PROTOCOL

Protocol Amendment 3.0

TITLE PAGE

Study Title:	An Open-Label Phase 2 Study to Evaluate the Safety and Efficacy of CCX168 in Subjects with IgA Nephropathy on Stable RAAS Blockade
Protocol Number:	CL005_168
Investigational Product:	Complement 5a Receptor Antagonist CCX168
Indication:	IgA nephropathy
Sponsor:	ChemoCentryx, Inc.
Development Phase:	2
IND number	123187
EUDRACT number	2014-003402-33
Sponsor's Responsible Medical Officer:	[redacted] ChemoCentryx, Inc. [redacted]
Sponsor Signatory:	[redacted]
Approval Date:	8 September 2014—FINAL **5 November 2014—Protocol Amendment 1.0** **13 May 2015—Protocol Amendment 2.0** **17 July 2015—Protocol Amendment 3.0**

INVESTIGATOR SIGNATORY PAGE

Protocol Number: CL005_168

Protocol Title: An Open-Label Phase 2 Study to Evaluate the Safety and Efficacy of CCX168 in Subjects with IgA Nephropathy on Stable RAAS Blockade

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: CL005_168

Protocol Title: An Open-Label Phase 2 Study to Evaluate the Safety and Efficacy of CCX168 in Subjects with IgA Nephropathy on Stable RAAS Blockade

Medical Officer [redacted]
Chief Medical Officer
ChemoCentryx, Inc.
[redacted]

Clinical Operations Managers [redacted]
Clinical Operations Manager
ChemoCentryx, Inc.
[redacted]

and

[redacted]
Clinical Operations Manager
ChemoCentryx, Inc.
[redacted]

SPONSOR SIGNATURE FOR APPROVAL

Protocol Number: CL005_168

Protocol Title: An Open-Label Phase 2 Study to Evaluate the Safety and Efficacy of CCX168 in Subjects with IgA Nephropathy on Stable RAAS Blockade

_____ _____

[redacted] Date

Chief Medical Officer

PROTOCOL AMENDMENT 3.0: SUMMARY OF CHANGES

In compliance with a recommendation from FDA, the following changes were made to the protocol:

1. **Stopping rules for individual subjects, based on white blood cell, neutrophil, and lymphocyte counts, as well as hepatic aminotransferase or bilirubin elevations were added to section 7.2.4 of the protocol. The statement regarding potential re-challenging of subjects with hepatic aminotransferase or bilirubin elevations was removed. FDA's rationale is that, in general, IgA nephropathy is a slowly progressive disease and, at this time, FDA does not believe the potential benefits of re-exposing a subject who develops a significant aminotransferase elevation would outweigh the risk. Hence, these subjects should not be rechallenged.**
2. **The stopping rule for the study based on hepatic aminotransferase or bilirubin elevation in section 7.2.4 was modified to indicate that the Sponsor will consider stopping the study if at least one subject develops severe liver injury believed to be caused by CCX168. FDA's rationale is that patients with IgAN are relatively healthy, and even one case of severe liver injury caused by CCX168 would be a concern.**

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STUDY SYNOPSIS

Name of Sponsor ChemoCentryx, Inc.	**Name of Active Ingredient** CCX168	**Study number:** CL005_168
Title An Open-Label Phase 2 Study to Evaluate the Safety and Efficacy of CCX168 in Subjects with IgA Nephropathy on Stable RAAS Blockade		
Investigators Several		
Study centers Multi-center		
Study period 24 months	**Phase of development** Phase 2	

Aim

The aim of this study is to evaluate the treatment to induce remission of proteinuria in patients with IgA nephropathy (IgAN) and persistent proteinuria despite supportive therapy with a maximally tolerated dose of renin-angiotensin-aldosterone system (RAAS) blockade (angiotensin converting enzyme inhibitor [ACE-I], angiotensin II receptor blocker [ARB], or aldosterone blocker). The intent is to reduce proteinuria to normal levels without the use of high dose glucocorticoids.

Objectives

The primary safety objective of this study is to evaluate the safety and tolerability of CCX168 in subjects with IgAN on background supportive therapy with a maximally tolerated dose of RAAS blockade.

The primary efficacy objective is to evaluate the efficacy of CCX168 based on an improvement in proteinuria.

The secondary objectives of this study include assessment of:

1. Change in albuminuria with CCX168 treatment;
2. Change in renal function based on estimated glomerular filtration rate (eGFR) with CCX168 treatment;
3. Change in hematuria with CCX168 treatment;
4. Change in renal inflammatory activity based on urinary monocyte chemoattractant protein-1 (MCP-1):creatinine ratio and urinary epidermal growth factor (EGF):MCP-1 ratio with

CCX168 treatment;

5. Change in serum IgA:plasma C3 ratio with CCX168 treatment;
6. Changes in pharmacodynamic markers in plasma and urine with CCX168 treatment, e.g., C3a, C5a, properdin, and sC5b-9**;**
7. Evaluation of the pharmacokinetic profile of CCX168 in subjects with IgAN.

Rationale

IgAN is reported as the most common glomerulonephritis worldwide. It is associated with a wide spectrum of disease severity and rate of progression of renal failure. The best well established risk factor of progressive loss of renal function from IgAN is the persistent presence of proteinuria > 1 g/day, with some studies suggesting that the persistence of even lower levels of proteinuria (> 500 mg/day) may be associated with worse prognosis. Other clinical and histologic factors have also been associated with a faster decline in renal function, although these are not as well documented.

Despite the relative high prevalence of disease worldwide, there is a paucity of evidence-based therapy available for the treatment of IgAN. Current guidelines include initiating therapy of patients with hypertension and persistent proteinuria > 1 g/day with RAAS blockade with an ACE inhibitor or ARB to attain a level of proteinuria below that threshold.

For patients who fail to attain a reduction of proteinuria to < 1 g/day, it is currently "suggested" that patients be treated with a course of glucocorticoids (KDIGO Clinical Practice Guideline for Glomerulonephritis, 2012). However this "suggestion" carries an evidence-based grade of 2C, given the "weakness" of the data supporting the efficacy of such therapy in altering long term outcomes of patients. In addition, the use of glucocorticoids for several months (e.g., 6 months in the "Pozzi" protocol; Pozzi et al., 1999) is associated with significant risk of adverse effects especially in the adult population.

Therefore, patients with relatively modest degree of proteinuria and well preserved eGFR (or stable eGFR if the decline is attributable to a cause other than IgAN) represent a large pool of patients with a perceived increased risk of GFR decline, but no established, safe and effective treatment.

This patient population is ideal for a pilot study of CCX168. Phase 2 study data in patients with ANCA-associated vasculitis suggest a significant anti-proteinuric effect of CCX168 in the majority of treated patients (mean decrease of approximately 60% in urinary ACR over 12 weeks of treatment with CCX168). This treatment effect was observed in patients receiving CCX168 plus glucocorticoids, but also in patients receiving CCX168 with no glucocorticoids.

For patients with IgAN who have already demonstrated a decline in eGFR, more aggressive therapy with corticosteroids is warranted, and a delay in such treatment for the duration of the pilot study with a medication of unproven efficacy would be inappropriate at this early stage of clinical development.

Methodology

This is a pilot study to test the safety, tolerability, and efficacy of CCX168 in reducing proteinuria in patients with IgAN and persistent proteinuria despite supportive therapy with a maximally tolerated RAAS blocker.

Patients will be screened for enrolment based on biopsy proven IgAN, and documentation of proteinuria > 1 g/g creatinine (by first morning urinary protein:creatinine). The screening period will be up to 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, viral screening, and estimated glomerular filtration rate (eGFR) assessment. If a patient did not have a renal biopsy in the past 3 years to confirm the diagnosis of IgAN, a renal biopsy needs to be done for eligibility assessment. Patients meeting inclusion and exclusion criteria will be enrolled for blood pressure/RAAS blockade titration and run-in period.

At screening, patients should ideally be on one or two RAAS blocker(s) and have BP <140/90 mmHg. Patients not on an RAAS blocker can be started, and have the medication dose adjusted to a maximally tolerated dose (MTD) within a period not to exceed 4 weeks.

MTD for RAAS blockade is defined as:

- a dose attaining a target blood pressure less than 125/75 mmHg, or
- the maximum recommended dose (according to the label of the RAAS blocker), or
- the maximum dose tolerated by the subject from a safety/tolerability perspective.

If the blood pressure target of <125/75 mmHg is not achieved during the titration period, additional anti-hypertension medication (non-ACE-I or ARBs) should be considered to achieve this blood pressure goal. All patients must participate in an 8-week run-in period during which they must be on a stable, MTD of an RAAS blocker before starting treatment with CCX168 on Day 1. If a patient is on two RAAS blockers, e.g., an ACE inhibitor and an ARB at the time of screening, the patient must remain on stable doses of these medications throughout the 8-week run-in period. Titration to an MTD for both RAAS blockers is not needed in this case, if the blood pressure goal has been achieved.

After the 8-week run-in period has been completed, two back-to-back first morning urine collections need to be obtained for protein and creatinine measurements. The geometric mean of the two urinary PCR measurements must be > 1 g/g creatinine for eligibility for further study participation.

On Day 1, patients meeting inclusion criteria will start CCX168 treatment. Patients will take CCX168 30 mg orally twice daily for 12 weeks (84 days). The CCX168 dose will be taken in the morning optimally within one hour after breakfast and in the evening optimally within one hour after dinner. After the 84-day treatment period, patients will be followed for 12 weeks (84 days) while continuing to take their RAAS blocker treatment at a stable dose.

At post-Day 1 study visits, blood and urine samples will be collected for safety**,** efficacy, and pharmacokinetic measurements. A serum pregnancy test for women of childbearing potential

will be done on Days 29, 43, 57, 85, 113, and 169. Physical examinations and vital signs assessments will be performed throughout the study. Concomitant medication and adverse event assessments will be made at every study visit. An optional renal biopsy could be performed after the 12-week treatment period to assess the effect of CCX168 treatment on kidney histology.

During the 12-week treatment period and the 12-week follow-up period, the dose(s) of RAAS blocker(s) must remain unchanged. No new RAAS blocker or non-dihydropyridine calcium channel blocker or diuretic may be added during the study period (active treatment period or follow up).

During the treatment period with study medication and the 12 weeks of follow up thereafter, no new immunomodulatory medication may be started including, but not limited to cyclosporine, tacrolimus, mycophenolate mofetil, azathioprine, cyclophosphamide, or glucocorticoids (e.g. prednisone).

Concomitant use of omega-3 fatty acid supplements (e.g., fish oil) is permitted IF the medication is started at the time of, or before screening, and is maintained at a stable dose during the rest of the study until the end of the follow-up period (Day 169).

Patients will visit the study center on Days 1, 8, 15, 29, 43, 57, 85, 113, 141, and 169 for the treatment and follow-up period.

Duration of treatment with study medicine: 84 days

Duration of follow up after end of treatment with study medicine: 84 days

Subjects who experience a decrease from baseline in eGFR > 10 ml/min/1.73 m^2 or > 20%, (confirmed by repeat after 2 weeks) which is otherwise not explained (e.g., dehydration, new medication), or an increase in proteinuria of > 3 g/g creatinine from baseline or to a level > 8 g/g (confirmed by repeat after 2 weeks) during the 12-week treatment period, will exit the treatment phase of the study and be treated at the discretion of their primary nephrologist. They will remain in the study for follow up and outcome recording.

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

Number of Subjects

Up to approximately 20 male or female subjects with IgAN will be enrolled in this study. Subjects who started the CCX168 treatment period and drop out prematurely will not be replaced. However, subjects who drop out during the titration and run-in periods may be replaced.

Main Criteria for Inclusion

1. Biopsy-proven IgAN performed for clinical purposes within 3 years prior to screening;
2. eGFR >60 mL/min/1.73 m^2 (by MDRD equation) OR eGFR >45 mL/min/1.73 m^2 if eGFR has not declined > 10 mL/min/1.73 m^2 over the previous 24 weeks;

3. Proteinuria, defined as first morning urinary PCR > 1 g/g creatinine;
4. Male or female subjects, aged at least 18 years; Where allowed by local regulations, female subjects of childbearing potential may participate if adequate contraception is used during, and for at least the three months after study completion; Male subjects with partners of childbearing potential may participate in the study if they had a vasectomy at least 6 months prior to randomization or if adequate contraception is used during, and for at least the three months after study completion; Adequate contraception is defined as resulting in a failure rate of less than 1% per year (combined estrogen and progestogen [oral, intravaginal, or transdermal], or progestogen-only hormonal contraception (oral, injectable, or implantable), intra-uterine device, intra-uterine hormone releasing system, bilateral tubal occlusion, vasectomized partner, or sexual abstinence);
5. Willing and able to give written Informed Consent and to comply with the requirements of the study protocol; and
6. Judged to be otherwise healthy by the Investigator, based on medical history, physical examination, 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 renal disease as determined by rapid decline in eGFR (defined as >10 mL/min/1.73 m^2 over 24 weeks prior to screening, not otherwise explained);
2. Pregnant or nursing;
3. Proteinuria > 8 g/day (or >8 g/g creatinine);
4. Patients with systemic manifestations of Henoch-Schönlein purpura within the last 2 years prior to screening;
5. Patients with IgAN deemed secondary to underlying disease: e.g., diabetes, liver disease, cirrhosis, celiac disease, HIV, inflammatory bowel disease, lymphoma, or associated with any other multi-system autoimmune disease;
6. Biopsy report demonstrating severe crescentic IgAN (>25% crescents), OR >50% interstitial fibrosis and/or tubular atrophy ("T2") (Cattran et al. 2009), OR a high likelihood of rapid decline in eGFR based on an MEST ("Oxford") classification (M = mesangial hypercellularity; E = endocapillary proliferation; S = segmental glomerulosclerosis/adhesion; T = tubular atrophy/interstitial fibrosis) score of M1, E0, T1, or M0/1, E1, T1 (Cattran et al. 2009);
7. History of treatment with glucocorticoids, cyclophosphamide, azathioprine, mycophenolate mofetil, or any biologic immunomodulatory agent within the 24 weeks prior to screening;
8. Symptomatic congestive heart failure requiring prescription medication, clinically evident peripheral edema of cardiac origin, poorly-controlled hypertension (systolic blood

pressure >160 or diastolic blood pressure >95), history of unstable angina, myocardial infarction or stroke within 6 months prior to screening;

9. History or presence of any form of cancer within the 5 years prior to screening, with the exception of excised basal cell or squamous cell carcinoma of the skin, or cervical carcinoma *in situ* or breast carcinoma *in situ* that has been excised or resected completely and is without evidence of local recurrence or metastasis;
10. Positive HBV, HCV, or HIV viral screening test;
11. History of tuberculosis;
12. Any infection requiring antibiotic treatment that has not cleared prior to starting CCX168 treatment on Day 1;
13. WBC count less than 4000/μL**,** or neutrophil count less than 2000/μL, or lymphocyte count less than 1000/μL;
14. Hemoglobin less than 9 g/dL (or 5.56 mmol/L) at screening;
15. Evidence of hepatic disease; AST, ALT, alkaline phosphatase, or bilirubin > 3 x the upper limit of normal;
16. Participated in any clinical study of an investigational product within 30 days prior to screening or within 5 half-lives after taking the last dose; and
17. History or presence of any medical condition or disease which, in the opinion of the Investigator, may place the subject at unacceptable risk for study participation.

Test Product

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

Subjects will receive two bottles of CCX168 capsules on Day 1 and Day 8, respectively, four bottles on Day**s** 15, 29, and 43, respectively, and six bottles on Day 57.

Subjects will be asked to take 3 capsules every morning and 3 capsules every evening, approximately 12 hours after the morning dose, as instructed. Study medication should be taken optimally within 1 hour after breakfast in the morning and optimally within 1 hour after dinner in the evening for 84 days continuously. Capsules will be taken with water, preferably with 50 mL (~one fifth of a cup), but not to exceed 100 mL (~one half cup).

Duration of Treatment and Observation

Subjects will be screened within a period not to exceed 14 days prior to the RAAS titration and run-in period. The RAAS blocker titration period could be up to 4 weeks. All subjects must take a stable dose of a RAAS blocker at the maximally tolerated dose (MTD) for 8 weeks before they could start the 12-week CCX168 treatment period. Alternatively, subjects who take two RAAS blockers must take a stable dose of each (not necessarily at the MTD) for 8 weeks before starting the CCX168 treatment period. The CCX168 treatment period is 12 weeks (84 days) and all subjects will be followed for 12 weeks (84 days) after the dosing period.

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

Safety Assessments

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

Efficacy Assessments

Efficacy assessments include:

1. First morning urinary PCR and ACR;
2. eGFR by Modification of Diet in Renal Disease (MDRD) formula based on serum creatinine;
3. Hematuria based on microscopic urinary RBC count;
4. Urinary MCP-1:creatinine ratio;
5. Serum IgA:C3 ratio;
6. Urinary EGF:MCP-1 ratio, and
7. Plasma and urine pharmacodynamic markers, e.g., C3a, C5a, properdin, and sC5b-9.

Pharmacokinetic Assessments

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

Pharmacodynamic Markers

A plasma sample will be collected on Days 1, 8, 15, 29, 57, 85, 113, 141, and 169 for pharmacodynamic marker measurements, including for example galactose-deficient IgA1, complement factor H, cystatin C, complement fragments, and inflammatory cytokine and chemokine levels. The plasma samples may also be used to determine CCX168 (and relevant

metabolite) concentrations.

Urine samples will also be collected on Days 1, 8, 15, 29, 57, 85, 113, 141, and 169 for biomarker assessments including for example complement fragments, inflammatory chemokine and cytokine levels.

Statistical Methods

Demographics and Baseline Characteristics

All subject baseline characteristics and demographic data (age, sex, race, ethnicity, weight, height, body mass index, smoking status, viral test results, IgAN disease duration (from time of first diagnosis based on renal biopsy), eGFR, proteinuria (PCR and ACR), urinary MCP-1:creatinine ratio, physical examination abnormalities, medical history, previous (within 6 months of screening) and concomitant medications (including RAAS blockers) at study entry will be listed by study center and subject number, and will also be summarized.

Safety Analysis

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

Other safety endpoints include:

1. Change from baseline in all safety laboratory parameters;
2. Change from baseline in vital signs;

All subjects who are enrolled 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 subject and will be summarized. Treatment-emergent adverse events will be listed and summarized by System Organ Class, by relatedness and by maximum severity. Serious adverse events and adverse events leading to withdrawal will be listed and summarized. Individual vital signs and change from baseline in vital signs will be listed by subject, and study visit, and summarized descriptively. Laboratory data (actual values and change from baseline) will be listed by subject and study visit. Abnormal laboratory values will be flagged.

Efficacy Analysis

The primary efficacy endpoint is the change in slope of first morning urinary PCR from the 8-week RAAS blocker run-in period to the 12-week CCX168 treatment period.

Other efficacy endpoints include:

1. The proportion of subjects achieving renal response, defined as an improvement in proteinuria based on a decrease from baseline to Day 85 in proteinuria to a level < 300 mg/g creatinine and maintaining estimated glomerular filtration rate (eGFR) within 15% of baseline;
2. The proportion of subjects achieving a partial renal response, defined as an improvement in proteinuria based on a decrease from baseline to Day 85 in proteinuria to a level < 1 g/g creatinine and maintaining estimated glomerular filtration rate (eGFR) within 15% of

baseline;

3. Change in slope from the run-in period to the treatment period for urinary ACR, eGFR, urinary MCP-1:creatinine, urinary EGF:MCP-1, and urinary microscopic RBC counts;
4. The percent change from baseline to Day 85 in urinary PCR and ACR;
5. The change from baseline to Day 85 in eGFR;
6. In patients with hematuria at baseline, the percent change from baseline in urinary RBC count;
7. The percent change from baseline to Day 85 in urinary MCP-1:creatinine ratio;
8. The percent change from baseline to Day 85 in serum IgA:plasma C3 ratio;
9. The percent change from baseline to Day 85 in urinary EGF:MCP-1 ratio;
10. The percent change from baseline in plasma and urinary biomarkers, e.g., C3a, C5a, properdin, and sC5b-9.

Changes from baseline in all efficacy measurements at time points other than Day 85 will also be assessed. The 84-day follow-up period results for the endpoints listed above will also be summarized. Summary statistics will be calculated for each of the efficacy endpoints. For categorical endpoints, numbers and percentages will be calculated. For continuous variables, numbers, means, medians, ranges, and standard deviations will be calculated. Geometric means will be calculated for urinary PCR, ACR, and MCP-1:creatinine, and other measurements that are not normally distributed.

The slope of the urinary PCR, urinary ACR, eGFR, urinary MCP-1:creatinine, urinary EGF:MCP-1, and urinary microscopic RBC count during the 8-week run-in period, the initial 4-week, as well as the full 12-week treatment period will be calculated for each subject. The mean slope for the 8-week run-in period will be compared to the mean slope for the initial 4-week, as well as the full 12-week treatment period to evaluate the treatment effect of CCX168. If the slope for the first 4 weeks of the run-in period is steeper than the slope of the last 4 weeks of the run-in period, indicating that steady state has not been achieved over the first 4 weeks, the slope of the last 4 weeks of the run-in period may be used as the baseline slope, instead of the slope over the 8 weeks of the run-in period.

The sample size for the study is based on the slope of the urinary ACR observed in a study in patients with ANCA-associated vasculitis while receiving CCX168. The mean slope was -1.32, with a standard deviation of 1.67 over 12 weeks, and -4.62, with a standard deviation of 4.77 over the initial 4-week treatment period with CCX168 in ANCA-associated vasculitis. Assuming a mean difference in pre-treatment and on-treatment slopes of 4.6, a sample size of 15 subjects will provide approximately 80% power and 20 subjects approximately 90% power to detect a difference in slopes.

Pharmacokinetic analysis

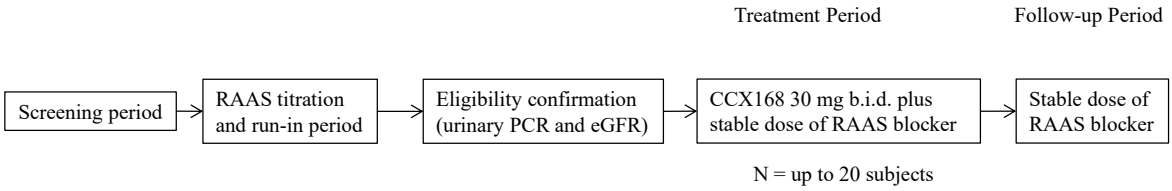
Plasma samples will be collected at Baseline (Day 1) and Days 8, 15, 29, 43, 57, and 85 to determine the PK profile of CCX168 (and metabolites). Individual plasma concentrations of

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 urinary ACR, PCR, eGFR, urinary MCP-1:creatinine ratio, and other biomarkers may be used as PD markers.

STUDY SCHEMA



Duration:	≤14 days	Up to 12 weeks; On stable, maximally tolerated dose (MTD) of RAAS blocker for 8 weeks	≤ 7 days	84 days	84 days
Study visits:		RAAS blocker dose titration period: Up to 4 weeks; Once on MTD of RAAS blocker, visits on Day -63 and on Day -35 for U-PCR and eGFR measurements	Two visits in the Day -7 to -2 window for U-PCR and eGFR measurements	Visits: Days 1, 8, 15, 29, 43, 57, 71, and 85	Visits: Days 113, 141, and 169

TIME AND EVENTS TABLE

			Study Day[1]												
	Screening[2]	**Titrat-ion**	**Run-in**			**Treatment**							**Follow-up**		
	≤ 14 days	**≤ 28 days**	**-63**	**-35**	**-7 to -2[3]**	**1[4]**	**8**	**15**	**29**	**43**	**57**	**85**	**113**	**141**	**169**
Informed consent	X														
Demographics, medical history, prior medications	X														
Physical examination[5]	X					X[6]			X	X	X	X	X		X
Blood pressure[7]	X	X	X	X	X, **X**	X[6]	X	X	X	X	X	X	X	X	X
RAAS blocker dose titration[8]		(X)													
RAAS blocker stable dosing at MTD			X→	→	→	→	→	→	→	→	→	→	→	→	→
Other vital signs[9]	X					X[6]	X	X	X	X	X	X	X	X	X
Serum pregnancy test for women of childbearing potential	X				X				X	X	X	X	X		X
HIV, HBV, HCV testing	X														
Serum chemistry[10], hematology	X					X[6]	X	X	X	X	X	X	X	X	X
Serum creatinine (not full chemistry)			X	X	X										
Urinalysis[11]	X					X[6]	X	X	X	X	X	X	X	X	X
Urine protein and creatinine assays	X		X	X	X, **X**	X[6]	X	X	X		X	X	X	X	X
Renal biopsy[12]	X											X			
Urine albumin, MCP-1, EGF, and microscopic RBC count			X	X	X	X[6]	X	X	X		X	X	X	X	X
Serum IgA and plasma C3 samples						X[6]			X		X	X	X	X	X
CCX168 dispensing						X[6]	X	X	X	X	X				
CCX168 dosing 30 mg b.i.d.						X →	→	→	→	→	→	→X			

			Study Day[1]												
	Screening[2]	**Titrat-ion**	**Run-in**			**Treatment**							**Follow-up**		
	≤ 14 days	**≤ 28 days**	**-63**	**-35**	**-7 to -2[3]**	**1[4]**	**8**	**15**	**29**	**43**	**57**	**85**	**113**	**141**	**169**
CCX168 accountability							X	X	X	X	X	X			
PD plasma sample collection[13]						X[6]	X	X	X		X	X	X	X	X
PD urine sample collection						X[6]	X	X	X		X	X	X	X	X
PK plasma sample collection[14]						X	X	X	X	X	X	X			
Concomitant medications	X	X	X	X	X, **X**	X	X	X	X	X	X	X	X	X	X
Adverse event assessment		X	X	X	X, **X**	X	X	X	X	X	X	X	X	X	X

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

[2] Screening must occur within a period not to exceed 14 days.

[3] See Section 6.3.3 for the list of procedures identified for only the first, or for both of the back-to-back study days.

[4] Start of dosing with CCX168.

[5] 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.

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

[7] Blood pressure needs to be measured in the supine position after 3 minutes of rest.

[8] Four-week dose titration period only needed for patients who are not on a maximum tolerated dose of a RAAS blocker, or stable dose of two RAAS blockers.

[9] Assessment of heart rate and body temperature

[10] Serum chemistry including creatinine measurements

[11] Subjects will be asked to void their bladders completely, and a representative clean catch, midstream urine sample will be collected. Urinalysis includes pH, specific gravity, glucose, nitrite, ketones, bilirubin, urobilinogen, RBCs, and WBCs.

[12] Renal biopsy is an optional procedure for this study, except if necessary for eligibility assessment.

[13] Blood samples will be put in wet ice immediately after collection, centrifuged in a refrigerated centrifuge and plasma put at -70 °C.

[14] PK blood sample (4 mL) will be collected prior to the morning dose on Day 1 and at 0.5, 1, 2, 3, 4, and 6 hours following dosing.

LIST OF ABBREVIATIONS AND ACRONYMS

AAV	anti-neutrophil cytoplasmic antibody associated vasculitis
ACE-I	angiotensin converting enzyme inhibitor
ACR	albumin:creatinine ratio
AE	adverse event
ALT	alanine aminotransferase (also called SGPT)
ANCA	anti-neutrophil cytoplasmic antibodies
API	active pharmaceutical ingredient
ARB	angiotensin II receptor blocker
AST	aspartate aminotransferase (also called SGOT)
b.i.d.	twice daily
BUN	blood urea nitrogen
BVAS	Birmingham Vasculitis Activity Score version 3
C3	complement 3
C3a	complement 3a
C4a	complement 4a
C5a	complement 5a
C5aR	complement 5a receptor
C5b-9	complement 5b-9
CA	competent authority
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
CTCAE	Common Terminology Criteria for Adverse Events
EC	ethics committee
ECG	electrocardiogram
EDC	electronic data capture
EGF	epidermal growth factor
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
g	gram
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
IgAN	IgA nephropathy
IRB	Institutional Review Board
KDIGO	Kidney Disease: Improving Global Outcomes

kg	kilogram
LDH	lactate dehydrogenase
MAC	membrane attack complex
MCH	mean cell hemoglobin
MCHC	mean cell hemoglobin concentration
MCP-1	monocyte chemoattractant protein-1
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Drug Regulatory Affairs
mg	milligram
mL	milliliter
MPA	microscopic polyangiitis
MPO	myeloperoxidase
MTD	maximum tolerated dose
N	number
NOAEL	No observed adverse effect level
PCR	protein:creatinine ratio
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
q.d.	once daily
RAAS	renin-angiotensin-aldosterone system
RBC	red blood cell
SAE	serious adverse event
sC5b-9	soluble C5b-9 fragment
SGPT	serum glutamic pyruvic transaminase (also called ALT)
SGOT	serum glutamic oxaloacetic transaminase (also called as AST)
SLE	systemic lupus erythematosus
SOC	standard of care
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
T_{max}	time of maximum (plasma) concentration
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 8 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.

IgA nephropathy (IgAN) is a form of glomerulonephritis characterized by deposition of IgA in the glomeruli. Complement fragment C5a and C3a presence have been shown in the glomerular deposits, and C5aR and C3aR expression increased with increasing grades of renal pathology in patients with IgAN (Liu et al., 2013). Glomerular IgA deposits are insufficient to cause renal injury, since 16.1% of healthy allographs shows IgA deposition (Suzuki et al., 2003). However, mild mesangial proliferative changes are associated with C3 deposition as well as IgA deposition (Suzuki et al., 2003). This indicates that complement activation is associated with renal injury in these patients. Furthermore, a major susceptibility locus within the CFH gene cluster was found in a genome wide association study (Gharavi et al., 2011). Properdin, C5b-9 (Stangou et al., 2008; Rauterberg et al., 1987), C4d, mannose-binding lectin, ficolin (Roos et al., 2006), and C4-binding protein (Miyazaki et al., 1984) have been described in renal biopsy samples from patients with IgAN. All of these findings support an important role for complement activation in the pathology of IgAN.

In a clinical trial (CL002_168) with CCX168 in patients with ANCA-associated vasculitis (AAV), CCX168 showed promise based on effect on renal disease parameters, including estimated glomerular filtration rate (eGFR), hematuria, albuminuria, monocyte chemoattractant protein-1 (MCP-1):creatinine ratio (a marker of renal inflammation), and the Birmingham Vasculitis Activity Score (BVAS). In particular, first morning urinary albumin:creatinine ratio (ACR) decreased approximately 60% from baseline in patients receiving CCX168 plus cyclophosphamide with or without corticosteroids compared to approximately 9% in the control group receiving cyclophosphamide plus full-dose corticosteroids.

Several reports have also 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 substantially ameliorated by genetic deletion of either C5 or C5aR (Schreiber et al., 2009).

CCX168 was shown to be effective in human C5aR transgenic knock-in mouse model of MPO-induced glomerulonephritis. CCX168 markedly reduced the percentage of glomeruli with crescents or necrosis, as well as the degree of proteinuria, hematuria, and leukocyturia (Xiao et al., 2014).

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 is deleted from that genetic background. This further supports a role for C5aR blockade in renal inflammatory conditions.

A therapeutic indication being pursued for CCX168, a potent and selective C5aR antagonist, is in the treatment of patients with IgAN.

IgAN currently is treated with angiotensin converting enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (ARB), fish oil, glucocorticosteroids and/or immunosuppressive drugs in severe cases.

1.2. Study Drug Development

1.2.1. Non-Clinical Pharmacology

1.2.1.1. In-Vitro Efficacy and Selectivity for C5aR

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

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

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).

1.2.1.2. Efficacy Models

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

ChemoCentryx generated a human C5aR knock-in (hC5aR KI) mouse strain in which the mouse C5aR gene has been replaced with the human C5aR gene. The innate immune cells of these mice respond normally to C5a, in a manner highly sensitive to CCX168. *In vitro*, CCX168 blocks hC5a-mediated chemotaxis of leukocytes freshly isolated from these hC5aR KI mice with high potency (IC_{50} = 0.5 nM in 100% mouse plasma). This value is nearly identical to the potency (1.7 nM) exhibited by CCX168 in its inhibition of neutrophil migration to hC5a in whole human blood, indicating that the hC5aR KI mice are suitable for pharmacodynamic evaluation of CCX168. In the human C5aR knock-in mice, an intravenous dose of 20 μg/kg hC5a robustly induces this leukopenia within one minute after injection. Pretreatment of the mice with an oral dose of 0.3 mg/kg CCX168, which resulted in a plasma concentration of approximately 75 nM at 60 min. post-dose, almost completely blocked the C5a-induced leukopenia. A dose of 0.03 mg/kg CCX168, producing a plasma concentration of 15 nM, resulted in a 50% reduction in the C5a-induced leukopenic response.

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

The efficacy of CCX168 in a mouse model of ANCA-associated glomerulonephritis was evaluated in order to assess the clinical potential of CCX168 in the treatment of ANCA-associated vasculitis. In these studies, intravenous injection of mouse anti-myeloperoxidase (anti-MPO) IgG into the human C5aR knock-in mice caused glomerulonephritis in a manner mimicking ANCA disease in humans. At daily oral doses of 30 mg/kg CCX168, a marked inhibition of anti-MPO induced glomerulonephritis was documented histologically, as assessed by the number of necrotic (8.2% with vehicle, 1.1% with CCX168; $p<0.0001$) and crescent-containing glomeruli (30.5% 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 Phase 1 clinical trial CL001_168 in healthy volunteers 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.

1.2.2. Non-Clinical Safety and Toxicology

The toxicology program was designed to support this Phase 2 study to assess the safety, tolerability, and efficacy of CCX168 in subjects with IgAN. 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

Study Type	Method of Administration/Dosing Schedule	Species	Doses
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
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 in patients with AAV, the risk for serious or unanticipated untoward events to occur in this clinical trial is considered low.

1.2.3. Non-Clinical ADME

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

methylcellulose (HPMC) suspension and high bioavailability for the PEG-400/Solutol HS-15 solution.

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

a. Intravenous dosing

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

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

b. Oral dosing

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

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

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

monkey and human hepatocytes and through monohydroxylation, dealkylation, and glucuronidation in rat and dog hepatocytes. A Phase I monohydroxylation metabolite, CCX168-M1, was found to be a significant circulating metabolite in human volunteers in the Phase 1 study. Its exposure was adequately covered in rats and cynomolgus monkeys in the toxicology studies that support the current Phase 2 clinical trial.

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

The compound is very highly protein bound in mouse, rat, dog, and human plasma, at 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.

1.3. Prior Human Experience

A Phase 1 study in 48 healthy volunteers has been completed. This is a randomized, double-blind, placebo-controlled, two-period study in which subjects received either CCX168 or placebo (3:1 ratio) as a single dose in Period 1 and as multiple once daily or twice daily doses in Period 2. Single doses of 1, 3, 10, 30, and 100 mg CCX168 were studied, 6 subjects in each dose cohort received CCX168 and 2 received placebo, except in cohort 1 in which 5 subjects received CCX168 and 3 received placebo. In Period 2, CCX168 doses of 1, 3, and 10 mg once daily for 7 days, and 30 and 50 mg twice daily for 7 days, were studied.

CCX168 appeared to be well tolerated by study subjects in this study. No serious adverse events or withdrawals due to adverse events have been observed. A summary of all the treatment-emergent adverse events observed in the single-dose period 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. 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. 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 q.d. 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 b.i.d. 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 q.d.) or high accumulation (10 mg q.d. or 30 – 50 mg b.i.d.) of CCX168, consistent with the observed terminal half-life in these dosing groups. After q.d. dosing, the exposure of CCX168 as measured by C_{max} and AUC is approximately dose proportional in the 1 – 10 mg dose range. After b.i.d. 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 **significant** circulating metabolite in humans. Following 7 days of oral administration of CCX168 at 30 mg and 50 mg b.i.d., 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.

In study CL001_168, pharmacodynamics assays indicated that a dose of 30 mg CCX168 twice daily was highly effective in blocking C5a-mediated upregulation of CD11b on circulating leukocytes obtained from these subjects.

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.

Clinical trial CL003_168 in patients with AAV is being initiated in 2014. This is a randomized, double-blind, placebo-controlled trial in up to approximately 45 subjects.

1.4. Rationale for the Study

IgAN is reported as the most common glomerulonephritis worldwide. It is associated with a wide spectrum of disease severity and rate of progression of renal failure. The best well established risk factor of progressive loss of renal function from IgAN is the persistent presence of proteinuria > 1 g/day, with some studies suggesting that the persistence of even lower levels of proteinuria (> 500 mg/day) may be associated with worse prognosis. Other clinical and histologic factors have also been associated with a faster decline in renal function, although these are not as well documented.

Despite the relative high prevalence of disease worldwide, there is a paucity of evidence-based therapy available for the treatment of IgAN. Current guidelines include initiating therapy of patients with hypertension and persistent proteinuria > 1 g/day with renin-angiotensin-aldosterone system (RAAS) blockade with an ACE inhibitor or ARB to attain a level of proteinuria below that threshold.

For patients who fail to attain a reduction of proteinuria to < 1 g/day, it is currently "suggested" that patients be treated with a course of glucocorticoids (KDIGO Clinical Practice Guideline for Glomerulonephritis, 2012). However this "suggestion" carries an evidence-based grade of 2C, given the "weakness" of the data supporting the efficacy of such therapy in altering long term outcomes of patients. In addition, the use of glucocorticoids for several months (e.g., 6 months in the "Pozzi" protocol; Pozzi et al., 1999) is associated with significant risk of adverse effects especially in the adult population.

Therefore, patients with relatively modest degree of proteinuria and well preserved eGFR (or stable eGFR if the decline is attributable to other cause than IgAN) represent a large pool of patients with a perceived increased risk of GFR decline, but no established, safe and effective treatment.

This patient population is ideal for a pilot study of CCX168. Phase 2 study data in patients with ANCA-associated vasculitis suggest a significant anti-proteinuric effect of CCX168 in the majority of treated patients (mean decrease of approximately 60% in urinary ACR over 12 weeks of treatment with CCX168). This treatment effect was observed in patients receiving CCX168 plus glucocorticoids, but also in patients receiving CCX168 with no glucocorticoids.

For patients with IgAN who have already demonstrated a decline in eGFR, more aggressive therapy with corticosteroids is warranted, and a delay in such treatment for the duration of the pilot study with a medication of unproven efficacy would be inappropriate at this early stage of clinical development.

A dose regimen of 30 mg CCX168 given twice daily is being tested in study CL002_168 in AAV and showed promising efficacy and a good safety profile. This dose regimen has been selected for this clinical trial in patients with IgAN.

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 IgAN on background supportive therapy with a maximally tolerated dose of RAAS blockade.

The primary efficacy objective is to evaluate the efficacy of CCX168 based on an improvement in proteinuria.

2.2. Secondary Objectives

The secondary objectives of this study include assessment of:

1. Change in albuminuria with CCX168 treatment;
2. Change in renal function based on eGFR with CCX168 treatment;
3. Change in hematuria with CCX168 treatment;
4. Change in renal inflammatory activity based on urinary monocyte chemoattractant protein-1 (MCP 1):creatinine ratio and urinary epidermal growth factor (EGF):MCP-1 ratio with CCX168 treatment;
5. Change in serum IgA:plasma C3 ratio with CCX168 treatment;
6. Changes in pharmacodynamic markers in plasma and urine with CCX168 treatment, e.g., C3a, C5a, properdin, and sC5b-9;
7. Evaluation of the pharmacokinetic profile of CCX168 in subjects with IgAN.

3. STUDY DESIGN

This is a pilot study to test the safety, tolerability, and efficacy of CCX168 in reducing proteinuria in patients with IgAN and persistent proteinuria despite supportive therapy with a maximally tolerated RAAS blocker.

Patients will be screened for enrolment based on biopsy proven IgAN, and documentation of proteinuria > 1 g/g creatinine (by first morning urinary protein:creatinine). The screening period will be up to 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, viral screening, and estimated glomerular filtration rate (eGFR) assessment. To be eligible for study participation, a patient must have had a renal biopsy in the past 3 years confirming the diagnosis of IgAN. If not done, a renal biopsy needs to be done for eligibility assessment. Patients meeting inclusion and exclusion criteria will be enrolled for blood pressure/RAAS blockade titration and run-in period.

At screening, patients should ideally be on one or two RAAS blocker(s) and have BP <140/90 mmHg. Patients not on an RAAS blocker can be started, and have the medication dose adjusted to a maximally tolerated dose (MTD) within a period not to exceed 4 weeks.

MTD for RAAS blockade is defined as:

- a dose attaining a target blood pressure less than 125/75 mmHg, or
- the maximum recommended dose (according to the label of the RAAS blocker), or
- the maximum dose tolerated by the subject from a safety/tolerability perspective.

If the blood pressure target of <125/75 mmHg is not achieved during the titration period, additional anti-hypertension medication (non-ACE-I or ARBs) should be considered to achieve this blood pressure goal. All patients must participate in an 8-week run-in period during which they must be on a stable, MTD of an RAAS blocker before starting treatment with CCX168 on Day 1. If a patient is on two RAAS blockers (any combination of ACE inhibitor, ARB, and aldosterone blocker) at the time of screening, the patient must remain on stable doses of these medications throughout the 8-week run-in period. Titration to an MTD for both RAAS blockers is not needed in this case if the blood pressure goal has been achieved.

After the 8-week run-in period has been completed, two back-to-back first morning urine collections need to be obtained for protein and creatinine measurements. The geometric mean of the two urinary PCR measurements must be > 1 g/g creatinine for eligibility for further study participation.

On Day 1, patients meeting inclusion criteria will start CCX168 treatment. Patients will take CCX168 30 mg orally twice daily for 12 weeks (84 days). The CCX168 dose will be taken in the morning optimally within one hour after breakfast and in the evening optimally within one hour after dinner. After the 84-day treatment period, patients will be followed for 12 weeks (84 days) while continuing to take their RAAS blocker treatment at a stable dose.

At post-Day 1 study visits, blood and urine samples will be collected for safety, efficacy, and pharmacokinetic measurements. A serum pregnancy test for women of childbearing potential will be done on Days 29, 43, 57, 85, 113, and 169. Physical examinations and vital signs assessments will be performed throughout the study. Concomitant medication and adverse event assessments will be made at every study visit. An optional renal biopsy could be performed after the 12-week treatment period to assess the effect of CCX168 treatment on kidney histology.

During the 12-week treatment period and the 12-week follow-up period, the dose(s) of RAAS blocker(s) must remain unchanged. No new RAAS blocker or non-dihydropyridine calcium channel blocker or diuretic may be added during the study period (active treatment period or follow up).

During the treatment period with study medication and the 12 weeks of follow up thereafter, no new immunomodulatory medication may be started including, but not limited to cyclosporine, tacrolimus, mycophenolate mofetil, azathioprine, cyclophosphamide, or glucocorticoids (e.g. prednisone).

Concomitant use of omega-3 fatty acid supplements (e.g., fish oil) is permitted IF the medication is started at the time of, or before screening, and is maintained at a stable dose during the rest of the study until the end of the follow-up period (Day 169).

Patients will visit the study center on Days 1, 8, 15, 29, 43, 57, 85, 113, 141, and 169 for the treatment and follow-up period.

Duration of treatment with study medicine: 84 days

Duration of follow up after end of treatment with study medicine: 84 days

Subjects who experience a decrease in eGFR from baseline of > 10 mL/min/1.73 m^2 or > 20% (confirmed by repeat after 2 weeks), which is otherwise not explained (e.g., dehydration, new medication), or an increase in proteinuria by > 3 g/g creatinine from baseline or to a level > 8 g/g (confirmed by repeat after 2 weeks) during the 12-week treatment period, will exit the treatment phase of the study and be treated at the discretion of their primary nephrologist. They will remain in the study for follow up and outcome recording.

The cumulative safety data from the study will be reviewed in near real time by the Sponsor's Medical Monitor.

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). Appropriate standard of care medical treatment will be implemented to all subjects as determined by their primary nephrologist.

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

Up to approximately 20 male or female subjects with IgAN will be enrolled in this study. Subjects who started the CCX168 treatment period and drop out prematurely will not be replaced. However, subjects who drop out during the titration and run-in periods may be replaced.

4.2. Inclusion Criteria

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

1. Biopsy-proven IgAN performed for clinical purposes within 3 years prior to screening;
2. eGFR >60 mL/min/1.73 m^2 (by MDRD equation) OR eGFR >45 mL/min/1.73 m^2 if eGFR has not declined > 10 mL/min/1.73 m^2 over the previous 24 weeks;
3. Proteinuria, defined as first morning urinary PCR > 1 g/g creatinine;
4. Male or female subjects, aged at least 18 years; Where allowed by local regulations, female subjects of childbearing potential may participate if adequate contraception is used during, and for at least the three months after study completion; Male subjects with partners of childbearing potential may participate in the study if they had a vasectomy at least 6 months prior to randomization or if adequate contraception is used during, and for at least the three months after study completion; Adequate contraception is defined as resulting in a failure

rate of less than 1% per year (combined estrogen and progestogen [oral, intravaginal, or transdermal], or progestogen-only hormonal contraception (oral, injectable, or implantable), intra-uterine device, intra-uterine hormone releasing system, bilateral tubal occlusion, vasectomized partner, or sexual abstinence);

5. Willing and able to give written Informed Consent and to comply with the requirements of the study protocol; and
6. Judged to be otherwise healthy by the Investigator, based on medical history, physical examination, 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 renal disease as determined by rapid decline in eGFR (defined as >10 mL/min/1.73 m^2 over 24 weeks prior to screening, not otherwise explained);
2. Pregnant or nursing;
3. Proteinuria > 8 g/day (or >8 g/g creatinine);
4. Patients with systemic manifestations of Henoch-Schönlein purpura within the last 2 years prior to screening;
5. Patients with IgAN deemed secondary to underlying disease: e.g., diabetes, liver disease, cirrhosis, celiac disease, HIV, inflammatory bowel disease, lymphoma, or associated with any other multi-system autoimmune disease;
6. Biopsy report demonstrating severe crescentic IgAN (>25% crescents), OR >50% interstitial fibrosis and/or tubular atrophy ("T2") (Cattran et al. 2009), OR a high likelihood of rapid decline in eGFR based on an MEST ("Oxford") classification (M = mesangial hypercellularity; E = endocapillary proliferation; S = segmental glomerulosclerosis/adhesion; T = tubular atrophy/interstitial fibrosis) score of M1, E0, T1, or M0/1, E1, T1 (Cattran et al. 2009);
7. History of treatment with glucocorticoids, cyclophosphamide, azathioprine, mycophenolate mofetil, or any biologic immunomodulatory agent within the 24 weeks prior to screening;
8. Symptomatic congestive heart failure requiring prescription medication, clinically evident peripheral edema of cardiac origin, poorly-controlled hypertension (systolic blood pressure >160 or diastolic blood pressure >95), history of unstable angina, myocardial infarction or stroke within 6 months prior to screening;
9. History or presence of any form of cancer within the 5 years prior to screening, with the exception of excised basal cell or squamous cell carcinoma of the skin, or cervical carcinoma in situ or breast carcinoma in situ that has been excised or resected completely and is without evidence of local recurrence or metastasis;
10. Positive HBV, HCV, or HIV viral screening test;
11. History of tuberculosis;

12. Any infection requiring antibiotic treatment that has not cleared prior to starting CCX168 treatment on Day 1;
13. WBC count less than 4000/μL, or neutrophil count less than 2000/μL, or lymphocyte count less than 1000/μL;
14. Hemoglobin less than 9 g/dL (or 5.56 mmol/L) at screening;
15. Evidence of hepatic disease; AST, ALT, alkaline phosphatase, or bilirubin > 3 x the upper limit of normal;
16. Participated in any clinical study of an investigational product within 30 days prior to screening or within 5 half-lives after taking the last dose; and
17. 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 or Assessment

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

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

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

Subjects who experience a decrease from baseline in eGFR > 10 mL/min/1.73 m^2 or > 20%, (confirmed by repeat after 2 weeks) which is otherwise not explained (e.g., dehydration, new medication), or an increase in proteinuria of > 3 g/g creatinine from baseline or to a level > 8 g/g (confirmed by repeat after 2 weeks) during the 12-week treatment period, will exit the treatment phase of the study and be treated at the discretion of their primary nephrologist. They will remain in the study for follow up and outcome recording.

In the event of treatment failure where rescue treatment such as corticosteroid therapy is needed, the study drug (CCX168) will be discontinued, and appropriate 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 all receive CCX168 30 mg twice daily for 84 days. There will not be any randomization or stratification.

5.3. Doses and Regimens

After the screening period, eligible subjects will fall into two categories:

1. Those who are already on a maximum tolerated dose (MTD) of a RAAS blocker such as an ACE-I or an ARB, or on a stable dose of two RAAS blockers must complete an 8-week run-in period. During this run-in period, subjects must continue to take their RAAS blocker(s) at a stable dose(s) before entering the 12-week CCX168 treatment period.
2. Those who are NOT already on a RAAS blocker, or who are not on a MTD of a RAAS blocker must complete a dose-titration period not to exceed 4 weeks, during which time the dose of the RAAS blocker will be titrated up to the MTD. After this titration period, all subjects must complete an 8-week run-in period. During this run-in period, subjects must continue to take their RAAS blocker at a stable MTD before entering the 12-week CCX168 treatment period.

MTD for RAAS blockade is defined as:

- a dose attaining a target blood pressure less than 125/75 mmHg, or
- the maximum recommended dose (according to the label of the RAAS blocker), or
- the maximum dose tolerated by the subject from a safety/tolerability perspective.

The blood pressure goal is <125/75 mmHg. If this target is not achieved during the titration period, additional anti-hypertension medication (non-ACE-I or ARBs) should be considered to achieve this blood pressure goal. After the 8-week run-in period, all eligible subjects (based on urinary PCR) will receive CCX168 30 mg twice daily for 84 days.

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 will receive two bottles of CCX168 capsules on Day 1 and Day 8, respectively, four bottles on Days 15, 29, and 43, respectively, and six bottles on Day 57.

Subjects will be asked to take 3 capsules every morning and 3 capsules every evening, approximately 12 hours after the morning dose, as instructed. Study medication should be taken optimally within 1 hour after breakfast in the morning and optimally within 1 hour after dinner in

the evening for 84 days continuously. Capsules will be taken with water, preferably with 50 mL (~one fifth of a cup), but not to exceed 100 mL (~one half cup).

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 and showed promising efficacy, particularly with regards to albuminuria. Therefore, this dose regimen has been selected for this Phase 2 study in patients with IgAN. At steady state, this dose regimen is anticipated to provide at least 90% C5aR coverage on circulating leukocytes continuously throughout the day. It is anticipated that this CCX168 dose regimen would be well tolerated in patients with IgAN.

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 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 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.

5.5.2. Storage

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

5.6. Blinding

This is an open-label study.

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 capsules will be self-administered by participating study subjects. The morning dose 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 capsules. This information will be recorded in the EDC.

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 and RAAS blocker(s) for treatment of IgAN is prohibited over the course of the 84-day treatment period. This includes use of glucocorticoids, cyclophosphamide, azathioprine, mycophenolate mofetil, or any biologic immunomodulatory agent. Concomitant use of omega-3 fatty acid supplements (e.g., fish oil) is permitted IF the medication is started at the time of, or before screening, and is maintained at a stable dose during the rest of the study until the end of the follow-up period (Day 169).

Subjects will also be encouraged to remain on stable doses of all other concomitant medication over the course of the study, including diuretics and other anti-hypertension treatment.

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

Subjects will also be advised to maintain their usual dietary and exercise patterns over the course of the clinical trial.

6. STUDY PROCEDURES

6.1. Screening and Enrollment

Informed Consent must be obtained prior to performance of any study-specific tests or evaluations. Within a period not to exceed 14 days prior to randomization, subjects will undergo the following evaluations to determine their eligibility for study participation:

- Ensure that subject has a biopsy report showing IgA nephropathy from a renal biopsy conducted within the prior 3 years; If a patient does not have a renal biopsy in the past 3 years to confirm the diagnosis of IgAN, a renal biopsy needs to be done for eligibility assessment;
- Demographics, medical history, and prior (within 6 months) and concomitant medication usage;
- 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;
- Virology screening, including HIV, HBV, and HCV screening;
- Blood chemistry and hematology; An eGFR will be calculated for eligibility assessment based on the following Modification of Diet in Renal Disease (MDRD) study equation:
  - eGFR (mL/min/1.73 m^2) = 175 x (serum creatinine in mg/dL)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.212 if African-American/Black);
- Urinalysis, including pH, specific gravity, glucose, nitrite, ketones, bilirubin, urobilinogen, RBCs, and WBCs;
- Urinary protein and creatinine measurement on a first morning urine sample collection;
- 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.

6.2. Titration Period

There are three categories of potentially eligible subjects at the end of the screening period:

1. Subjects who are currently receiving a RAAS blocker, such as an ACE-I or ARB, but not at the MTD; these subjects need to participate in this titration period.
2. Subjects who are not currently receiving any RAAS blocker; these subjects need to participate in this titration period.
3. Subjects who are currently receiving a single RAAS blocker at the MTD, or subjects who are currently receiving two RAAS blockers, not necessarily at the MTD; these subjects do not need to participate in the titration period.

MTD for RAAS blockade is defined as:

- a dose attaining a target blood pressure less than 125/75 mmHg, or
- the maximum recommended dose (according to the label of the RAAS blocker), or
- the maximum dose tolerated by the subject from a safety/tolerability perspective.

The titration period can last up to 4 weeks. During this period, the dose of the RAAS blocker will be titrated up to the MTD. The blood pressure treatment target for eligible subjects (with urinary PCR >1 g/g during the screening period) is less than 125/75 mmHg (KDIGO Clinical Practice Guideline for Glomerulonephritis, 2012). As soon as the MTD is reached, subjects will be eligible to enter the run-in period. If this target is not achieved during the titration period, additional anti-hypertension medication (non-ACE-I or ARBs) should be considered to achieve this blood pressure goal.

6.3. Run-In Period

After the titration period, all subjects will enter the run-in period. During thus 8-week period, all subjects will remain on a stable MTD (if they are on a single RAAS blocker), or stable doses (if they are on two RAAS blockers). The following study visits and procedures will be performed during the 8-week run-in period.

6.3.1. Study Day -63

The following study procedures will be performed on Day -63:

- Blood pressure in the supine position after at least 3 minutes of rest;
- Serum creatinine for an eGFR calculation;
- First morning urinary protein and creatinine measurements for a PCR calculation;
- First morning urinary albumin, MCP-1, EGF, and microscopic RBC count for ACR, MCP-1:creatinine, EGF:MCP-1 ratio, and hematuria assessment;
- Recording of changes in concomitant medication;
- Recording of all adverse events;
- The subjects will be reminded to stay on a stable dose(s) or their RAAS blocker(s), and to come back to the study center for their Study Day -35 visit.

6.3.2. Study Day -35

This visit may occur within a +/- 7 day window, relative to Study Day -63. The following procedures will be performed on Day -35:

- Blood pressure in the supine position after at least 3 minutes of rest;
- Serum creatinine for an eGFR calculation;
- First morning urinary protein and creatinine measurements for a PCR calculation;
- First morning urinary albumin, MCP-1, EGF, and microscopic RBC count for ACR, MCP-1:creatinine, EGF:MCP-1 ratio, and hematuria assessment;
- Recording of changes in concomitant medication;
- Recording of all adverse events;
- The subjects will be reminded to stay on a stable dose(s) or their RAAS blocker(s), and to come back to the study center for two back-to-back study visits in the Day -7 to -2 window.

6.3.3. Study Day -7 to -2 Window

Two back-to-back study visits will occur within the Study Day -7 to -2 window, relative to Study Day -63. The following procedures will be performed on these two study days:

- Blood pressure in the supine position after at least 3 minutes of rest (on both days);
- Serum pregnancy test for women of child-bearing potential (on the first of the two days);

- Serum creatinine for an eGFR calculation (on the first of the two days);
- First morning urinary protein and creatinine measurements for a PCR calculation (on both days);
- First morning urinary albumin, MCP-1, EGF, and microscopic RBC count for ACR, MCP-1:creatinine, EGF:MCP-1 ratio, and hematuria assessment (on the first of the two days);
- Recording of changes in concomitant medication;
- Recording of all adverse events;
- If the subject is still eligible for study continuation, i.e.:
  - If the geometric mean of the two first morning urinary PCR levels is still > 1 g/g creatinine but ≤ 8 g/g creatinine,
  - If the subject's eGFR has not deteriorated >10 mL/min/1.73 m^2 over the prior 8-week run-in period,

  the subject will come for their Study Day 1 visit. The subjects will be reminded to stay on a stable dose(s) or their RAAS blocker(s). If a subject is not eligible at this stage, the subject will be discontinued from study.

6.4. Study Day 1

If eligible for continuation in the study, the subject will visit the study center on Day 1 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) will be measured supine after at least 3 minutes of rest;
- Serum chemistry and hematology; an eGFR will be calculated based on MDRD equation;
- Urinalysis, including pH, specific gravity, glucose, nitrite, ketones, bilirubin, urobilinogen, RBCs, and WBCs on a first morning urine sample collection;
- Urinary protein, creatinine, albumin, MCP-1, EGF, and microscopic RBC count on a first morning urine sample collection;
- Serum IgA and plasma C3 measurement;
- A plasma sample will be collected for baseline PD marker and PK measurement;
- A urine sample will collected for PD marker assessment;
- Any changes in concomitant medication use will be recorded;

Note that the above listed procedures must be performed prior to taking study medication.

- Two bottles of CCX168 study medication will be dispensed to the subject, with dosing instructions;

- The subject will be asked to take the first dose of study medication, 3 x 10 mg CCX168 capsules, while at the study center; the time of dosing will be recorded;
- Blood samples will be collected at 0.5, 1, 2, 3, 4, and 6 hours following CCX168 dosing for plasma CCX168 concentration measurements; the actual time of each blood sample collection will be recorded;
- Any post-dosing adverse events will be recorded;
- After all study procedures have been completed, the subject will be reminded to:
  - Come to the study center for the Day 8 study visit with their first morning urine sample;
  - Store the study medications in a cool and dry place according to label instructions for the duration of the study;
  - Take the CCX168 medication every morning and in the evening approximately 12 hours after the morning dose;
  - Not to take CCX168 medication on the morning of Day 8, unless the visit is scheduled in the afternoon, in which case CCX168 medication should be taken the morning of Day 8;
  - To bring all study medication bottles, whether empty or not, when s/he comes back for the next study visit, and
  - Continue taking their RAAS blocker(s) at a stable dose, and all their other concomitant medications as usual.

6.5. Study Day 8

The Study Day 8 visit must occur on the scheduled date. The subject will visit the study center on Day 8 for the following procedures:

- Vital signs (temperature, blood pressure, heart rate) will be measured supine after at least 3 minutes of rest;
- Serum chemistry and hematology; an eGFR will be calculated;
- Urinalysis, including pH, specific gravity, glucose, nitrite, ketones, bilirubin, urobilinogen, RBCs, and WBCs on a first morning urine sample collection;
- Urinary protein, creatinine, albumin, MCP-1, EGF, and microscopic RBC count on a first morning urine sample collection;
- Plasma samples will be collected for PD marker and PK assessment; the time of sample collection as well as the date and time of the last dose of CCX168 prior to sample collection will be recorded;
- A urine sample will collected for PD marker assessment;
- Any changes in concomitant medication use will be recorded;
- Study drug accountability will be performed on all returned study medication;

- Two bottles of CCX168 study medication will be dispensed to the subject, with dosing instructions;
- The subject will be asked to take the dose of study medication, 3 x 10 mg CCX168 capsules, while at the study center, unless the medication has already been taken that morning; the time of dosing will be recorded;
- All adverse events will be recorded;
- After all study procedures have been completed, the subject will be reminded to:
  - Come to the study center for the Day 15 study visit with their first morning urine sample;
  - Store the study medications in a cool and dry place according to label instructions for the duration of the study;
  - Take the CCX168 medication every morning and evening, approximately 12 hours after the morning dose;
  - Not to take CCX168 medication on the morning of Day 15, unless the visit is scheduled in the afternoon, in which case CCX168 medication should be taken the morning of Day 15; and
  - Continue taking their RAAS blocker(s) at a stable dose, and all their other concomitant medications as usual.

6.6. Study Day 15

The Study Day 15 visit must occur on the scheduled date. During this visit, the following study procedures will be performed:

- Vital signs (temperature, blood pressure, heart rate) will be measured supine after at least 3 minutes of rest;
- Serum chemistry and hematology; an eGFR will be calculated;
- Urinalysis, including pH, specific gravity, glucose, nitrite, ketones, bilirubin, urobilinogen, RBCs, and WBCs on a first morning urine sample collection;
- Urinary protein, creatinine, albumin, MCP-1, EGF, and microscopic RBC count on a first morning urine sample collection;
- Plasma samples will be collected for PD marker and PK assessment; the time of sample collection as well as the date and time of the last dose of CCX168 prior to sample collection will be recorded;
- A urine sample will collected for PD marker assessment;
- Any changes in concomitant medication use will be recorded;
- Study drug accountability will be performed on all returned study medication;
- Four bottles of CCX168 study medication will be dispensed to the subject, with dosing instructions;

- The subject will be asked to take the dose of study medication, 3 x 10 mg CCX168 capsules, while at the study center, unless the medication has already been taken that morning; the time of dosing will be recorded;
- All adverse events will be recorded;
- After all study procedures have been completed, the subject will be reminded to:
  - Come to the study center for the Day 29 study visit with their first morning urine sample;
  - Store the study medications in a cool and dry place according to label instructions for the duration of the study;
  - Take the CCX168 medication every morning and evening, approximately 12 hours after the morning dose;
  - Not to take CCX168 medication on the morning of Day 29, unless the visit is scheduled in the afternoon, in which case CCX168 medication should be taken the morning of Day 29; and
  - Continue taking their RAAS blocker(s) at a stable dose, and all their other concomitant medications as usual.

6.7. Study Day 29

The Study Day 29 visit may occur within ± a 2-day window 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 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;
- Serum chemistry and hematology; an eGFR will be calculated;
- Urinalysis, including pH, specific gravity, glucose, nitrite, ketones, bilirubin, urobilinogen, RBCs, and WBCs on a first morning urine sample collection;
- Urinary protein, creatinine, albumin, MCP-1, EGF, and microscopic RBC count on a first morning urine sample collection;
- A blood sample will be collected for IgA and C3 measurements;
- Plasma samples will be collected for PD marker and PK assessment; the time of sample collection as well as the date and time of the last dose of CCX168 prior to sample collection will be recorded;
- A urine sample will collected for PD marker assessment;
- Any changes in concomitant medication use will be recorded;
- Study drug accountability will be performed on all returned study medication;

- Four bottles of CCX168 study medication will be dispensed to the subject, with dosing instructions;
- The subject will be asked to take the dose of study medication, 3 x 10 mg CCX168 capsules, while at the study center, unless the medication has already been taken that morning; the time of dosing will be recorded;
- All adverse events will be recorded;
- After all study procedures have been completed, the subject will be reminded to:
  - Store the study medications in a cool and dry place according to label instructions for the duration of the study;
  - Take the CCX168 medication every morning and evening, approximately 12 hours after the morning dose;
  - Not to take CCX168 medication on the morning of Day 43, unless the visit is scheduled in the afternoon, in which case CCX168 medication should be taken the morning of Day 43; and
  - Continue taking their RAAS blocker(s) at a stable dose, and all their other concomitant medications as usual.

6.8. Study Day 43

The Study Day 43 visit may occur within ± a 2-day window 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 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;
- Serum chemistry and hematology; an eGFR will be calculated;
- Urinalysis, including pH, specific gravity, glucose, nitrite, ketones, bilirubin, urobilinogen, RBCs, and WBCs on a first morning urine sample collection;
- A plasma sample will be collected for PK assessment; the time of sample collection as well as the date and time of the last dose of CCX168 prior to sample collection will be recorded;
- Any changes in concomitant medication use will be recorded;
- Study drug accountability will be performed on all returned study medication;
- Four bottles of CCX168 study medication will be dispensed to the subject, with dosing instructions;

- The subject will be asked to take the dose of study medication, 3 x 10 mg CCX168 capsules, while at the study center, unless the medication has already been taken that morning; the time of dosing will be recorded;
- All adverse events will be recorded;
- After all study procedures have been completed, the subject will be reminded to:
  - Come to the study center for the Day 57 study visit with their first morning urine sample;
  - Store the study medications in a cool and dry place according to label instructions for the duration of the study;
  - Take the CCX168 medication every morning and evening, approximately 12 hours after the morning dose;
  - Not to take CCX168 medication on the morning of Day 57, unless the visit is scheduled in the afternoon, in which case CCX168 medication should be taken the morning of Day 57; and
  - Continue taking their RAAS blocker(s) at a stable dose, and all their other concomitant medications as usual.

6.9. Study Day 57

The Study Day 57 visit may occur within ± a 2-day window 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 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;
- Serum chemistry and hematology; an eGFR will be calculated;
- Urinalysis, including pH, specific gravity, glucose, nitrite, ketones, bilirubin, urobilinogen, RBCs, and WBCs on a first morning urine sample collection;
- Urinary protein, creatinine, albumin, MCP-1, EGF, and microscopic RBC count on a first morning urine sample collection;
- A blood sample will be collected for IgA and C3 measurements;
- Plasma samples will be collected for PD marker and PK assessment; the time of sample collection as well as the date and time of the last dose of CCX168 prior to sample collection will be recorded;
- A urine sample will collected for PD marker assessment;
- Any changes in concomitant medication use will be recorded;
- Study drug accountability will be performed on all returned study medication;

- Six bottles of CCX168 study medication will be dispensed to the subject, with dosing instructions;
- The subject will be asked to take the dose of study medication, 3 x 10 mg CCX168 capsules, while at the study center, unless the medication has already been taken that morning; the time of dosing will be recorded;
- All adverse events will be recorded;
- After all study procedures have been completed, the subject will be reminded to:
  - Come to the study center for the Day 85 study visit with their first morning urine sample;
  - Store the study medications in a cool and dry place according to label instructions for the duration of the study;
  - Take the CCX168 medication every morning and evening, approximately 12 hours after the morning dose;
  - Not to take CCX168 medication on the morning of Day 85; and
  - Continue taking their RAAS blocker(s) at a stable dose, and all their other concomitant medications as usual.

6.10. Study Day 85/Early Termination Prior to Day 85

The Study Day 85 visit may occur within ± a 2-day window 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 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;
- Serum chemistry and hematology; an eGFR will be calculated;
- Urinalysis, including pH, specific gravity, glucose, nitrite, ketones, bilirubin, urobilinogen, RBCs, and WBCs on a first morning urine sample collection;
- Urinary protein, creatinine, albumin, MCP-1, EGF, and microscopic RBC count on a first morning urine sample collection;
- A blood sample will be collected for IgA and C3 measurements;
- Plasma samples will be collected for PD marker and PK assessment; the time of sample collection as well as the date and time of the last dose of CCX168 prior to sample collection will be recorded;
- A urine sample will collected for PD marker assessment;
- Any changes in concomitant medication use will be recorded;

- Study drug accountability will be performed on all returned study medication;
- All adverse events will be recorded;
- An optional renal biopsy could be performed after the 12-week treatment period;
- After all study procedures have been completed, the subject will be reminded to:
  - Come to the study center for the Day 113 study visit with their first morning urine sample; and
  - Continue taking their RAAS blocker(s) at a stable dose, and all their other concomitant medications as usual.

6.11. Study Day 113

The Study Day 113 visit may occur within ± a 4-day window 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 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;
- Serum chemistry and hematology; an eGFR will be calculated;
- Urinalysis, including pH, specific gravity, glucose, nitrite, ketones, bilirubin, urobilinogen, RBCs, and WBCs on a first morning urine sample collection;
- Urinary protein, creatinine, albumin, MCP-1, EGF, and microscopic RBC count on a first morning urine sample collection;
- A blood sample will be collected for IgA and C3 measurements;
- A plasma sample will be collected for PD marker assessment;
- A urine sample will collected for PD marker assessment;
- Any changes in concomitant medication use will be recorded;
- All adverse events will be recorded;
- After all study procedures have been completed, the subject will be reminded to:
  - Come to the study center for the Day 141 study visit with their first morning urine sample; and
  - Continue taking their RAAS blocker(s) at a stable dose, and all their other concomitant medications as usual.

6.12. Study Day 141

The Study Day 141 visit may occur within ± a 4-day window of the scheduled date. During this visit, the following study procedures will be performed:

- Vital signs (temperature, blood pressure, heart rate) will be measured supine after at least 3 minutes of rest;
- Serum chemistry and hematology; an eGFR will be calculated;
- Urinalysis, including pH, specific gravity, glucose, nitrite, ketones, bilirubin, urobilinogen, RBCs, and WBCs on a first morning urine sample collection;
- Urinary protein, creatinine, albumin, MCP-1, EGF, and microscopic RBC count on a first morning urine sample collection;
- A blood sample will be collected for IgA and C3 measurements;
- A plasma sample will be collected for PD marker assessment;
- A urine sample will collected for PD marker assessment;
- Any changes in concomitant medication use will be recorded;
- All adverse events will be recorded;
- After all study procedures have been completed, the subject will be reminded to:
  - Come to the study center for the Day 169 study visit with their first morning urine sample; and
  - Continue taking their RAAS blocker(s) at a stable dose, and all their other concomitant medications as usual.

6.13. Study Day 169/Early Termination Prior to Day 169

The Study Day 169 visit may occur within ± a 4-day window 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 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;
- Serum chemistry and hematology; an eGFR will be calculated;
- Urinalysis, including pH, specific gravity, glucose, nitrite, ketones, bilirubin, urobilinogen, RBCs, and WBCs on a first morning urine sample collection;
- Urinary protein, creatinine, albumin, MCP-1, EGF, and microscopic RBC count on a first morning urine sample collection;
- A blood sample will be collected for IgA and C3 measurements;
- A plasma sample will be collected for PD marker assessment;
- A urine sample will collected for PD marker assessment;
- Any changes in concomitant medication use will be recorded;

- All adverse events will be recorded;
- 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 by their treating nephrologist.

7. STUDY ASSESSMENTS

7.1. Efficacy Assessments

7.1.1. Urinary Protein:Creatinine and Albumin:Creatinine

Proteinuria will be assessed by measuring the protein, albumin, and creatinine concentrations on first morning urinary samples, and calculating the urinary protein:creatinine ratio and urinary albumin:creatinine ratio. Results will be expressed as mg protein/g creatinine or mg albumin/g creatinine. This will be done by the central laboratory.

7.1.2. Estimated Glomerular Filtration Rate

Estimated glomerular filtration rate (eGFR) will be calculated at the study visits indicated in the Time and Events Table using the following MDRD equation:

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

Cystatin C measurements may be used to calculate eGFR using the following equation:

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

7.1.3. Other Urinary Assessments

First morning urine samples will be analyzed for hematuria, when appropriate at the study visits indicated in the Time and Events Table. 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.

Urine MCP-1 and EGF levels will also be measured by the central laboratory in urine samples by specific ELISA at the study visits indicated in the Time and Events Table. Urine creatinine will be measured in the same urine samples. MCP-1 and EGF levels will be standardized to urine creatinine and expressed as pg MCP-1/mg creatinine and pg EGF/mg creatinine. Urinary EGF:MCP-1 ratios will be calculated from the creatinine-corrected values.

7.1.4. Serum IgA and Plasma C3

Serum samples will be collected for Immunoglobulin A and plasma for complement C3 measurements by specific nephelometry assays by the central laboratory at the study visits indicated in the Time and Events Table.

7.1.5. Plasma and Urinary Pharmacodynamic Markers

Plasma and urine samples will be collected at the study visits indicated in the Time and Events Table. These samples will be stored at -70 °C until measurement. These samples may be used to measure galactose-deficient IgA1, complement factor H, C3a, C5a, properdin, and sC5b-9, cystatin C, other relevant cytokine, chemokine, inflammatory, and other complement markers.

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, 29, 43, 57, 85, 113, and 169. Physical examination will include a neurological examination including speech, consciousness level, mood, cranial nerves, motor, coordination and gait, reflexes, and sensory systems. Findings must be recorded in the source documents.

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

Body weight will be measured at all visits where a physical examination is performed. Body mass index will be calculated based on height, measured at Screening, and each of the body weight assessments.

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.

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.

- Urinalysis: At the central laboratory, pH, specific gravity, glucose, nitrite, ketones, bilirubin, urobilinogen, RBC, and WBC tests.
- Virology (measured only at Screening at the local laboratory): hepatitis B surface antigen, hepatitis C antibodies, HIV 1 and 2 antibodies.

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

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

A suspected unexpected serious adverse reaction (SUSAR) is defined as an SAE that is considered at least possibly related to study drug (CCX168) 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 7.2.5. All pregnancies must be followed up until conclusion and the outcome of the pregnancy reported within 24 hours of awareness as indicated in section 7.2.5.

7.2.4. Stopping Criteria

Decreases in WBC counts (mostly neutrophil and lymphocyte counts) have been observed in previous clinical trials with CCX168 (see Investigator's Brochure). In an ANCA-associated vasculitis study (CL002_168), subjects have also received cyclophosphamide, which is known to cause leukopenia. Therefore, the contribution of CCX168 to this effect on WBCs is unclear. In this study, CCX168 will not be given cytotoxic compounds such as cyclophosphamide. Therefore, the same extent of decrease in WBC counts is not anticipated. Nevertheless, WBC counts will be monitored regularly over the course of the study. When more than 4 subjects have been enrolled **and dosed with CCX168**, and if more than 25% of these subjects develop **severe** leukopenia, neutropenia, or lymphopenia, **defined as WBC count < 2000/µL, neutrophil count <1000/µL, or lymphocyte count <500/µL,** deemed possibly related to CCX168 use, the **Sponsor will consider stopping the study**. **If any subject who receives CCX168 develops severe leukopenia, neutropenia, or lymphopenia, defined as WBC count < 2000/µL, neutrophil count <1000/µL, or lymphocyte count <500/µL, CCX168 use will be interrupted and will not be re-started until the WBC, neutrophil, or lymphocyte count is above the lower limit of normal. If leukopenia/neutropenia/lymphopenia recurs upon re-challenge, CCX168 use will be discontinued permanently in this subject.**

One serious unexpected suspected adverse reaction of elevated liver enzymes has been reported in study CL002_168 in ANCA-associated vasculitis. The study is still blinded as to treatment assignment. The subject also received concomitant cyclophosphamide, pantoprazole, and sulfamethoxazole plus trimethoprim, which all have documented evidence of hepatotoxicity. Nevertheless, hepatic enzymes and bilirubin will be monitored regularly over the course of the

study. **The Sponsor will consider stopping the study if at least one subject develops severe liver injury believed to be caused by CCX168**. **Severe liver injury is based on Hy's law (elevated aminotransferase of >3 x upper limit of normal [ULN], alkaline phosphatase <2 x ULN, and associated with an increase in total bilirubin ≥2 x ULN). If any subject who receives CCX168 develops hepatic aminotransferase or total bilirubin elevations of >3 x ULN, CCX168 use will be stopped in this subject.**

7.2.5. Reporting of Serious Adverse Events

Any serious adverse event, whether or not considered study related, will be reported immediately (within 24 hours) to the Sponsor. 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 Medical Monitor and Clinical Operations Manager notifying them of the SAE.

Any medication or other therapeutic measures used to treat the event will be recorded in the EDC in addition to the outcome of the adverse event. The Sponsor will report all SUSARs to all applicable national health authorities, IRBs, and ethics committees in an expedited manner.

7.3. Pharmacokinetic Assessments

Concentrations of CCX168 (and potential metabolites) will be determined in plasma from 4-mL blood samples collected in K_3EDTA tubes on Days 1, 8, 15, 29, 43, 57, 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, 29, 43, 57, 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 ~0.6-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. These plasma samples may also be used to measure cytokines, complement fragments, or other markers associated with IgAN.

7.4. 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 by their treating nephrologist. 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.

7.5. 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 in accordance with applicable SOPs.

7.6. Subject Populations

For the purposes of data analysis, the ITT Population will include all subjects who are enrolled, have received at least one dose of study drug, and have at least one post baseline urinary PCR 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.

7.7. Safety Endpoints

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

Other safety endpoints include:

1. Change from baseline in all safety laboratory parameters;
2. Change from baseline in vital signs.

7.8. Efficacy Endpoints

The primary efficacy endpoint is the change in slope of first morning urinary PCR from the 8-week RAAS blocker run-in period to the 12-week CCX168 treatment period.

Other efficacy endpoints include:

1. The proportion of subjects achieving renal response, defined as an improvement in proteinuria based on a decrease from baseline to Day 85 in proteinuria to a level < 300 mg/g creatinine and maintaining estimated glomerular filtration rate (eGFR) within 15% of baseline;
2. The proportion of subjects achieving a partial renal response, defined as an improvement in proteinuria based on a decrease from baseline to Day 85 in proteinuria to a level < 1 g/g creatinine and maintaining estimated glomerular filtration rate (eGFR) within 15% of baseline;
3. Change in slope from the run-in period to the treatment period for urinary ACR, eGFR, urinary MCP-1:creatinine, urinary EGF:MCP-1, and urinary microscopic RBC counts;
4. The percent change from baseline to Day 85 in urinary PCR and ACR;
5. The change from baseline to Day 85 in eGFR;
6. In patients with hematuria at baseline, the percent change from baseline in urinary RBC count;
7. The percent change from baseline to Day 85 in urinary MCP-1:creatinine ratio;
8. The percent change from baseline to Day 85 in serum IgA:plasma C3 ratio;

9. The percent change from baseline to Day 85 in urinary EGF:MCP-1 ratio;
10. The percent change from baseline in plasma and urinary biomarkers, e.g., C3a, C5a, properdin, and sC5b-9.

Changes from baseline in all efficacy measurements at time points other than Day 85 will also be assessed.

7.9. Pharmacokinetic Endpoints

Plasma samples will be collected on Days 1, 8, 15, 29, 43, 57, 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

7.10. Statistical Analysis Methodology

A statistical analysis plan (SAP) with specific details of all the planned analyses will be generated. As the SAP may be updated based on the evaluation of the data distribution assumption, when differences exist between the SAP and the methods described in this section, the SAP takes the primacy.

7.10.1. Titration and Run-In Period

The following data collected during the titration (if applicable) and run-in periods will be listed by subject and summarized:

- Blood pressure measurements (supine, after at least 3 minutes of rest);
- RAAS blocker(s) type and dose titration detail;
- Serum creatinine and eGFR measurements;
- Urinary PCR and ACR measurements;
- Urinary MCP-1:creatinine ratio, EGF:MCP-1 ratio, and urinary microscopic RBC count data;
- Changes in concomitant medications, with particular attention to the dose(s) of RAAS blocker(s), and
- Any pre-treatment adverse events reported.

7.10.2. Baseline Characteristics and Subject Disposition

All subject baseline characteristics and demographic data (age, sex, race, ethnicity, weight, height, body mass index, blood pressure, smoking status, viral test results, IgAN disease duration

(from time of first renal biopsy diagnosis), urinary PCR, urinary ACR, eGFR, hematuria, urinary MCP-1:creatinine ratio, physical examination abnormalities, medical history, previous (within 6 months of screening) and concomitant medications (including IgAN medication use such as RAAS blocker(s)) at start of CCX168 dosing will be listed by study center and subject number, and will also be summarized. Baseline is defined as the last value prior to start of dosing with CCX168 (typically the Day 1 pre-dose value). For urinary PCR, baseline will be the geometric mean of the two measurements made in the Day -7 to -2 window plus the Day 1 (pre-dose) value. For the eGFR, urinary ACR, MCP-1:creatinine ratio, EGF:MCP-1 ratio, and microscopic RBC count, baseline will be the geometric mean of the one measurement made in the Day -7 to -2 window plus the Day 1 (pre-dose) value.

The number of patients screened, and the number of patients who entered, discontinued from, and completed each of the titration period, run-in period, treatment period, and follow-up period, along with the reason for discontinuation, will be presented.

7.10.3. Safety Analyses

Safety analyses will be performed on the Safety Population. The CCX168 treatment group will be summarized descriptively in terms of the subject incidence of adverse events.

All safety data will be summarized descriptively.

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, action taken, and outcome. Adverse events will be flagged in the data listings as “pre-treatment” if these occur prior to the time of administration of the first dose of CCX168, “on-treatment” if these occur during the treatment period, or “post-treatment” if these occur after the last dose of CCX168. All “on-treatment” and “post-treatment” adverse events will be considered “treatment-emergent” and will be summarized as appropriate. Symptoms or signs of IgAN 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. AEs will be summarized separately for maximum severity and relationship to study drug. If applicable, AEs leading to withdrawal and SAEs will be tabulated separately.

Safety laboratory data will be listed by subject number and will be summarized. 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 may also be generated for safety laboratory parameters, if appropriate. Vital signs data will be listed and summarized similarly.

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

7.10.4. Efficacy Analyses

The primary efficacy endpoint is the change in slope of first morning urinary PCR from the 8-week RAAS blocker run-in period to the 12-week CCX168 treatment period.

For the primary efficacy endpoint analysis, the slope of the urinary PCR during the 8-week run-in period, during the initial 4-week, as well as the full 12-week treatment period will be calculated for each subject. The mean slope for the 8-week run-in period will be compared to the mean slope for the initial 4-week, as well as the full 12-week treatment period to evaluate the

treatment effect of CCX168. If the slope for the first 4 weeks of the run-in period is steeper than the slope of the last 4 weeks of the run-in period, indicating that steady state has not been achieved over the first 4 weeks, the slope of the last 4 weeks of the run-in period may be used as the baseline slope, instead of the slope over the 8 weeks of the run-in period. This comparison will be performed by the random coefficients regression model with the test for slope-by-period (pre and on-treatment) interaction.

Similar analyses will be performed for the urinary ACR, eGFR, urinary MCP-1:creatinine ratio, urinary EGF:MCP-1 ratio, and urinary microscopic RBC count.

The proportion of subjects achieving renal response, defined as an improvement in urinary PCR based on a decrease from baseline to each subsequent time point in urinary PCR to a level < 300 mg/g creatinine and maintaining estimated glomerular filtration rate (eGFR) within 15% of baseline, will be calculated and summarized.

The same summary will be provided for subjects achieving partial renal response, i.e., a urinary PCR reduction to a level < 1 g/g creatinine while maintaining an eGFR within 15% of baseline.

Summary statistics at each time point 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 at each time point for urinary PCR, ACR, and MCP-1:creatinine, and other measurements that are not normally distributed.

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

Shift tables will be generated for urinary parameters such as urinary PCR, ACR, and hematuria for each measured time point. The categories of interest are < 300 mg/g, 301-1000 mg/g, ≥ 1001 mg/g for PCR and ACR, and ≤ 5 RBCs/hpf, >5 but <30 RBCs/hpf, and ≥30 RBCs/hpf for urinary RBC count.

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

7.10.5. Pharmacokinetic Analysis

Individual plasma concentrations of CCX168 and relevant metabolites 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 IgAN 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 urinary ACR, PCR, eGFR, urinary MCP-1:creatinine ratio, or other markers may be used as PD markers.

7.11. Sample Size Justification

The sample size for the study is based on the slope of the urinary ACR observed in a study in patients with ANCA-associated vasculitis while receiving CCX168 (CL002_168). The mean

slope was -1.32, with a standard deviation of 1.67 over 12 weeks, and -4.62, with a standard deviation of 4.77 over the initial 4-week treatment period with CCX168 in ANCA-associated vasculitis. Assuming a mean difference in pre-treatment and on-treatment slopes of 4.6, a sample size of 15 subjects will provide approximately 80% power and 20 subjects approximately 90% power to detect a difference in slopes using the paired t-test.

7.12. 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 evaluated. If warranted, sensitivity analyses of select efficacy endpoints will be conducted excluding subjects and/or study visits with significant protocol deviations.

8. STUDY COMPLETION AND TERMINATION

8.1. Study Completion

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

8.2. Study Termination

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

9. REGULATORY AND ADMINISTRATIVE REQUIREMENTS

9.1. Investigator Responsibilities

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

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

9.2. Institutional Review Board or Ethics Committee

Prior to initiating the study, the Investigator will obtain written confirmation from the IRB/EC that the IRB/EC was properly constituted and met the definition of all United States Code of Federal Regulations Title 21, Section 312.3(b) and Part 56, and/or the applicable local, regional

or national Regulatory requirements. A copy of the confirmation will be provided to the Sponsor. The Principal Investigator will provide the IRB/EC with all appropriate materials, including the protocol and Informed Consent documents. The trial will not be initiated until IRB/EC approval of the protocol, the Informed Consent document, and all recruiting materials are obtained in writing by the Investigator and copies are received by the Sponsor. Appropriate reports on the progress of the study will be made to the IRB/EC and the Sponsor by the Principal Investigator in accordance with applicable governmental regulations and in agreement with the policy established by the Sponsor.

9.3. Informed Consent

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

9.4. Protocol Modifications

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

9.5. Regulatory Documentation

All regulatory documentation including regulatory submissions, 1572 forms, and correspondence regarding this study will be kept by the Sponsor. The Sponsor will maintain all study

documentation according to their SOPs. Clinical trial related documents will be archived for at least 10 years according to national Swedish and EU regulations (LVFS 2003:3).

9.6. Subject Identification Register

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

9.7. Record Retention

The Investigator must retain all study records required by the Sponsor and by the applicable regulations in a secure and safe facility. The Investigator must consult a Sponsor CRA before disposal of any study records, and must notify the Sponsor of any change in the location, disposition, or custody of the study files. The FDA requires retention of records for two years following the date a marketing application is approved, or for two years after the FDA is notified that the IND is discontinued if there is no marketing application. Records must be retained for a period at least as long as that specified by FDA regulations. Clinical trial related documents will be archived for at least 10 years according to national Swedish and EU regulations (LVFS 2003:3).

9.8. Case Report Form Completion

Electronic Case Report Forms (CRFs) will be generated for each subject. The electronic system must comply with CFR 21 Part 11.

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

9.9. Monitoring

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

9.10. On-site Audits

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

In certain circumstances, a secondary audit may be conducted by members of a Quality Assurance group designated by the Sponsor. The Investigator will be informed if this is to take place and advised as to the nature of the audit. Representatives of the 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. Clinical trial related documents will be archived for at least 10 years according to national Swedish and EU regulations (LVFS 2003:3).

11.2. Informed Consent Form

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

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

ADDITIONAL ELEMENTS OF INFORMED CONSENT

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