MEDPACE

STATISTICAL ANALYSIS PLAN

A Randomized, Double-Blind, Placebo-Controlled Dose-Ranging Study to Evaluate the Safety and Efficacy of CCX140-B in Subjects with Focal Segmental Glomerulosclerosis (FSGS)

Protocol Number:	CL011_140
Protocol Version/Date:	V4.0 / 29 October 2018
Investigational Product:	Selective antagonist of human C-C chemokine receptor type 2 (CCR2)
Sponsor:	ChemoCentryx, Inc.
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SIGNATURE PAGE

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Prepared by:

Sharon Gettelfinger

We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

Signature	Date
[redacted]	
[redacted]	

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VERSION HISTORY

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADaM	Analysis Data Model
ANCOVA	Analysis of Covariance
AUC_{0-6}	Area under the plasma concentration-time curve from time of dosing to 6 hours post-dose
CCL2	CC Chemokine Ligand 2, also known as MCP-1
CCR2	CC Chemokine Receptor 2
CCX140-B	Sodium Salt of CCX140
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	Maximum Plasma Concentration
C_{min}	Minimum Plasma Concentration
CPK	Creatine Phosphokinase
CS	Compound Symmetry
CSR	Clinical Study Report
DB	Double Blind
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
EOS	End of Study
FSGS	Focal Segmental Glomerulosclerosis
IMP	Investigational Medicinal Products
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
MAR	Missing at Random
MCP-1	Monocyte Chemoattractant Protein 1, also known as CCL2
MCP-MOD	Multiple Comparison Procedure - Modelling
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effects Model for Repeated Measures
OLE	Open Label Extension
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per-Protocol
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
TFL	Tables, Listings, Figures
T_{max}	Time of Maximum Plasma Concentration

Abbreviation	Definition
UACR	Urinary Albumin to Creatinine Ratio
UPCR	Urine Protein to Creatinine Ratio

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with protocol number CL011_140. The SAP will be finalized prior to database lock. For the final Clinical Study Report (CSR), the analysis outlined in the SAP will supersedes those described in the protocol.

2 STUDY OVERVIEW

2.1 Study Objectives

The aim of this study is to evaluate the effect of treatment with CCX140-B (sodium salt of CCX140), a selective antagonist of C-C chemokine receptor type 2 (CCR2), in subjects with focal segmental glomerulosclerosis (FSGS).

2.1.1 Primary Objective

The primary safety objective of this study is to evaluate the safety and tolerability of CCX140-B in subjects with FSGS with proteinuria.

The primary efficacy objective of this study is to evaluate the effect of CCX140-B treatment on urinary protein excretion in subjects with FSGS, as assessed by change from baseline in the urine protein to creatinine ratio (UPCR) at Week 12.

2.1.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the effect of CCX140-B on renal function, as assessed by estimated glomerular filtration rate (eGFR) at Weeks 12 and 24;
- To evaluate the effect of CCX140-B treatment on fraction of subjects achieving complete and partial renal remission (by 2 different partial remission definitions);
- To evaluate the pharmacokinetic (PK) profile of CCX140-B in subjects with FSGS.

2.1.3 Exploratory Objective

The exploratory objectives are:

- To evaluate the effect of CCX140-B on urinary monocyte chemoattractant protein-1 (MCP-1, also known as CCL2) and other serum and urinary markers of renal function and inflammation;
- To explore the effect of CCX140-B on levels of blood monocytes, T, B and NK cells, and other blood and urinary markers potentially associated with CCR2 antagonism;
- To explore the effect of CCX140-B on Health-related Quality of Life changes based on answers to the Short Form 36 version 2 (SF-36 v2) and EuroQuality of Life-5 Domains-5 Levels (EQ-5D-5L) questionnaires;

- To explore the relationship among exposure (PK) of CCX140-B, serum albumin level, and UPCR.

2.2 Study Design

2.2.1 Overview

This study will evaluate the efficacy, safety, tolerability, and pharmacokinetics of up to 12 weeks of treatment with each of three dose regimens of CCX140-B or placebo, when used in combination with stable standard of care therapy in subjects with FSGS with significant proteinuria, assessed as UPCR > 1g/g at Screening.

The target is to enroll 40 adult male or female subjects in this randomized, double-blind, placebo-controlled, Phase 2 study. Subjects will be randomized 1:1:1:1 to one of four treatment groups:

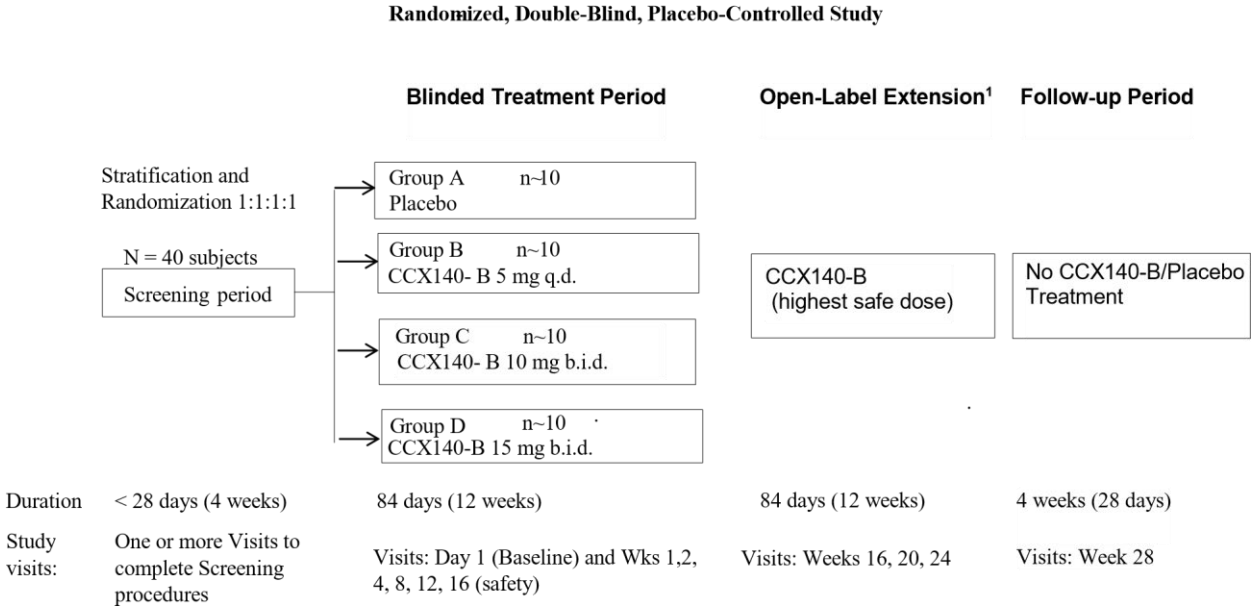
- Group A: Placebo (N=10)
- Group B: CCX140-B 5 mg once daily (N=10)
- Group C: CCX140-B 10 mg twice daily (N=10)
- Group D: CCX140-B 15 mg twice daily (N=10)

Subjects will be screened within a period not to exceed 28 days prior to Study Day 1 (the first day of dosing). All subjects will take blinded study medication in the morning and evening, with or without food, for 84 consecutive days. Following the 84-day blinded dosing period, all subjects will take open label CCX140-B for an additional 84 days at the highest dose under evaluation, currently planned to be 15 mg twice daily.

During the treatment period, eligible subjects will visit the study center on Study Days 1, 8, 15, 29 (Week 4), and Weeks 8, 12 (primary endpoint), 13, 16, 20, and 24 for study procedures including interval history, physical examination and vital signs, ECG, study questionnaires, and collection of blood and urine. Subjects will discontinue study drug as of Study Day 169 (Week 24) and will return for a follow up visit on Week 28. When feasible, upon discontinuation of treatment for any reason a sample of whole blood should be collected for assessment of elimination 2, 7 and 14 days after the final dose of CCX140-B (or placebo).

A study schema is depicted in Figure 1. All study procedures are presented in Table 1.

Figure 1 Study Schema



[1]If eligible subjects wish to participate in an Open-Label Extension; all subjects including those on placebo will be switched to CCX140-B (at the highest safe dose) after the completion of 12 weeks of blinded study drug treatment.

Table 1. Time and Events Table

Assessments	**Screening**	**Double-Blind Treatment[1]**						**Open-Label Treatment**				**Follow-Up**	**Variable**
		Initial Study Phase						**Extension Phase**					**Elimination**
Days	**≤ 28 days**	**1**	**8**	**15**	**29**	**57**	**85[7]**	**92**	**113**	**141**	**170**	**113[7] &198**	**2,7 & 14 days post final dose**
Weeks	**≤4 weeks**		**1**	**2**	**4**	**8**	**12[7]**	**13**	**16**	**20**	**24**	**16[7] & 28**	
Informed consent	X												
Demographics, medical history, prior medications	X												
HIV, HBV, HCV testing	X												
Screening for tuberculosis[4]	X												
Renal needle biopsy for FSGS confirmation (if not done previously and if diagnosis not based on genetic information)	X												
Enrollment, Stratification and Randomization		X											
Physical examination[2]	X	X[3]	X	X	X	X	X	X	X	X	X	X	
Vital signs	X	X[3]	X	X	X	X	X	X	X	X	X	X	
12-lead ECG	X	X					X	X			X	X	
Serum pregnancy test for women of childbearing potential	X	X			X		X		X	X	X	X	
Hematology, Serum chemistry (coagulation panel and lipids included at specified visits[9])	X	X[3,9]	X[9]	X	X[9]	X	X[9]	X[9]	X[9]	X	X[9]	X[9]	
Whole blood for DNA		X											
Lymphocyte subset[8]	X	X	X	X	X		X		X		X	X	
Urinalysis	X	X[3]	X	X	X	X	X	X	X	X	X	X	

Assessments	**Screening**	**Double-Blind Treatment[1]**						**Open-Label Treatment**				**Follow-Up**	**Variable**
		Initial Study Phase						**Extension Phase**					**Elimination**
Days	**≤ 28 days**	**1**	**8**	**15**	**29**	**57**	**85[7]**	**92**	**113**	**141**	**170**	**113[7] &198**	**2,7 & 14 days post final dose**
Weeks	**≤4 weeks**		**1**	**2**	**4**	**8**	**12[7]**	**13**	**16**	**20**	**24**	**16[7] & 28**	
First morning void for urine protein and creatinine assays (UPCR, UACR and Cystatin C assessment)	X	X	X	X	X	X	X	X	X	X	X	X	
24-hour urine collection		X					X				X		
ACTG Brief Peripheral Neuropathy Screening Tool	X	X[3]	X	X	X	X	X	X	X	X	X	X	
SF-36 v2 & EQ-5D-5L		X[3]			X		X		X		X	X	
CCX140-B/Placebo dispensing		X			X	X							
CCX140-B/Placebo double-blind dosing		X →	→	→	→	→							
CCX140-B Open label dispensing							X		X	X			
CCX140-B Open label dosing[6]							X →	→	→	→	→		
CCX140-B accountability			X	X	X	X	X	X	X	X	X		
Plasma MCP-1		X[3]	X	X	X		X	X	X		X	X	
PD plasma/serum sample collection		X[3]	X	X	X		X	X	X		X	X	
Urine MCP1-1, MCP-1/Creatinine		X[3]	X	X	X		X	X	X		X	X	
PD urine sample collection		X[3]	X	X	X		X	X	X		X	X	
PK plasma sample collection		X[3,5]	X	X[5]	X	X	X	X	X	X	X	X[11]	X[11]

Assessments	**Screening**	**Double-Blind Treatment[1]**						**Open-Label Treatment**				**Follow-Up**	**Variable**
		Initial Study Phase						**Extension Phase**					**Elimination**
Days	**≤ 28 days**	**1**	**8**	**15**	**29**	**57**	**85[7]**	**92**	**113**	**141**	**170**	**113[7] &198**	**2,7 & 14 days post final dose**
Weeks	**≤4 weeks**		**1**	**2**	**4**	**8**	**12[7]**	**13**	**16**	**20**	**24**	**16[7] & 28**	
Concomitant medications	X[10]	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	

[1]Week 1 and 2 visits must occur with a ± 1 day window. Week 4 through Week 28 visits may occur within a ± 3 day window.

[2]Physical examination will include body weight measurements. Height will only be measured at Screening. Full physical examination will be performed at Screening and Day 1. At all other visits, limited, physical examination will be performed directed by review of systems, laboratory findings and Investigator discretion.

[3]These procedures must be performed before taking the first dose of CCX140-B on Day 1; in addition, CBC and bilirubin will be assessed at 2 and 6 hours following dosing in blood to be drawn at the same time as the PK sample

[4]TB screening **by** Interferon γ release assay (IGRA) done within 6 weeks prior to Screening or done during Screening.

[5]PK blood sample will be collected on Days 1 and 15 prior to the morning dose (time 0), and at 0.5, 1, 2, 3, 4, and 6 hours following dosing. PK samples at all other visits will be collected at time 0 only, just prior to administration of the first daily dose.

[6] Eligible subjects may enter an Open-Label Extension at the highest safe dose of CCX140-B. The minimum eligibility requirements for the Open-Label Extension include no withdrawal of subject consent and no new infections that in the judgment of the investigator would preclude addition of a new immunosuppressive or immunomodulatory treatment, no requirement for addition of new immunosuppressive treatment during the prior 12 weeks and no anticipated requirement during the next 12 weeks.

[7]The Week 16 visit is a safety follow up visit for subjects stopping study drug at Week 12, and not going onto the Open-Label Extension. For those going on the Open-Label Extension, Week 16 is a regularly scheduled study visit.

[8]Whole blood for analysis of absolute count of T-cells, B-cells and Natural Killer Cells

[9] Serum chemistry at each visit to include liver panel (total, direct and indirect bilirubin, LDH, AST, ALT), alkaline phosphatase, etc. (see Section 8.2.2 of the protocol); at specified visits, to include coagulation panel (PT, PTT & INR) and lipids (HDL, LDL, Triglycerides and Total Cholesterol) as well

[10] Concomitant medications will be recorded for all medications taken 12 weeks prior to screening. Glucocorticoids and immunosuppressives will be recorded for up to 6 months prior to screening. If the subject has received prior rituximab treatment or other B-cell depleting antibodies, the medication use, as well as any available urinary protein values, should be recorded for up to 1 year prior to screening.

[11] PK blood samples will be collected at 2 days, 7 days and 14 days following the last dose of study drug, as well at the Follow-up Visit (Week 16 or Week 28) to assess elimination.

2.2.2 Randomization and Blinding

Randomization will be stratified by UPCR <3.5 g protein/g creatinine versus UPCR ≥3.5 g protein/g creatinine at baseline and by the current use of glucocorticoids and/or immunosuppressive medications (yes vs no).

Blinded study medication will be taken by the subjects for 84 days, as follows:

- Group A: Three placebo tablets, taken twice daily;
- Group B: One 5 mg CCX140-B tablet and two placebo tablets in the morning; three placebo tablets in the evening;
- Group C: Two 5 mg CCX140-B tablets and one placebo tablet, taken twice daily;
- Group D: Three 5 mg CCX140-B tablets, taken twice daily.

Following the 84-day blinded dosing period, all subjects will take open label CCX140-B for an additional 84 days at the highest dose under evaluation, currently planned to be 15 mg twice daily.

2.2.3 Study Drug

Study drug will be administered as 3 tablets twice daily (5 mg CCX140-B tablets, matched placebo, or combination) for up to 12 weeks in a double-blind manner.

CCX140-B will be administered as up to 3 tablets (5 mg each) twice daily during study weeks 13 through 24 in an open-label manner.

Study drug will be supplied to the study center in plastic bottles, each bottle containing 30 tablets.

During the blinded portion of the study, study drug will be supplied to the subject in kits, each kit containing 3 bottles labeled with a yellow band for use in the morning and 3 bottles labeled with a blue band for use in the evening. Each bottle will be also labeled with a distinguishing number. Subjects will be instructed to take one tablet from each of the three yellow bottles in the morning, and one tablet from each of the three blue bottles in the evening and to maintain a dosing diary.

2.2.4 Sample Size Determination

Assuming the standard deviation (SD) for the group difference in change from baseline in the logarithmic transformation of UPCR is 0.70, with 10 subjects per treatment group, the 90% confidence interval (CI) for the between group difference in the log scale will have a ½ width of 0.543. In other words, if the ratio of the treatment over placebo is 0.5 (50% reduction from placebo) in UPCR, the 90% CI will be (0.29, 0.86) (i.e., 14% to 71% reduction).

Assuming SD =8.5 for the group difference in change from baseline in eGFR, with 10 subjects per group, the 90% CI for the between group difference will have a ½ width of 6.6. If the difference between treatment and placebo is observed to be 10 mL/min/1.73m2, the 90% CI will be (3.4, 16.6).

Note the above calculation is based on the SD estimated from Study CL005_140 and an unadjusted 2-sided alpha of 10%.

2.3 Study Endpoints

2.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in urine protein:creatinine ratio (UPCR) at Week 12.

2.3.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- Change from baseline in eGFR calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) cystatin C equation, CKD-EPI Creatinine equation, CKD-EPI Creatinine-Cystatin C equation and modification of diet in renal disease (MDRD) Creatinine equation at Weeks 12 and 24
- Proportion of subjects achieving complete renal remission by the following definition at Weeks 12 and 24:
    - reduction in UPCR to <0.3 g/g

      and
    - serum albumin within normal range

      and
        - for patients with abnormal serum creatinine levels at baseline, return to normal levels for that age group

          or
        - for patients with normal serum creatinine levels at baseline, final value within 20% of baseline levels
- Proportion of subjects achieving partial remission by the following two definitions assessed at Weeks 12 and 24:
    - UPCR reduction of ≥ 50% from baseline and UPCR < 3.5 g/g
    - decrease in UPCR to less than 1.5 g/g and at least a 40% reduction in proteinuria from baseline

2.3.3 Exploratory Endpoints

Exploratory endpoints include:

- Change from baseline of proteinuria in subjects treated with CCX140-B versus placebo over time
- Change from baseline (absolute and percent change) in urinary albumin:creatinine ratio (UACR). The response rate across dose groups for patients achieving 30% reduction in

UACR from baseline at Week 12 will be calculated, with the number of subjects in the respective treatment group in the ITT (or PP) population being the denominator. The analysis will be repeated for reductions of 20%, 40% and 50%.

- Change from baseline in urinary MCP-1:creatinine ratio
- Change from baseline in blood monocytes (absolute and %), T, B and NK cells
- Change from baseline in Health-related Quality of Life changes based on Short Form 36 version 2 (SF-36 v2) and EuroQuality of Life-5 Domains-5 Levels (EQ-5D-5L) questionnaires
- Change from baseline in serum albumin
- Relationship among PK, eGFR, serum albumin and UPCR

2.3.4 Pharmacokinetic Endpoints

Concentrations of CCX140 will be determined in plasma from 4.0-mL blood samples collected in K_2EDTA tubes according to Table 1. 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 and Day 15
- C_{min} Trough level plasma concentrations at post-Day 1 visits

On Days 1 and 15, samples will be taken at pre-dose, 0.5, 1, 2, 3, 4, and 6 hours after dosing. The blood samples collected on the other relevant study days need to be collected prior to taking the CCX140-B/ placebo dose.

The relationship between PK and serum albumin and between PK and UPCR may be explored, where possible.

Total plasma concentrations of CCX140 will be determined using validated analytical methods. These plasma samples may also be used to measure other markers associated with FSGS.

2.3.5 Pharmacodynamic Endpoints

Blood samples (plasma and serum) and urine samples for PD measurement will be collected according to the schedule in Table 1.

In addition to those included in the exploratory efficacy endpoints, the following PD endpoints may be assessed if measured:

- Profile of FSGS related gene mutations;
- Change from baseline in other urinary and blood exploratory markers potentially associated with activity of FSGS or inhibition of the CCR2/MCP-1 pathways. These may include measurement of:

- Transforming growth factor-beta (TGF-B), connective tissue growth factor (CTGF), Nacetylglucosamine (NAG), β2 microglobulin, adiponectin, C-reactive protein (CRP), cystatin C, synaptopodin, neutrophil gelatinase-associated lipocalin (NGAL), liverfatty acid-binding protein (LFABP), kidney injury molecule-1(KIM-1), intact PTH, leptin, reistin, chemerin, retinol binding protein 4 (RBP-4), MCP-1, IL-1β, IL-6, suPAR, miR-193a, CLCF-1 and TNF-α.

2.3.6 Safety Endpoints

2.3.6.1 Adverse Events

Safety endpoints related to adverse events include subject incidence of treatment-emergent adverse events (TEAE), adverse events leading to study withdrawal, and serious adverse events. An adverse event will be considered treatment-emergent if the start date of the event is on or after the date of administration of the first dose of study medication.

2.3.6.2 Clinical Laboratory Assessments

Safety endpoints related to clinical laboratory assessments include change from baseline and shifts from baseline in all safety laboratory parameters.

The following tests will be performed at the visits identified in the Time and Events Table (Table 1).

- Hematology: hemoglobin, hematocrit, RBC count, WBC count with differential, platelet count, mean cell hemoglobin, mean cell hemoglobin concentration, mean corpuscular volume, reticulocyte count and schistocytes;
- Serum Chemistry: liver panel (total, direct and indirect bilirubin, lactate dehydrogenase [LDH], AST, ALT), renal panel (BUN, creatinine), creatine phosphokinase (CPK), albumin, sodium, potassium, magnesium, bicarbonate, chloride, calcium, inorganic phosphorus, glucose, total protein, alkaline phosphatase, uric acid, serum amylase, serum lipase, and cystatin C; at specified visits, coagulation panel (PT, PTT, INR), lipid panel (HDL, LDL, Triglycerides, Total Cholesterol) will be included
- Urinalysis: At the central laboratory, nitrite, blood, and protein, will be tested. If positive, microscopy will be performed;
- Virology (measured only at screening): hepatitis B surface antigen, hepatitis C antibodies, HIV 1 and 2 antibodies; virology tests done within 6 weeks prior to screening are acceptable for eligibility assessment;
- TB screen: Only interferon γ release assay (IGRA) done within 6 weeks prior to screening is allowed for eligibility assessment.

2.3.6.3 Vital Signs

Safety endpoints include change from baseline in vital signs. Vital signs will be measured during screening and on each as specified in Table 1. Vital signs assessments will be performed after the subject has rested for at least three minutes while seated, and will include the following:

- Blood pressure
- Pulse rate
- Body temperature

2.3.6.4 Electrocardiogram

Safety endpoints include clinically significant abnormal electrocardiogram (ECG) findings. A 12-lead ECG, after resting for at least 3 minutes, will be performed at screening and assessed for any clinically significant abnormalities. All abnormalities will be recorded in the EDC system. Assuming the ECG abnormality does not preclude study entry, an ECG may be repeated as clinically indicated.

2.3.6.5 Physical Examination

Safety endpoints include physical examination findings. 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, assessments will be performed at visits indicated in Table 1.

Body weight will be measured as part of the physical examinations. Height needs to be recorded at screening only. BMI will be calculated from the body weight and height measurements.

2.3.6.6 ACTG-BPNST

Safety endpoints include change from baseline in score on the AIDS Clinical Trial Group Brief Peripheral Neuropathy Screening Test (ACTG-BPNST). ACTG-BPNST will be completed by the study subject and the study doctor to assess changes in neuropathy. Proven translations will be used for non-English speaking subjects, whenever possible.

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Analysis Day

Analysis day will be calculated from the date of first dose of study drug. The day of the first dose of study drug will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

3.1.2 Analysis Visits for Efficacy

Scheduled visits will be assigned to analysis visits as recorded in the electronic data capture (EDC) system. If a scheduled visit is not available, unscheduled and early termination visits will be assigned to analysis visits using analysis visit windows based on the actual date the assessment took place. The start day of the analysis window will be calculated as the midpoint between the scheduled assessment and previously scheduled assessment for that parameter. The end day of the analysis window will be calculated as the midpoint between the scheduled assessment and the next scheduled assessment for that parameter. Where multiple measurements

for a particular parameter appear within an analysis window, the scheduled visit will be used. If no scheduled visit appears in the analysis window, the result closest to the target day will be used. If equidistant and both are unscheduled and/or early termination visits, the later result will be used for the summary measure.

Though all measures may not be used in data summaries (e.g., two lab measures within the same analysis visit window), all measurements appear in the datasets and listings. For subjects where the event date is missing, the study day and analysis window will also be missing. See the following table for an example of analysis windows.

Analysis Visit	Analysis Day Target	Analysis Day Window
Week 1	8	2 - 11
Week 2	15	12 - 22
Week 4	29	23 - 43
Week 8	57	44 - 71
Week 12	85	72 - 88
Week 13	92	89 - 102
Week 16	113	103 - 127
Week 20	141	128 - 155
Week 24	170	156 - 181
Week 28	198	≥ 182

3.1.3 Definition of Baseline

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

3.1.4 Summary Statistics

Categorical data will be summarized with counts and percentages of subjects. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation, minimum, and maximum.

3.1.5 Hypothesis Testing

As this is an exploratory study in a rare disease, unless specified otherwise, all statistical tests and confidence intervals will be based on a 2-sided alpha of 0.10. No multiplicity adjustment will be applied to the multiple dose and multiple endpoints comparisons.

3.1.6 Evaluation of Site Effect

This is a multi-center study enrolling subjects from approximately 40 study sites across North America, Europe, and Australia and New Zealand. Site effect will not be evaluated since the number of subjects at each site is expected to be too small.

3.2 Analysis Populations

3.2.1 Intent-to-Treat (ITT) Population

The ITT Population is defined as all randomized subjects.

3.2.2 Intent-to-Treat (ITT) Population

The ITT Population is defined as all randomized subjects who received at least one dose of study drug and have a baseline assessment and at least one post baseline efficacy assessment. This will be the primary analysis population for the evaluation of efficacy.

3.2.3 Per-Protocol (PP) Population

The PP Population is defined as all subjects in the ITT Population who have ≥80% compliance with the study drug administration and do not have protocol deviations that could significantly affect the interpretation of the results for the primary endpoints. The PP Population will be a secondary population for analysis of the primary efficacy endpoint.

The following aspects will be considered for subjects to be excluded from the PP analysis:

- Subjects with significant protocol deviations regarding inclusion and exclusion criteria that may impact evaluation of the primary endpoints.
- Subjects with significant lack of compliance of study medication administration (CCX140-B /placebo) defined as: All subjects who were <80% compliant with taking CCX140-B /placebo based on study medication accountability records.
- Subjects administered non-protocol allowed medications such as, calcineurin inhibitors, ACE-inhibitors or ARBs, sprironolactone, eplerenone, antihypertensive, diuretics, immunosuppressants or calcineurin inhibitors or subjects with dose increases of such drugs during the course of the study.

Subjects to be excluded from the PP population will be identified and documented prior to the database lock and unblinding for analysis. A subject's data could be partially excluded from analysis depending on when the deviation occurred. For example, if a deviation occurred during the open-label extension (OLE) that did not impact the data from the double-blind period, only the data during the OLE will be excluded.

3.2.4 Safety Population

The Safety Population is defined as all randomized subjects who received at least one dose of study drug. All safety data will be analyzed using the Safety Populations by the treatment groups that subjects are randomized to. In the event that a subject takes the wrong study drug (i.e., did not take the randomized study drug), the actual treatment received will be used for analysis.

Notations for Treatment Groups

Period A: initial 12-week blinded treatment period, Day 1 –Week12

Period B: open-label treatment period plus 4 Weeks of Follow-up, Week 12 to End of Study (EOS)

We have defined 3 Safety Populations for this study:

1. The Safety Population in Period A (Safety_A) is defined as all subjects who received at least one dose of study drug in Period A.
2. The Safety Population in Period B (Safety_B) is defined as all subjects who received at least one dose of study drug in Period B.
3. The All CCX140-B Treated Population is defined as all subjects received at least one dose of CCX140-B in the study.

3.2.5 Pharmacokinetic Population

The PK Population is defined as all randomized subjects who received at least one dose of study drug and have at least one evaluable PK sample. Subjects with major protocol deviation such as PK deviation or compliance issues may be excluded from the PK analyses (i.e. descriptive statistics) upon agreement with the Sponsor on case by case basis but all data will be listed. Values that are excluded from the analysis will be footnoted appropriately.

3.2.6 Pharmacodynamic Population

The PD Population is defined as all randomized subjects who received at least one dose of study drug and have at least one evaluable PD sample.

3.3 Subject Data and Study Conduct

3.3.1 Subject Disposition

The number and percent of subjects who were screened, screen failed (by reason), completed Week 12, who completed the Open-Label Extension, withdrew early from the study, along with the reasons for withdrawal, will be presented by treatment group.

3.3.2 Protocol Deviations

Major protocol deviations, i.e., those pertaining to GCP violations and those that may majorly affect the efficacy or safety evaluation, will be captured in the Study Management System as CSR Reportable deviations. These major deviations will be listed and summarized by category. These deviations will be reviewed prior to database lock to determine the potential impact on the interpretation of the efficacy and safety outcomes. The effect of any major protocol deviations and compliance will be assessed by conducting per-protocol analyses for the primary efficacy endpoint excluding subjects and/or study visits with major protocol deviations. This will be determined and documented prior to unblinding the study.

3.3.3 Analysis Populations

Counts and percentages of subjects in each analysis population will be summarized by treatment group and in total based on all randomized subjects. Reasons for exclusion from each analysis population will also be summarized.

3.3.4 Demographic and Baseline Characteristics

All subject baseline characteristics and demographic data (age, sex, race, ethnicity, weight, height, body mass index), viral test results, FSGS duration (from time of first diagnosis based on renal

biopsy), eGFR, proteinuria (UPCR), level of proteinuria (UPCR <3.5 vs UPCR ≥3.5 g/g), proteinuria (UACR), prior Glucocorticoids or Immunosuppressant treatment, Calcineurin Inhibitor treatment (Cyclosporine, Tacrolimus), and diagnosis of nephrotic syndrome (defined as UPCR ≥3.5 g/g) will be listed and summarized by treatment group and in total based on all randomized subjects.

3.3.5 Medical History

Medical history will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1. Counts and percentages of subjects with medical history by system organ class and preferred term will be summarized by treatment and in total based on all randomized subjects.

3.3.6 Concomitant Medications

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (September 2016E B2). Prior medications are defined as any medication taken prior to the first dose of study medication (within 12 weeks of screening). Concomitant medications are defined as any medication taken on or after the first dose of study medication. A medication can be classified as both prior and concomitant if it started before or during the screening period and continued into the treatment period. All prior and concomitant medications will be listed and summarized by Anatomic Therapeutic Chemistry (ATC) classification. All B-cell depleting antibodies, glucocorticoids and immunosuppressants taken within 6 months prior to screening may be summarized separately.

3.3.7 Study Drug Exposure and Compliance

Duration of exposure to study drug will be calculated as (date of last dose – date of first dose + 1). If date of last dose is not available, the date of discontinuation from study will be used. Duration of exposure to study medication will be summarized with descriptive statistics for double-blind period, open-label period and both periods. Exposure data will be provided for the following intervals, defined to align with the efficacy endpoints:

- <=4 weeks (days 1-29)
- >4 and <=12 weeks (days 30-85)
- >12 and <=24 weeks (day 86-169)
- >24 weeks (days >169)

Percent compliance to study drug will be summarized for double-blind period, open-label period and both periods, calculated as follows:

Percent Compliance = 100 × number of capsules taken / (6 × number of days in the specified period).

Percent compliance to the study drug regimen will be summarized by treatment group based on the Safety Population using counts and percentages of subjects with compliance in the following categories:

- <80%
- 80-120%
- >120%

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

- UPCR <3.5 g protein/g creatinine versus UPCR ≥3.5 g protein/g creatinine at baseline
- UPCR <1.5 g protein/g creatinine versus UPCR ≥1.5 g protein/g creatinine at baseline
- Concomitant use of glucocorticoids and/or immunosuppressive medications (yes vs no)
- Concomitant use of Calcineurin Inhibitor (Cyclosporine, Tacrolimus) therapy (yes vs no)
    a. Cyclosporin (yes vs.no)
    b. All Calcineurin Inhibitors combined, i.e. Cyclosporin,or tacrolimus, etc. (yes vs.no)
- Concomitant use of ACE inhibitor or ARB or Aldosterone antagonist use vs not
- Concomitant use of use of diuretic/additional antihypertensive agent
    a. Diuretics
    b. Additional antihypertensive treatments
- Serum Albumin <3.5 g/dl vs ≥3.5 g/dl at baseline
- Urinary albumin-to-creatinine ratio/Urinary protein-to-creatinine ratio ≥1.5 vs < 1.5
- Patients with podocyte effacement of ≥30% versus <30% based on electron microscopy
- Patients with glomeruli showing segmental lesions >1 vs ≤1 based on electron microscopy

3.4 Efficacy Assessment

The overall efficacy hypothesis for this study is that CCX140-B will be effective in reduction in urine protein:creatinine ratio (UPCR) in treatment of subjects with FSGS. All available efficacy data will be listed for the ITT Population. Analyses of the efficacy endpoints will be performed using the ITT and PP populations, with the ITT population being the primary analysis population.

3.4.1 Primary Efficacy Endpoint

UPCR Change from Baseline

The primary efficacy endpoint (UPCR) will be summarized by treatment group over time using descriptive statistics. Spaghetti plots of UPCR as well as percent change of UPCR (derived from morning void spot urine. If missing 24 hour urine evaluations will be used, if available) from baseline to weeks 4, 8, 12, 13, 16, 20, 24, and week 28 (if available) will be produced by treatment group and for all individual patients for visual inspection. Additionally, percent change of UPCR from week 12 to week 13, 16, 20, 24, and week 28 will be summarized by prior treatment group during the open-label period. The same analyses of for UPCR will be performed at baseline, week 12 and week 24 solely using UPCR values derived from 24-hour urine evaluations (missing assessments will not be replaced with morning void spot urine values).

The primary analysis will use the morning void spot urine results. If baseline or post-baseline morning void spot urine results are not available, 24 hour urine results will be used where available. Please note 24-hour urine assessments at Day 1, Week 12 and Week 24 were added after Protocol Amendment 4.0.

For inferential analysis of the ratio to baseline, UPCR will be $\log_e$-transformed to alleviate skewness of the data since data are not normally distributed. A mixed effect model for repeated measures (MMRM) will be performed in the ITT population with treatment, group, visit, and treatment-by-visit interaction as factors and baseline value and age as covariates. Least squares mean differences and the corresponding 90% confidence intervals (CI) between each of the CCX140-B (5, 10, or 15 mg) groups and the placebo group will be back transformed to the original scale. Corresponding P-values will also be presented.

In the MMRM model, missing data will not be imputed. This analysis is unbiased under the missing at random (MAR) assumption. Toeplitz covariance matrix will be used to model within-subject variance-covariance structure for the model errors. If the model does not converge using the Toeplitz covariance matrix, AR(1) covariance matrix will be used. If convergence is still not met, then compound symmetry (CS) will be used.

The code used to generate the MMRM analysis will be similar to the following:

```
*******************************************************************************
Note:
TRT01AN = randomized treatment group (numeric):
          1=Placebo, 2=CCX140-B 5 mg, 3=CCX140-B 10 mg, 3=CCX140-B 15 mg
VISITN = Visit Number
LR2BASE = Ratio of Visit Value to Baseline Value (log-transformed)
LBASE = Baseline value of response (log transformed)
      proc mixed data=lab_log;
      class SUBJID TRT01AN(ref='1') VISITN;
      model LR2BASE = TRT01AN LBASE AGE AVISITN TRT01AN*VISITN/ residual
      outp=residual ddfm=kr;
      Repeated VISITN / TYPE=TOEP sub=SUBJID;
            **use AR(1) if no convergence, then CS;
      lsmeans VISITN*TRT01AN / alpha=.10 cl pdiff slice=VISITN;
      ods output LSMeans=LSM
                 Diffs=DiffLSM;
      run;

*******************************************************************************
```

The same analysis described above will be performed for change from baseline in the open-label period and change from Week 12 in the open-label period.

Sensitivity analyses

1. Given the high variability in morning void spot urine UPCR values, the baseline will be defined as the average of the screening and Day 1 morning void spot urine UPCR values if both are available. The UPCR analyses will be repeated using this baseline definition. If only one of 2 morning void spot urine values is available, that value will be used as the baseline. Post-baseline assessments will use the same approach as for the primary analysis prioritizing morning void spot urine and replacing missing assessments with 24 hour urine results where available.
2. As 24-hour urine evaluations were not available for all subjects. The following analysis will be conducted:

   -Baseline will be calculated by averaging the screening and Day 1 values using 24 hour urine results where available.

   -Post baseline assessments will prioritize the 24 hour results where available. Spot urine values will be used when 24 hour assessments are not available.
3. A sensitivity analysis will be conducted using the same approach as the primary analysis, however, for subjects who have been identified as taking non-allowed medications, all data after the initiation of the non-allowed medication will be imputed using the last observation prior to the initiation of the non-allowed medication.

Per-Protocol Analysis of UPCR

The primary analysis of UPCR during the double-blind period will be run using the Per-Protocol population.

Responder Analyses

The response rate across dose groups for patients achieving 30% reduction in UPCR (whenever available 24-hour urine evaluations will be used) from baseline at Week 12 will be calculated, with the number of subjects in the respective treatment group in the ITT (or PP) population being the denominator. The 90% Clopper-Pearson exact CIs will be estimated for the response rates in each treatment group. The estimated difference and its associated 90% CIs of response rates between each of the CCX140-B (5, 10, or 15 mg) groups and the placebo group will be provided using stratified analysis using the Newcombe hybrid-score method. The Stratification factors are the same as used in the randomization: UPCR <3.5 g protein/g creatinine versus UPCR ≥3.5 g protein/g creatinine at baseline and by the current use of glucocorticoids and/or immunosuppressive medications (yes vs no) if there are enough responders. If there are not enough patients in any strata, the stratification variable will be removed from the model.

Non-responder imputation for non-allowed medications:

All subjects who started new therapy or increased the doses of an existing therapy that is clinically significant and was not allowed per protocol will be imputed as non-responders for the responder analysis. For example, the new use or clinically significant increase doses of an angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB) or other blocker of the renin angiotensin aldosterone system (RAAS) or new use of glucocorticoids, a calcineurin inhibitor or other immunomodulatory or immunosuppressive therapy will be reviewed before database lock.

Dose-Response Analysis

To demonstrate the dose-response relationship between CCX140-B treatment (including placebo) and the primary endpoint, a Multiple Comparison Procedure – Modelling (MCP-MOD) approach (Bretz et al., 2005) will be carried out. This analysis allows for uncertainty in the dose-response relationship through inclusion of contrasts from multiple pre-specified candidate models to assess dose-response. If a dose-response relationship exists, then the primary efficacy endpoint will be estimated in each of the treatment groups using the selected dose-response models. Four candidate models will be considered for the primary analysis. The models include a linear model, a logistic model, a quadratic model and an Emax model. Within each model, dose-response will be tested using dese levels of 0 (placebo), 1 (CCX140-B 5mg), 2 (CCX140-B 10mg) and 3 (CCX140-B 15mg).

The MCP-Mod procedure requires pre-specified parameter estimates for the candidate models based on available information in order to derive optimum contrast coefficients for testing the null hypothesis that a dose-response does not exist in any of the candidate models. The procedure will be carried out by the R package MCPMod (Bornkamp et al., 2017).

Point estimates and the corresponding 90% CIs from the selected dose-response models will be displayed.

3.4.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include eGFR calculated by CKD-EPI cystatin C equation, CKD-EPI Creatinine equation, CKD-EPI Creatinine-Cystatin C equation and MDRD Creatinine equation. They will be summarized by treatment group over time using descriptive statistics. The analysis of these endpoints may be performed using a mixed-effects model for repeated measures (MMRM) with treatment group, visit, and treatment-by-visit interaction as factors, and baseline value and age as covariates. Point estimates, standard errors, the corresponding 90% confidence intervals and p-values for the differences between treatment groups will be displayed. The treatment comparisons of most interest will be the Least squares (LS) means contrasts of treatment difference at Week 12 and Week 24. In the MMRM model, missing data will not be imputed. For sensitivity analysis, the change in eGFR from baseline may also be analyzed using an analysis of covariance (ANCOVA) model, including treatment group as a factor and baseline value and age

as covariates. Missing data will be imputed by the last observation carried forward (LOCF) method. LS means, standard errors, 90% confidence intervals and p-values for the differences between treatment groups will be displayed. Secondary efficacy endpoints also include the proportion of subjects achieving complete/partial renal remission at Weeks 12 and 24 as defined in section 2.3.2. The proportion will be calculated using the number of subjects in the respective treatment group in the ITT (or PP) population as the denominator. The 90% Clopper-Pearson exact CIs will be estimated for the proportion in each treatment group. The between group comparison will also be carried out using the Newcombe hybrid-score method with a two-sided significance level of 0.10.

Stratified analyses will be conducted for testing difference in proportions between groups. The stratification variables are defined below as used in the randomization stratification. The stratification factor values as collected in the electronic case report forms (eCRFs) will be used for all stratified efficacy analyses, subgroup analyses and summaries of baseline characteristics.

- UPCR <3.5 g protein/g creatinine at baseline versus UPCR ≥3.5 g protein/g creatinine at baseline;
- Current use of glucocorticoids/immunosuppressive medications (yes vs. no).

If there is not enough patients in any strata, the stratification variable will be removed from the model.

Analysis of Duration of Response

Duration of response analysis will be done only for the responders. The time of duration of response is defined as the time from the initial response of PR or CR to disease progression (not PR or CR). For the subjects without disease progression, the time will be censored at the last clinical assessment. K-M estimate of median time and 90% CI will be provided. If there is not enough responders, this analysis will not be conducted. This analysis may be applied to the responder analyses, such as responders of 30% and 40% reduction of proteinuria.

Combining CCX140-B dose groups:

CCX140-B doses groups maybe combined to conduct pooled analysis if the efficacy responses are similar, i.e. all CCX 140 dose groups, and 10 mg and 15 mg BID combined.

Proteinuria changes based on 24 our urine collection (see also section 3.4.1):

Proteinuria analyses of UPCR and UACR described above that were derived from spot urine will be repeated for 24-hour urine analyses if available.

3.4.3 Exploratory Efficacy Endpoints

The exploratory endpoints in section 2.3.3 will be summarized by treatment group over time using descriptive statistics, including MCP-1 levels by treatment group.

An exploratory analysis of UPCR using the same MMRM analysis method as described in Section 3.4.1 will be carried out with the addition of baseline urinary MCP-1 to creatinine ratio and baseline plasma MCP-1 as covariates.

3.5 Pharmacokinetic and Pharmacodynamic Marker Analysis

3.5.1 Data Assembly

The concentration data of CCX140 as reported by the respective bioanalytical group will be used without rounding for all analysis.

Subjects with major protocol deviation such as PK deviation or compliance issues may be excluded from the PK analyses (i.e. descriptive statistics) upon agreement with the Sponsor on case by case basis but all data will be listed. Values that are excluded from the analysis will be footnoted appropriately.

The following general rules should apply for handling missing data or concentration below the lower limit of quantification (BLQ) on Day 1:

- All BLQs will be set to “0” for Day 1 visit.
- If the BLQ occurs between 2 quantifiable drug concentrations within a full PK profile for Day 1 visit, the BLQ is excluded from all PK assessments.
- Missing pre-dose concentrations on Day 1 will be set as “0” and included in PK evaluation
- Missing post-dose values on Day 1 will not be imputed and will be excluded from PK evaluation
- Values that are excluded from the analysis will be documented appropriately.
- Pre-dose values on Day 1 that are greater than 5% of C_{max} will be documented. A sensitivity analysis (with inclusion and exclusion of the subjects with the pre-dose concentration >5% of C_{max}) will be presented and documented in the study report.

The following general rules should apply for handling missing or BLQ data on Day 15:

- If the BLQ occurs between 2 quantifiable drug concentrations within a full PK profile for Day 15 visit, the BLQ is excluded from all PK assessments.
- Missing pre-dose concentrations on Day 15 will be not imputed and excluded from PK evaluation. In case of missing pre-dose concentration on Day 15, AUCs on Day 15 will not be calculated for this subject.
- Missing post-dose values on Day 15 will not be imputed and will be excluded from PK evaluation
- Values that are excluded from the analysis will be documented appropriately.

The sample time of the pre-dose samples on Day 1 and Day 15 will be uniformly considered as

time "0".

For the trough concentration for post-Day 1 visits and at 2 days, 7 days and 14 days after the last dose of study drug, all missing or BLQ concentration will not be imputed and will be excluded from the descriptive summary.

For Day 1 and Day 15 visits, individual PK plots or individual PK parameters, since there is no collection window specified for post-dose PK sampling, will be based on actual times recorded. For concentration versus time descriptive statistical summaries and mean plot preparation, nominal time points will be used. If the difference of post-dose sampling time is > 5 minutes from the nominal sampling times for time points <2 hours or >5% for time points ≥2 hours, the corresponding concentration data will be excluded from the concentration summary and mean plot preparation, but will still be used in the individual plots and the calculation of PK parameter.

For Day 1 and Day 15 visits, if the pre-dose PK sample is collected after dosing, the corresponding concentration will be treated as a post-dose value and will be used for individual plotting and PK parameter calculation.

CCX140 plasma concentration results will be used to calculate trough plasma concentrations (C_{min}) over the course of the clinical trial.

For post-Day 1 visits, the allowable time window for PK trough sampling is ± 3 hours (i.e. 25% of dosing interval of 12 hours) for 10 or 15 mg BID dosing groups (C and D), and ± 6 hours (i.e. 25% of dosing interval of 24 hours) for 5 mg QD dosing group (B) in the blinded treatment study phase (up to Week 12). However, in the open label extension phase (Week 13 to Week 24), all subjects will be given 15 mg BID, therefore, the allowable time window for PK trough sampling is ± 3 hours for all subjects. If the exact time (measured from dosing) is outside of the collection window, the corresponding concentration will be excluded from trough concentration versus time descriptive statistical summaries and median plot preparation, but will still be used in the individual plots.

For the PK blood samples collected at 2 days, 7 days and 14 days following the last dose of study drug, as well at the Follow-up Visit, the actual sampling time should not exceed 5% of the nominal sampling time. If the exact time (measured from dosing) is outside of the collection window, the corresponding concentration will be excluded from concentration versus time descriptive statistical summaries and median plot preparation, but will still be used in the individual plots.

Non-numerical readouts except BLQ [e.g. NA (not available) or NRE (not reliable)] will be set as missing and will not be included in the PK evaluation.

3.5.2 Pharmacokinetic Concentration

The individual plasma concentration of CCX140 will be listed.

For subjects with serial samples collected (pre-dose and at 0.5, 1, 2, 3, 4, and 6 hour post-dose after the CCX140-B dose on Day 1 and on Day 15):

- Individual plasma concentrations of CCX140 will be plotted on a linear and semi-logarithmic scale against actual sampling time points;
- Concentration data will be summarized by treatment at each nominal time point descriptively;

- Mean (±SD) plasma concentrations of CCX140 will be plotted on a linear and semi-logarithmic scale against nominal time points by treatment.

For subjects with pre-dose sample collected (Post-Day 1 visits):

- Individual plasma concentrations of CCX140 will be plotted by treatment on a linear and semi-logarithmic scale against visits;
- Trough concentration data, within allowable time windows, will be summarized by treatment at each visit descriptively.
- In addition, median trough concentrations (C_{min}) of CCX140 will be plotted overlaid with the scatter plot of individual trough concentrations by treatment on a linear and semi-logarithmic scale against visits.
- The average steady state trough concentration of CCX140 for each individual subject will be calculated for a to-be-defined steady-state time period (each subject needs to have at least 3 time points in this steady state period for the calculation). The global average steady state trough concentration of CCX140 will be listed and summarized descriptively by treatment. Box and whisker plots will be prepared by treatment for comparison.

For subjects with samples collected at 2 days, 7 days and 14 days following the last dose of study drug, as well at the Follow-up Visit:

- Individual plasma concentrations of CCX140 will be plotted on a linear and semi-logarithmic scale against actual sampling time points by the treatment in blinded phase;
- Concentration data will be summarized by the treatment in blinded phase at each nominal time point descriptively;
- Mean (±SD) plasma concentrations of CCX140 will be plotted on a linear and semi-logarithmic scale against nominal time points by the treatment in blinded phase.

3.5.3 Pharmacokinetic Parameter

For subjects with serial samples collected (pre-dose and at 0.5, 1, 2, 3, 4, and 6 hour post-dose after the first CCX140-B dose on Day 1 and on Day 15), C_{max}, T_{max}, and AUC_{0-6} will be determined based on individual CCX140 plasma concentration data. AUC_{0-12} or AUC_{0-24} will be determined for Day 15 assuming pre-dose level being the same as the concentration at the end of the dosing interval.

Parameters	Description
C_{max}	Maximum drug concentration after the first dose; observed directly from the data. If not unique, then the first maximum concentration is used
T_{max}	Time to C_{max}
AUC_{0-6}	Area under the concentration-time curve (AUC) from time 0 to 6 hours post-dose. For 6 hours post-dose sample, the corresponding observed concentrations will be used for AUC calculation if the difference of the actual time point is <5% from the nominal time point; otherwise, the concentration at the nominal 6-hour time point will be predicted and then used for the AUC calculation.
AUC_{0-12}	AUC from time 0 to 12 hours post-dose on Day 15 only following 10 or 15 mg BID dosing (Groups C and D). The concentration at 12-hour time point will be assumed to be the same as the pre-dose level.
AUC_{0-24}	AUC from time 0 to 24 hours post-dose on Day 15 only following 5 mg QD dosing (Group B). The concentration at 24-hour time point will be assumed to be the same as the pre-dose level.

PK parameter calculations will be based on all seven continuous time points from Day 1 and Day 15 (including Time 0). The PK parameters of those subjects with less than seven continuous time points are listed as NA.

Plasma PK parameters will be calculated by standard non-compartmental analysis. The actual collection times will be used for PK parameter calculation. The linear trapezoidal rule method (equivalent to the Linear Trapezoidal Linear Interpolation in WinNonlin® Professional) will be used in the computation of AUCs.

PK parameters will be listed and summarized by treatment descriptively.

The relationship between PK parameters and renal function based on eGFR, UPCR and UACR change of UPCR or UACR from baseline, and serum albumin will be evaluated through an exploratory analysis and summarized in a separate report.

3.6 Safety Assessment

Safety analyses will be performed for the Safety Population. All safety assessments will be based on actual treatments received by participants.

3.6.1 Adverse Events (AEs)

An overview of AEs will be provided including counts and percentages of subjects (and event counts) with the following:

- Any TEAEs (overall and by maximum severity)
- Any study drug related TEAEs (overall and by maximum severity)
- Any treatment-emergent serious AEs (TESEAEs)
- Any TEAEs leading to discontinuation of study drug
- Any AEs leading to death

Counts and percentages of subjects (and event counts) will also be presented by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1 any TEAEs and TESEAEs for 3 Safety Populations separately. Counts and percentages of subjects (and event counts) will also be presented by PT in decreasing frequency for any TEAEs and TESEAEs for 3 Safety Populations (see 3.2.4 for definitions) separately.

TEAEs for the Safety Population in each period are defined as an event with a start date on or after the first study drug treatment in each period and up to the final observation in each period. Treatment periods for analysis of adverse event are defined in Section 3.2.4. TEAEs for the All CCX140-B Treated Population are defined as an event with a start date on or after the first dose of CCX140-B up to the final observation.

Listings will be presented specifically for SAEs and TEAEs leading to discontinuation of study drug.

The severity of AEs was assessed by the investigator using the following protocol definitions:

- 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)

3.6.2 Clinical Laboratory Tests

Laboratory results and change from baseline will be summarized for each treatment group by visit using descriptive statistics. Summaries will be limited to values assessed by the Central Laboratory. Shift tables from baseline to subsequent study visits will also be generated. Counts and percentages of laboratory values outside the normal reference range will be summarized in the double-blind period and open-label period respectively.

Listings of laboratory values collected at local laboratories will be provided. Laboratory values outside the reference ranges will be flagged in the listings.

3.6.3 Vital Signs

Vital signs parameters will be summarized using descriptive statistics for each treatment group by visit. The change from baseline will also be summarized.

3.6.4 Electrocardiograms

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

3.6.5 Physical Examinations

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

3.6.6 ACTG-BPNST

ACTG-BPNST results and change from baseline will be summarized for each treatment group by visit. Listings of individual ACTG-BPNST will also be provided.

4 DATA MONITORING COMMITTEE

A Data Monitoring Committee (DMC) monitored the safety of subjects over the course of the study. The DMC met once or more during the subject enrollment period to examine the unblinded accumulated safety data. Subjects, investigators, site staff and in general all personnel directly involved in the conduct of the study will remain blinded to the subjects' treatment assignment until the completion of the study.

Details related to the DMC responsibilities, authorities, and procedures were documented in a DMC charter which was finalized prior the first subject being enrolled in the study.

5 ANALYSIS TIMING

5.1 Interim Analysis

No interim analyses were planned.

5.2 Final Analysis

After all data is cleaned and the study database is declared final, the final analysis will be generated. In addition to TFLs, SDTM data and ADaM data along with associated files will be provided. Associated files may include: annotated case report forms (CRFs), SDTM specifications, SDTM programs, ADaM specifications, ADaM programs, TFL programs, and CDISC Define packages for both SDTM and ADaM data and reviewer's guides.

6 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

Per ChemoCentryx's request, responder analysis and MCP-MOD have been added for the analysisof the primary efficacy endpoint.

7 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.3 or higher. All available data will be presented in subject data listings which will be sorted by subject and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.

APPENDIX A: REFERENCES

[1] Bretz F, Pinheiro JC, Branson M (2005). Combining Multiple Comparisons and Modeling Techniques in Dose-Response Studies. *Biometrics, 61*, 738-748.

[2] Bornkamp B, Pinheiro J and Bretz F (2017). *MCPMod: An R Package for the Design and Analysis of Dose-Finding Studies*. R package version 1.0-10, https://CRAN.R-project.org/package=MCPMod.