hours after the morning dose, daily for 84 days.
- Prednisone tablets equivalent to 60 mg orally per day, 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); no oral azathioprine will be given to subjects receiving rituximab.
- Rescue corticosteroids should be given to subjects with worsening disease.

- Group B (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 tablets equivalent to 60 mg orally per day, 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); no oral azathioprine will be given to subjects receiving rituximab.
  - Rescue corticosteroids should be given to subjects with worsening disease.
- Group C (Placebo twice daily):
  - Three matching placebo capsules in the morning and 3 capsules in the evening, approximately 12 hours after the morning dose, daily for 84 days.
  - Prednisone tablets equivalent to 60 mg orally per day, 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); no oral azathioprine will be given to subjects receiving rituximab.

– Rescue 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 pregnancy test for women of childbearing potential, 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 performed), 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 2 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 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. Serum pregnancy test for women of childbearing potential will be done on Days 29, 57, 85, 113, and 169. 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. 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 SOC 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

Up to approximately 45 male or 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.

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 female subjects, aged at least 18 years, with new (typically within 4 weeks prior to screening) or relapsed AAV where treatment with cyclophosphamide or rituximab would be required; Female subjects of childbearing potential may participate if adequate contraception is used during the study, and for at least 6 months after the last cyclophosphamide dose (if receiving cyclophosphamide) and at least 12 months after the last rituximab dose (if receiving rituximab); Male 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 the study, and for at least 6 months after the last cyclophosphamide dose (if receiving cyclophosphamide) and at least 12 months after the last rituximab dose (if receiving rituximab); Adequate contraception is defined as one highly effective method plus one effective method; highly effective methods include hormonal contraceptives, e.g., combined oral contraceptives, patch, vaginal ring, injectables, and implants; intrauterine device or intrauterine system; vasectomy and tubal ligation; effective methods include barrier methods of contraception, e.g., male condom, female condom, cervical cap, diaphragm, contraceptive sponge plus a spermicide;
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 per 1.73 m^2 (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, or 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);
2. Women who are pregnant (positive pregnancy test) or breastfeeding at study entry; women should not breastfeed during the study, and if receiving rituximab, until drug levels are no longer detectable after study completion;
3. 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;
4. Medical history of coagulopathy or bleeding disorder;
5. 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;
6. Received intravenous corticosteroids, >3000 mg methylprednisolone equivalent, within 12 weeks prior to screening;
7. 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 corticosteroids at the time of screening, the non-study supplied corticosteroids will be stopped when the subject starts taking the study supplied 60 mg prednisone dose on Day 1;
8. 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;
9. 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;
10. 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;

11. Evidence of tuberculosis based on chest X rays performed during screening as part of the BVAS assessment;
12. Positive HBV, HCV, or HIV viral screening test;
13. 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);
14. Received a live vaccine within 4 weeks prior to screening;
15. WBC count less than 4000/μL**,** or neutrophil count less than 2000/μL, or lymphocyte count less than 1000/μL;
16. Hemoglobin less than 9 g/dL (or 5.56 mmol/L) at screening;
17. Evidence of hepatic disease; AST, ALT, alkaline phosphatase, or bilirubin > 3 x the upper limit of normal;
18. Prothrombin time (PT) or partial thromboplastin time (PTT) above the normal reference limit;
19. Clinically significant abnormal ECG during screening, e.g., QTcF greater than 450 msec;
20. 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;
21. Known hypersensitivity to CCX168 or inactive ingredients of the CCX168 capsules (including gelatin, polyethylene glycol, or Cremophor), cyclophosphamide or its metabolites (for subjects scheduled to receive cyclophosphamide), or known Type I hypersensitivity or anaphylactic reactions to murine proteins, Chinese Hamster Ovary cell proteins, or to any component of rituximab (for subjects scheduled to receive rituximab);
22. Urinary outflow obstruction, active infection (especially *varicella zoster* infection), or platelet count < 50,000/μL (for subjects scheduled to receive cyclophosphamide treatment), and
23. 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 and Reference 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 (10 mg CCX168) will receive one kit containing 1 bottle of CCX168 capsules and 2 bottles of matching placebo capsules on Days 1, 15, 29, 43, 57, and 71. Subjects in Group B (30 mg CCX168) will receive one kit containing 3 bottles of CCX168 capsules on Days 1, 15, 29, 43, 57, and 71. Subjects in Group C (placebo) will receive one kit containing 3 bottles of matching placebo capsules on Days 1, 15, 29, 43, 57, and 71.

Subjects will be asked to take 1 capsule from each bottle every morning and 1 capsule from each bottle 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.

Prednisone will be given according to a standard tapering schedule. Prednisone 20 mg and 5 mg tablets from a commercial source will be used and provided to the study centers with dosing instructions.

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 SOC 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 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.

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 each CCX168 and the SOC control group.

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;
3. **Proportion of subjects achieving early disease remission (BVAS of 0) at Day 29 AND Day 85;**
4. Percent change from baseline to Day 85 in BVAS;
5. Change and percent change from baseline to Day 85 in eGFR;
6. In subjects with hematuria at baseline, the percent change from baseline to Day 85 in urinary RBC count;
7. In subjects with albuminuria at baseline, the percent change from baseline to Day 85 in urinary ACR;
8. Percent change from baseline to Day 85 in urinary MCP-1:creatinine ratio;

9. Proportion of subjects requiring rescue glucocorticoid treatment;
10. Change from baseline to Day 85 in the Vasculitis Damage Index (VDI);
11. 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.

All stated safety and efficacy endpoints will be assessed through the end of the follow-up period, Day 169. 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 by treatment group. 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 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. **Because of the relatively small sample size of the study, no inferential statistical analysis will be performed on the primary endpoint.**

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. Point estimates and corresponding 95% confidence intervals will be estimated for the difference between each CCX168 group and the placebo group **using simple contract 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 **summarized in a similar manner as described for the primary endpoint**. **These** include the proportion of subjects achieving **remission, defined as BVAS of 0, at Day 85, early remission, defined as BVAS of 0 at Day 29 AND Day 85, and** renal response at Day 85.

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**, on treatment** BVAS assessment.

The safety analysis will be performed on the safety population which includes all subjects who have signed informed consent to participate in the study, who were randomized in this study, and have received at least one dose of study drug.

The sample size estimation was based on practical and not statistical considerations.

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 metabolites). Individual plasma concentrations of CCX168 (and 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

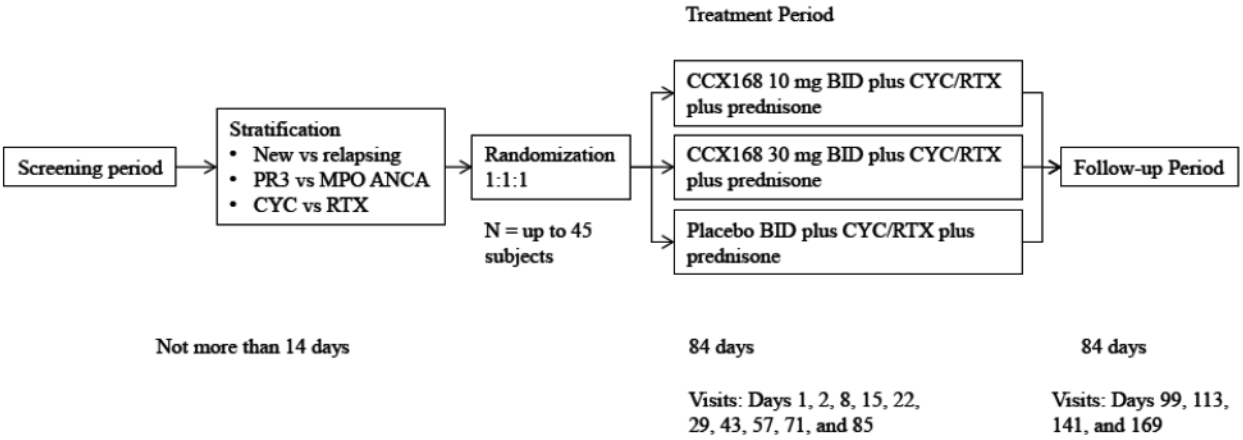
The relationship between PK parameters and renal function based on eGFR will be evaluated. The data may also be used to evaluate the PK/PD relationship of CCX168 treatment. To this end, the change and/or percent change from baseline in BVAS, eGFR, urinary ACR, urinary MCP-1:creatinine ratio, serum hsCRP,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



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
Serum pregnancy test for women of childbearing potential	X						X		X		X		X		X
12-lead ECG	X						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				
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]				

	Screening[1]	Study Day[2]													
	-14 to -1	**1[3]**	**2**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141**	**169**
Randomization		X[5]													
CCX168 or Placebo Dispensing		X			X		X	X	X	X					
CCX168 or Placebo Accountability					X		X	X	X	X	X				(X)[13]
Prednisone Dispensing		X		X	X	X		X	X	X	X	X	X		
Prednisone Accountability				X	X	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 corticosteroids at screening to stop when study prednisone is started	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. Physical examination will include a neurological examination including speech, consciousness level, mood, cranial nerves, motor, coordination and gait, reflexes, and sensory systems.

[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.

[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
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
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
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
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

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. Study Drug Development

1.1.1. Non-Clinical Pharmacology

1.1.1.1. *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).

One major metabolite (CCX168-M1) has been identified in human plasma in Phase 1 study CL001_168. This compound, also referred to a C0335273, has been shown to be equivalent to CCX168 in its potency towards hC5aR, having a potency (IC_{50}) of 3 nM for inhibition of C5a-mediated whole blood neutrophil chemotaxis and a potency of 7 nM for inhibition of C5a-mediated neutrophil CD11b upregulation assay in whole blood. Like CCX168, the metabolite CCX168-M1 has a comparable high potency for cynomolgus monkey, hamster, and human C5aR, moderate potency against rabbit C5aR (IC_{50} ~ 1.4 μM), but 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). CCX168-M1 was tested against a panel of 17 related chemotactic receptors and a panel of 55 unrelated receptors and membrane-associate proteins. The only activity detected was weak (>1,000-fold selectivity relative to hC5aR) against CB1 (53% inhibition with 10 μM CCX168-M1), the site 2 sodium channel (64% inhibition with 10 μM CCX168-M1) and the GABA-gated chlorine channel (51% inhibition with 10 μM CCX168-M1).

1.1.1.2. 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 benefit in inflammatory conditions associated with C5aR activation.

1.1.2. 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 safety pharmacology and toxicology program has been conducted in accordance with current ICH nonclinical toxicology guidance (including M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical trials for Pharmaceuticals; S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use, S7A Safety Pharmacology Studies for Human Pharmaceuticals, S7B Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals, and S8 Immunotoxicity Studies for Human Pharmaceuticals. The species selected for these studies (rats and monkeys) are well established models accepted by regulatory authorities for toxicology studies and were selected based upon metabolic, pharmacokinetic, and pharmacological properties of CCX168 in these species; information gained with these species was expected to be of predictive clinical utility. CCX168-M1, presumed to be the only major human metabolite, was appropriately qualified in both the rat and the cynomolgus monkey; no additional major human metabolites are anticipated based on existing extensive *in vitro* and *in vivo* data. Additionally, CCX168 and CCX168-M1 are highly active in the cynomolgus monkey which indicated the latter species should be predictive of any toxicity related to C5aR inhibition.

The toxicology studies (oral administration) conducted to date include a single-dose acute study in rats, dose-range finding studies in rats and cynomolgus monkeys, and GLP 28-day and 13/20-week studies in rats and cynomolgus monkeys, respectively. 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 and ophthalmological evaluations, clinical pathology and the microscopic assessment of a full list of tissues. The definitive cynomolgus studies 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. *In vitro* studies to assess the potential effects of CCX168 and CCX168-M1 upon hERG channel ionic conductance was also conducted. An assessment of CCX168 potential effects upon T-cell dependent humoral responses was performed in the rat. 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 rat toxicology and CCX168-M1 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
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
Respiratory	Oral/Single-Dose	Rat	0, 5, 25, 100 mg/kg
Renal	Oral/Single-Dose	Rat	0, 5, 25, 100 mg/kg
Cardiovascular – *In vivo*	Oral/Single-Dose	Cynomolgus monkey	0, 5, 15, 50 mg/kg

Table 2: Overview of Safety Pharmacology Studies Performed with CCX168 (Continued)

Cardiovascular – *In vitro* (hERG with CCX168)	*In vitro*	Human cells transfected with human K-channel gene	0.6, 1.2, 2.3 and 6.9 µM
Cardiovascular – *In vitro* (hERG with CCX168-M1)	*In vitro*	Human cells transfected with human K-channel gene	1, 3, 10, and 15.8 µM

There were no remarkable central nervous or respiratory system effects in rats following nominal single oral doses up to 100 mg/kg (actual dose of 73 mg/kg confirmed by dose solution analysis), or renal effects in rats following single oral doses up to 100 mg/kg, or effects on cardiovascular parameters in cynomolgus monkeys following single oral doses of up to 50 mg/kg. Additionally, no evidence of electrocardiographic abnormalities was seen *in vivo* in the 28-day and 20-week multiple dose studies in cynomolgus monkeys. In the *in vitro* cardiovascular safety studies, the IC_{50} values for hERG inhibition for CCX168 and CCX168-M1 were determined to be > 2.3 µM and 3 µM (the respective limits 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, effects of CCX168 on cyclophosphamide metabolic activation and prednisone metabolism, 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 indicate a significant risk for drug-drug interactions with other concurrent medications in the intended patient population. 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, CCX168 administered orally at doses up to 100 mg/kg/day, did not affect T-cell dependent antibody responses induced by KLH.

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. There were no CCX168-related changes in clinical observations, body weights, ophthalmic examinations, electrocardiographic examinations, blood pressure, and respiratory examinations, clinical pathology, gross observations, organ weights, and microscopic evaluation.

Given the lack of significant safety concerns in the toxicology studies and the Phase 1 study in healthy volunteers, and the safety results from clinical trial CL002_168 so far, the risk for serious or unanticipated untoward events to occur in this clinical trial is considered low.

1.1.3. 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 approximately 99% or higher, with corresponding unbound fractions at approximately 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.

1.2. 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 and the multi-dose period of the study is provided in the Investigator's Brochure.

All adverse events in the single-dose period 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 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 2.22x109/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 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.

No clinically significant changes in laboratory parameters, vital signs, or ECG parameters were observed. Key pharmacokinetic results (mean, SD) from the single-dose period and the multiple dose period of clinical trial CL001_168 are provided in the Investigator's Brochure.

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.

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.

Clinical trial CL002_168 in patients with AAV is ongoing. This is a randomized, double-blind, placebo-controlled clinical trial being conducted in three sequential steps. A total of 26 subjects have been enrolled in the first two steps of this clinical trial. A summary of the safety and efficacy results, as well as the PK results from the first two steps are provided in the Investigator's Brochure.

1.3. 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) or IV rituximab, plus oral corticosteroids, tapered over a period of time. Severe disease warrants addition of IV corticosteroids and/or plasma exchange. There are unmet needs to shorten the time to remission, improve complete remission rates and reduce corticosteroid exposure.

Based on encouraging results from preclinical studies in a human C5aR knock-in mouse model of ANCA-induced glomerulonephritis (described in Section 1.1.1.2, as well as the Investigator's Brochure), as well as results from the first two steps of study CL002_168 (see Investigator's Brochure), CCX168 could offer benefit in the treatment of patients with AAV.

A single dose regimen of 30 mg CCX168 given twice daily is being tested in study CL002_168. No assessment of other CCX168 dose regimens has been made to date. Hence, the rationale for this clinical trial is to evaluate safety and efficacy of another dose regimen, 10 mg CCX168 twice daily, in patients with AAV. Based on PK-PD modeling, this lower dose regimen may also provide efficacy.

CCX168 will be given on top of standard of care (SOC), i.e., either cyclophosphamide or rituximab plus glucocorticoids.

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 SOC cyclophosphamide or rituximab plus corticosteroid treatment.

The primary efficacy objective is to evaluate the efficacy of CCX168 based on the Birmingham Vasculitis Activity Score (BVAS) in subjects with AAV on SOC cyclophosphamide or rituximab plus corticosteroid treatment.

2.2. Secondary Objectives

The secondary objectives of the study include the following:

1. Evaluation of the efficacy of CCX168 compared to 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 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;
4. Assessment of changes in Vasculitis Damage Index (VDI) with CCX168 compared to SOC;
5. Assessment of changes in ANCA (anti-PR3 and anti-MPO) with CCX168 compared to SOC;
6. Assessment of changes in pharmacodynamic markers in plasma and urine with CCX168 compared to SOC;
7. 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 compelling results from preclinical studies in a mouse model of ANCA-induced glomerulonephritis, as well as early results from another clinical trial in patients with AAV (CL002_168), CCX168 has potential in the treatment of patients with AAV. A CCX168 dose regimen of 30 mg twice daily has been tested in study CL002_168. No other dose has been tested previously in AAV. Hence, the clinical hypothesis of the trial is to test whether a lower dose of CCX168, i.e., 10 mg twice daily as an alternative to 30 mg twice daily regimen is safe and efficacious in patients with AAV receiving SOC cyclophosphamide or rituximab plus corticosteroids. This hypothesis will be tested in this randomized, double-blind, placebo-controlled, Phase 2 clinical trial in up to approximately 45 subjects with new or relapsed AAV. An external data monitoring committee (DMC) will review safety data, including rescue corticosteroid use over the course of the study and advise the Sponsor regarding the study.

Up to approximately 45 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 SOC treatment.

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

Group A: CCX168 10 mg twice daily plus cyclophosphamide/rituximab plus corticosteroids;

Group B: CCX168 30 mg twice daily plus cyclophosphamide/rituximab plus corticosteroids;

Group C: Placebo twice daily plus cyclophosphamide/rituximab plus corticosteroids.

If necessary, rescue 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), ECG, chest X rays, viral screening, serology and complement measurements (if not done within the previous 12 months), estimated glomerular filtration rate (eGFR) assessment (MDRD), 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 performed), 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 2 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], 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 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. 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 SOC 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.

4. STUDY POPULATION

4.1. Size of the Population

The aim is to enroll up to approximately forty five (45) subjects for the study. Subjects who drop out of the study prematurely will not be replaced.

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 female subjects, aged at least 18 years, with new (typically within 4 weeks prior to screening) or relapsed AAV where treatment with cyclophosphamide or rituximab would be required; Female subjects of childbearing potential may participate if adequate contraception is used during the study, and for at least 6 months after the last cyclophosphamide dose (if receiving cyclophosphamide) and at least 12 months after the last rituximab dose (if receiving rituximab); Male 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 the study, and for at least 6 months after the last cyclophosphamide dose (if receiving cyclophosphamide) and at least 12 months after the last rituximab dose (if receiving rituximab); Adequate contraception is defined as one highly effective method plus one effective method; highly effective methods include hormonal contraceptives, e.g., combined oral contraceptives, patch, vaginal ring, injectables, and implants; intrauterine device or intrauterine system; vasectomy and tubal ligation; effective methods include barrier methods of contraception, e.g., male condom, female condom, cervical cap, diaphragm, contraceptive sponge plus a spermicide;
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. Estimated glomerular filtration rate $\geq$ 20 mL per minute per 1.73 m^2 (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, or 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);
2. Women who are pregnant (positive pregnancy test) or breastfeeding at study entry; women should not breastfeed during the study, and if receiving rituximab, until drug levels are no longer detectable after study completion;
3. 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;
4. Medical history of coagulopathy or bleeding disorder;
5. 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;
6. Received intravenous corticosteroids, >3000 mg methylprednisolone equivalent, within 12 weeks prior to screening;
7. 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 corticosteroids at the time of screening, the non-study supplied corticosteroids will be stopped when the subject starts taking the study supplied 60 mg prednisone dose on Day 1;
8. 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;
9. 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;
10. 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;
11. Evidence of tuberculosis based on chest X rays performed during screening as part of the BVAS assessment;
12. Positive HBV, HCV, or HIV viral screening test;
13. 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);

14. Received a live vaccine within 4 weeks prior to screening;
15. WBC count less than 4000/µL, or neutrophil count less than 2000/µL, or lymphocyte count less than 1000/µL;
16. Hemoglobin less than 9 g/dL (or 5.56 mmol/L) at screening;
17. Evidence of hepatic disease; AST, ALT, alkaline phosphatase, or bilirubin > 3 x the upper limit of normal;
18. Prothrombin time (PT) or partial thromboplastin time (PTT) above the normal reference limit;
19. Clinically significant abnormal ECG during screening, e.g., QTcF greater than 450 msec;
20. 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;
21. Known hypersensitivity to CCX168 or inactive ingredients of the CCX168 capsules (including gelatin, polyethylene glycol, or Cremophor), cyclophosphamide or its metabolites (for subjects scheduled to receive cyclophosphamide), or known Type I hypersensitivity or anaphylactic reactions to murine proteins, Chinese Hamster Ovary cell proteins, or to any component of rituximab (for subjects scheduled to receive rituximab),
22. Urinary outflow obstruction, active infection (especially *varicella zoster* infection), or platelet count < 50,000/µL (for subjects scheduled to receive cyclophosphamide treatment), and
23. 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.

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.

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 study-supplied prednisone/placebo will be discontinued, and appropriate open-label SOC 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 three strata: (1) newly diagnosed or relapsing disease, (2) PR3 or MPO ANCA, and (3) cyclophosphamide or rituximab use, and then randomized to one of the three treatment groups in a ratio of 1:1:1, 10 mg CCX168 twice daily:30 mg CCX168 twice daily:Placebo. Randomization will be performed centrally via an interactive voice response system (IVRS). 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 three groups in the study:

- Group A: CCX168 10 mg twice daily plus cyclophosphamide/rituximab plus corticosteroids;
- Group B: CCX168 30 mg twice daily plus cyclophosphamide/rituximab plus corticosteroids;
- Group C: Placebo twice daily plus cyclophosphamide/rituximab plus corticosteroids.

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

- Group A (10 mg CCX168 twice daily):
  - One 10-mg CCX168 capsule in the morning and 1 in the evening, approximately 12 hours after the morning dose, daily for 84 days.
  - Two matching placebo capsules in the morning and 2 in the evening, approximately 12 hours after the morning dose, daily for 84 days.
  - Prednisone tablets equivalent to 60 mg orally per day, 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); no oral azathioprine will be given to subjects receiving rituximab.
  - Rescue corticosteroids should be given to subjects with worsening disease (see Section 5.10).

- Group B (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 tablets equivalent to 60 mg orally per day, 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); no oral azathioprine will be given to subjects receiving rituximab.
  - Rescue corticosteroids should be given to subjects with worsening disease (see Section 5.10).
- Group C (Placebo twice daily):
  - Three matching placebo capsules in the morning and 3 capsules in the evening, approximately 12 hours after the morning dose, daily for 84 days.
  - Prednisone tablets equivalent to 60 mg orally per day, 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); no oral azathioprine will be given to subjects receiving rituximab.
  - Rescue corticosteroids should be given to subjects with worsening disease (see Section 5.10).

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 (10 mg CCX168) will receive one kit containing 1 bottle of CCX168 capsules and 2 bottles of matching placebo capsules on Days 1, 15, 29, 43, 57, and 71. Subjects in Group B (30 mg CCX168) will receive one kit containing 3 bottles of CCX168 capsules on Days 1, 15, 29, 43, 57, and 71. Subjects in Group C (placebo) will receive one kit containing 3 bottles of matching placebo capsules on Days 1, 15, 29, 43, 57, and 71.

Subjects will be asked to take 1 capsule from each bottle every morning and 1 capsule from each bottle 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.

Prednisone will be given according to a standard tapering schedule (see Section 11.5). Prednisone 20 mg and 5 mg tablets from a commercial source will be used and provided to the study centers with dosing instructions.

If a subject is on corticosteroids at the time of screening, the non-study supplied corticosteroids will be stopped on Day 1 when the study supplied dose of 60 mg prednisone is started.

For subjects 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).

For subjects in the rituximab stratum, rituximab IV will be given on Days 1, 8, 15, and 22 (375 mg/m^2 at each time point; see Section 11.7).

The protocol allows corticosteroid use, up to 3000 mg methylprednisolone equivalent, within the 12 weeks prior to Screening. This corticosteroid use must be documented in the electronic data capture (EDC) system.

Rescue glucocorticoid 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. All doses up to 100 mg (single dose) and 50 mg twice daily for 7 days were well tolerated with no significant safety concerns. A dose of 30 mg CCX168 twice daily has been tested in study CL002_168 in patients with AAV. No dose-ranging Phase 2 study has been performed previously. A dose of 10 mg CCX168 twice daily, in addition to the 30 mg twice daily dose regimen, has been selected for this Phase 2 study in subjects with AAV. It is anticipated that both CCX168 dose regimens would be well tolerated in patients with AAV. At steady state, both dose regimens are anticipated to provide at least 90% C5aR coverage on blood neutrophils continuously throughout the day.

Based on the good safety profile observed in the toxicology studies, and the safety and tolerability results from the Phase 1 clinical trial CL001_168 and Phase 2 clinical trial CL002_168, 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 three 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, 15, 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.

There will be three CCX168/placebo kit configurations:

1. For Group A, the 10 mg CCX168 twice daily group:
    - Bottle 1: Thirty 10-mg CCX168 capsules
    - Bottle 2: Thirty placebo capsules
    - Bottle 3: Thirty placebo capsules
2. For Group B, the 30 mg CCX168 twice daily group:
    - Bottle 1: Thirty 10-mg CCX168 capsules
    - Bottle 2: Thirty 10-mg CCX168 capsules
    - Bottle 3: Thirty 10-mg CCX168 capsules
3. For Group C, the placebo twice daily group:
    - Bottle 1: Thirty placebo capsules
    - Bottle 2: Thirty placebo capsules
    - Bottle 3: Thirty placebo capsules

Prednisone tablets, containing either 20 mg or 5 mg prednisone, will be packaged in high density polyethylene (HDPE) bottles with child-resistant screw caps and provided to the study sites. Each bottle will contain 30 tablets of either 20 mg or 5 mg prednisone. All bottles will be labeled appropriately to indicate, at a minimum, protocol number, the prednisone dose strength, the contents, storage conditions, cautionary statement to keep out of reach of children, and the expiry date. The prednisone bottles will be provided to each subject according to details provided in Section 11.5 with detailed dosing instructions.

Cyclophosphamide, rituximab, and azathioprine will be prescribed by the investigators according to instructions in Sections 11.6 and 11.7. The dose given and dosing dates and times (for IV infusions) must be recorded in the EDC.

5.5.2. Storage

CCX168 and CCX168 placebo capsules, as well as prednisone tablets 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 is a double-blind study. 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 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 azathioprine (where applicable) tablets, 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 dose unit 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, IV cyclophosphamide or rituximab, or rescue 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.

Since study subjects will receive a number of immunosuppressive drugs, all study subjects must receive *Pneumocystis carinii* pneumonia (PCP) prophylactic treatment. Prophylactic treatment for osteoporosis, gastroprotection, and anti-nausea medication (e.g., ondansetron), according to local practice, is recommended.

In case of neutropenic fever in a subject receiving cyclophosphamide, antibiotics and/or antimycotics must be given, according to the prescribing information.

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 non-study supplied corticosteroids at the time of screening, the non-study supplied corticosteroids will be stopped on Day 1 when the study supplied prednisone dose of 60 mg is started.

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

5.10. Criteria for Rescue Corticosteroid Use

Use of rescue 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 SOC.

If rescue corticosteroid treatment is necessary, it would be considered a treatment failure and study drug (CCX168 or placebo) and study-supplied prednisone will be discontinued. The subject will receive appropriate open-label SOC. 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:

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

  - 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;
- Serum pregnancy test for women of childbearing potential;
- 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 on corticosteroids at the time of screening, i.e., corticosteroids that are not considered part of the study medication, the subject will asked to stop the non-study supplied corticosteroids and start with the study supplied prednisone dose of 60 mg on 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 bottle of 20 mg prednisone tablets 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 tablets are taken;
- The time of the dosing of CCX168 or CCX168 placebo, as well as prednisone, 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;
- If a subject has been on non-study supplied corticosteroids, the non-study supplied corticosteroids need to be stopped and the 60 mg study supplied prednisone started;
- 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 tablets 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 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 prednisone bottles;

- Corticosteroid medication (1 bottle of 20 mg prednisone and 1 bottle of 5 mg prednisone) will be provided to the subject with dosing instructions; the subject will take the morning doses from the previously-supplied CCX168 or placebo kits and the new supply of prednisone while at the study site, unless the morning doses have already been taken by the subject;
- 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 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 bottles;
- Study medication and corticosteroids (1 kit of CCX168 or CCX168 placebo, 1 bottle of 20 mg prednisone and 1 bottle of 5 mg prednisone) 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;
- 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 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 prednisone bottles;
- Corticosteroid medication (1 bottle of 20 mg prednisone and 1 bottle of 5 mg prednisone) will be provided to the subject with dosing instructions; the subject will take the morning dose from the previously-supplied CCX168 or placebo kits and the new supply of prednisone 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;
- 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 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);
- Serum pregnancy test for women of childbearing potential;
- 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 (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 and from the previously-supplied prednisone while at the study site, unless the morning doses have already been taken by the subject;
- Drug accountability of prednisone 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 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 and corticosteroids (1 kit of CCX168 or CCX168 placebo, and 1 bottle of 20 mg prednisone) will be provided to the subject with dosing instructions; the subject will take the morning doses from the new supply while at the study site, unless the morning doses have already been taken by the subject;
- Drug accountability of prednisone bottles;
- 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 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);
- Serum pregnancy test for women of childbearing potential;
- 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 and corticosteroids (1 kit of CCX168 or CCX168 placebo, and 2 bottles of 5 mg prednisone) will be provided to the subject with dosing instructions; the subject will take the morning doses from the new supply while at the study site, unless the morning doses have already been taken by the subject;

- Drug accountability of prednisone 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 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;
- Drug accountability for prednisone bottles;

- Study medication and corticosteroids (1 kit of CCX168 or CCX168 placebo, and 1 bottle of 5 mg prednisone) will be provided to the subject with dosing instructions; the subject will take the morning dose from this new supply 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 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);
- Serum pregnancy test for women of childbearing potential;
- 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;

- 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 bottles;
- Corticosteroid medication (1 bottle of 5 mg prednisone) will be provided to the subject with dosing instructions; the subject will take the morning dose from this bottle 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 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 bottles;
- Corticosteroid medication (1 bottle of 5 mg prednisone) will be provided to the subject with dosing instructions; the subject will take the morning dose from this bottle 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 recommendations); Subjects in the rituximab stratum will not start azathioprine dosing;
- 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 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;
  - For the cyclophosphamide stratum, take the azathioprine dose as instructed;
  - 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);
- Serum pregnancy test for women of childbearing potential;
- 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 bottles;
- Corticosteroid medication (1 bottle of 5 mg prednisone) will be provided to the subject with dosing instructions; the subject will take the morning dose from this bottle while at the study site, unless the morning dose has already been taken by the subject;
- Azathioprine will be provided to subjects in the cyclophosphamide stratum;
- 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 dose as instructed;
  - For the cyclophosphamide stratum, take the azathioprine 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;
- Drug accountability of prednisone bottles;
- Azathioprine will be provided to subjects in the cyclophosphamide stratum;
- Any changes in concomitant medication use will be recorded; and
- After all study procedures have been completed, the subject will be reminded to:
  - Take the azathioprine dose as instructed through Day 168, if in the cyclophosphamide stratum;
  - 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);
- Serum pregnancy test for women of childbearing potential;
- 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 CCX168 or placebo, and prednisone 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 SOC 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 corticosteroids are needed, it is deemed a treatment failure for purposes of data analysis (see Section 5.10). Rescue corticosteroid use must be recorded in the EDC 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 will include a neurological examination including speech, consciousness level, mood, cranial nerves, motor, coordination and gait, reflexes, and sensory systems. 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) and VDI (see Section 11.4). 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 Days 29 and 85, 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), pancreatic enzymes (amylase and lipase), creatine phosphokinase (CPK), albumin, sodium, potassium, magnesium, 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, azathioprine, or rituximab 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, azathioprine, or rituximab use.
- Possibly Related: the corticosteroid, cyclophosphamide, azathioprine, or rituximab administration and the adverse event occurrence were reasonably related in time, and the AE was explained equally well by causes other than corticosteroid, cyclophosphamide, azathioprine, or rituximab use or was more likely explained by exposure to corticosteroid, cyclophosphamide, azathioprine, or rituximab 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 severe infections requiring antibiotics, leading to hospitalization, or meeting other seriousness criteria 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. Overnight hospitalization on Day 1 will not be considered an SAE.

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.

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, azathioprine, 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, azathioprine, and rituximab 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 or call their regional SAE hotline and fax the completed SAE report form within 24 hours of awareness. Contact details are as follows:

PPD SAE hotline – USA:

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 FDA and other relevant national health authorities, IRBs, and ethics committees in an expedited manner. Events related to the underlying disease where corticosteroid rescue medication is 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 EDC. 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 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 SOC 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 DMC will review data once every 3 to 6 months, depending on the enrollment rate, or if any unanticipated safety issues occur.

It is anticipated that there will be approximately 4 DMC meetings: a kick-off meeting and 3 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.

If there are unanticipated safety or tolerability issues in patients receiving CCX168 plus cyclophosphamide or rituximab plus corticosteroids, consideration will be given to an alternative dosing strategy, for example lowering the CCX168 or corticosteroid dose.

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.

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;
3. **Proportion of subjects achieving early disease remission (BVAS of 0) at Day 29 AND Day 85;**
4. Percent change from baseline to Day 85 in BVAS;
5. Change and percent change from baseline to Day 85 in eGFR;
6. In subjects with hematuria at baseline, the percent change from baseline to Day 85 in urinary RBC count;
7. In subjects with albuminuria at baseline, the percent change from baseline to Day 85 in urinary ACR;
8. Percent change from baseline to Day 85 in urinary MCP-1:creatinine ratio;
9. Proportion of subjects requiring rescue glucocorticoid treatment;
10. Change from baseline to Day 85 in the Vasculitis Damage Index (VDI);
11. 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.

All stated safety and efficacy endpoints will be assessed through the end of the follow-up period, Day 169.

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. Baseline is defined as the last value prior to start of dosing with study medication (typically the Day 1 pre-dose value). 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 groups will be summarized descriptively 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 listed and summarized similarly. Incidence of clinically significant ECG changes from baseline will be listed and 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 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 calculated for the comparison between each CCX168 group against the SOC group. **Because of the relatively small sample size of the study, no inferential statistical analysis will be performed on the primary endpoint.**

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. 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 **summarized in a similar manner as described for the primary endpoint. These include the proportion of subjects achieving remission, defined as BVAS of 0, at Day 85, early remission, defined as BVAS of 0 at Day 29 AND Day 85, and renal response at Day 85**. 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 provided for each of the efficacy endpoints. For categorical endpoints, numbers and percentages will be calculated. For continuous variables, numbers, means, medians, ranges, standard deviations**, and standard errors of mean** 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 by treatment group. 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.

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 cyclophosphamide, 4-hydroxycyclophosphamide (and possible other metabolites), 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, or urinary MCP-1:creatinine ratio may be used as PD markers.

7.14. Sample Size Justification

The sample size estimation for this study was based on practical and not statistical considerations.

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.

When all subjects have completed the 84-day treatment period, data may be analyzed to make decisions regarding future clinical development plans. Because this is a Phase 2 study, multiplicity adjustment will not be applied to the alpha level for the final analysis.

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), and Canadian Guidance Document: "Considerations for Inclusion of Women in Clinical Trials and Analysis of Sex Differences", May 29, 2013, 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 FDA and other applicable competent authorities of the reasons for, and content of, these amendments.

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.

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.

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 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

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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 institutional review board (IRB)/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 IRB/EC approvals (protocols, amendments, Informed Consent, etc.), IRB/EC charter and membership, and communications between the IRB/EC and the Investigator.

Clinical Investigator

A. IRB/EC

The Investigator must assure the monitor that the IRB/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 IRB/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 IRB/EC and maintains an active up-to-date roster of all IRB/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 IRB/EC minutes and correspondence, (b) written guidelines or by-laws governing IRB/EC functions, (c) protocols, (d) protocol information to be supplied to the subject, (e) correspondence between the IRB/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 IRB/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 IRB/EC and the Investigator.
2. The following documents:
    a. IRB/EC-approved protocols.
    b. IRB/EC-approved protocol amendments.

c. IRB/EC-approved Informed Consent Form and information supplied to the subject.
d. IRB/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.

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

Subjects will be allowed to receive up to 3000 mg of IV methylprednisolone equivalent within 12 weeks prior to the Screening period.

Subjects 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.

The tapering schedule for all subjects is provided in the table below:

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

Subjects will receive prednisone bottles containing either 20 mg prednisone tablets or 5 mg prednisone tablets or both, depending on the study visit (see table below):

Study Visit	Prednisone dose	Number of 20 mg prednisone bottles dispensed	Dosing instructions for 20 mg bottle	Number of 5 mg prednisone bottles dispensed	Dosing instructions for 5 mg bottle
Day 1	60 mg	1	Take 3 tablets per day	0	NA
Day 8	45 mg	1	Take 2 tablets per day	1	Take 1 tablet per day
Day 15	30 mg	1	Take 1 tablet per day	1	Take 2 tablets per day
Day 22	25 mg	1	Take 1 tablet per day	1	Take 1 tablet per day
Day 43	20 mg	1	Take 1 tablet per day	0	NA
Day 57	15 mg	0	NA	2	Take 3 tablets per day
Day 71	10 mg	0	NA	1	Take 2 tablets per day
Day 85	10 mg	0	NA	1	Take 2 tablets per day
Day 99	5 mg	0	NA	1	Take 1 tablet per day
Day 113	5 mg	0	NA	1	Take 1 tablet per day
Day 141	0	0	NA	0	NA

NA = not applicable

11.6. Cyclophosphamide and Azathioprine Dosing

- For subjects in the cyclophosphamide stratum, 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. 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.