PROTOCOL

TITLE PAGE

Study Title:	An Open Label, Intra-Subject Dose Escalation Study of CCX140-B in Subjects with Primary Focal Segmental Glomerulosclerosis (FSGS) and Nephrotic Syndrome
Protocol Number:	CL012_140
Investigational Product:	CCX140-B, a selective antagonist of human C-C chemokine receptor 2 (CCR2)
Indication:	Primary Focal Segmental Glomerulosclerosis (FSGS)
Sponsor:	ChemoCentryx, Inc.
Development Phase:	2
IND number	134007
EUDRACT number	2017-003022-32
Sponsor's Responsible Medical Officer:	[redacted] ChemoCentryx, Inc. Mountain View, California 94043, USA
Sponsor Signatory:	[redacted] Vice President, Translational Research and Clinical Development ChemoCentryx, Inc. Mountain View, California 94043, USA
Approval Date:	**15 December 2017** **17 April 2018 Amendment 1.0**

Confidential

The information contained herein is the property of the Sponsor and may not be reproduced, published or disclosed to others without written authorization of the Sponsor.

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

INVESTIGATOR SIGNATORY PAGE

Protocol Number: CL012_140

Protocol Title: An Open-Label, Intra-Subject Dose Escalation Study of CCX140-B in Subjects with Primary Focal Segmental Glomerulosclerosis (FSGS) and Nephrotic Syndrome

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 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: CL012_140

Protocol Title: An Open-Label, Intra-Subject Dose Escalation Study of CCX140-B in Subjects with Primary Focal Segmental Glomerulosclerosis (FSGS) and Nephrotic Syndrome

Medical Officer [redacted]
ChemoCentryx, Inc.
Mountain View,
California 94043, USA
Office telephone number: [redacted]
Fax number: [redacted]
Email: [redacted]

Clinical Operations Manager [redacted]
ChemoCentryx, Inc.
Mountain View, California 94043, USA
Office telephone number: [redacted]
Fax number: [redacted]
Email: [redacted]

SPONSOR SIGNATURE FOR APPROVAL

Protocol Number: CL012_140

Protocol Title: An Open-Label, Intra-Subject Dose Escalation Study of CCX140-B in Subjects with Primary Focal Segmental Glomerulosclerosis (FSGS) and Nephrotic Syndrome

[redacted]

19 Apr., 2018

Date

Vice President, Translational Research and Clinical Development

PROTOCOL AMENDMENT 1.0: SUMMARY OF CHANGES

Section(s)	Original Text	Revised Text	Rationale for Change
Synopsis (Efficacy Objectives and Endpoints)	The Primary Efficacy Objective is to evaluate the effect of CCX140-B on proteinuria in subjects with primary FSGS with nephrotic syndrome, assessed as achievement of partial or complete remission of urine protein to creatinine ratio (UPCR) through Study Week 12, where partial and complete remission are defined as follows: **Partial Remission (includes all of the following):** - reduction from baseline by ≥50 percent in UPCR -reduction in UPCR to a level that is < 3.5 g/g -serum albumin within normal range -subject may not be a treatment failure (e.g. has not received rescue therapy, has not required discontinuation of study drug) **Complete Remission (includes all of the following):** -reduction in UPCR to < 0.3 g/g -serum albumin	The Primary Efficacy Objective is to evaluate the effect of CCX140-B on proteinuria in subjects with primary FSGS with nephrotic syndrome, assessed as a median reduction from baseline of urine protein to creatinine ratio (UPCR) of at least 20%, i.e. ≥ 20%, by week 12. Secondary efficacy endpoints of this study will be assessed through Study Week 12 and through End of Treatment and include: Achievement of partial or complete remission of urine protein to creatinine ratio (UPCR): **Partial Remission (includes all of the following)** • reduction from baseline by ≥50 percent in UPCR • reduction in UPCR to a level that is < 3.5 g/g • subject may not be a treatment failure • **Complete Remission (includes all of the following)** • reduction in UPCR to < 0.3 g/g • serum albumin within normal range • For patients with abnormal serum creatinine levels at baseline, return to normal levels for that age group • For patients with normal	Moved partial and complete remission from primary to secondary objective and evaluate median reduction of UPCR as primary efficacy. This was based on discussions with lead investigators of the study and is aligned with previously observed treatment effects with CCX140-B in subjects with diabetic nephropathy. Redefined partial and complete remission based on expert input from investigators.

Section(s)	Original Text	Revised Text	Rationale for Change
	within normal range -subject may not be a treatment failure (e.g. has not received rescue therapy and has not required discontinuation of study drug)	serum creatinine levels at baseline, final value within 20% of baseline levels • subject may not be a treatment failure (e.g. has not received rescue therapy and has not required discontinuation of study drug)	
Synopsis: Primary Efficacy Objectives	eGFR, calculated by the CKD-EPI equation, based on cystatin C	eGFR, calculated by the CKD-EPI Cystatin C equation, CKD-EPI Creatinine equation, CKD-EPI Creatinine-Cystatin C equation and MDRD Creatinine equation.	To allow calculating eGFR by several equations including creatinine instead of solely Cystatin C, based on FDA recommendation in study CL011_140
Synopsis: Dose and dose adjustments	… 10 mg twice daily, then to 15 mg twice daily while monitoring efficacy …	„, 10 mg twice daily on day 15, then to 15 mg twice daily on day 43 while monitoring efficacy … If planned dose escalation to 10 mg (on day 15) or 15 mg twice daily (on day 43) was previously halted the dose may be escalated further if subjects are not considered treatment failures and who otherwise meet criteria for continuation. In such case the subject will return approximately 2 weeks later for blood draws to assess PK (AUC_{0-6}). Subjects will return 2 weeks after the PK assessment to evaluate the safety and need for further dose adjustment. Subjects who completed 12 weeks of treatment and who are not considered treatment failures and who otherwise meet criteria for continuation may be extended for up to an additional 40 weeks to assess degree and duration of response. During the extension period the dose may be adjusted if indicated based on	Clarification of procedure The full list of conditions for subjects being allowed to enter the extended treatment period was inadvertently omitted and is now provided.

Section(s)	Original Text	Revised Text	Rationale for Change
		assessment of safety, PK and efficacy. (see Table 1 and Figure 1 for guidelines). Starting with the extended treatment period (Day 85 and beyond) if the dose is adjusted upward or downward for any reason at Day 85 or during the extended treatment period the subject will return approximately 2 weeks later for blood draws to assess PK (AUC_{0-6})	
	In subjects who have achieved at least a Partial Response by Week 12 (Study Day 85), treatment may be extended for up to an additional 40 weeks to assess degree of response and duration of response. During the extension period dose may be adjusted if indicated based on assessment of safety, PK and efficacy.		
Figure 1	Blank	Added Figure 1	Added Figure 1 to accompany Table 1 for further clarification
Table 1: Dose Modification Schedule and Rules Through Study Day 85	**Day 43:** At Day 43 based on results of the Day 29 PK, the dose may be adjusted to the next higher planned dose level (15 mg twice daily for subjects receiving 10 mg twice daily; 10 mg twice daily for subjects receiving 5 mg twice daily) if all of the following are true: Subject is not a Treatment Failure, and • Subject has not achieved and maintained at least a Partial Remission, and • Projected AUC_{0-12} on the next higher planned dose level does not	**Day 43:** At Day 43 based on results of the Day 29 PK, the dose may be adjusted to the next higher planned dose level (15 mg twice daily for subjects receiving 10 mg twice daily; 10 mg twice daily for subjects receiving 5 mg once daily) if all of the following are true: • Subject is not a Treatment Failure, and • Meets all criteria for continuation: - Subject has not achieved and maintained at least a Partial Remission, and - Projected AUC_{0-12} on the next higher planned dose level does not exceed 240 µg•h/mL and - The next higher dose does not	Clarifications and standardization of all titration requirements on day 43 or beyond.

Section(s)	Original Text	Revised Text	Rationale for Change
	exceed 240 µg•h/mL • The next higher dose does not exceed the Maximum Tolerated Dose (MTD) **Day 71:** Based on results of Day 57 PK, dose will be adjusted to the next higher planned dose level if all of the following are true: The next higher dose does not exceed 15 mg twice daily or the MTD, whichever is lower • Subject has not previously been treated at the next higher dose and required downward dose adjustment • Subject is not a Treatment Failure, and • Subject has not achieved and maintained at least a Partial Remission, and • Projected AUC_{0-12} on the next higher planned dose level does not exceed 240 µg•h/mL	exceed the Maximum Tolerated Dose (MTD) **Day 71:** Based on results of Day 57 PK, subjects can be considered for dose escalation if all of the following are true: • Subject is not already treated with 15 mg twice daily and ● Subject did not require previous downward dose adjustment and • Subject is not a Treatment Failure, and• Meets all criteria for continuation: - Subject has not achieved and maintained at least a Partial Remission, and - Projected AUC_{0-12} on the next higher planned dose level does not exceed 240 µg•h/mL and - The next higher dose does not exceed the Maximum Tolerated Dose (MTD)	
Table 1: Dose Modification Schedule and Rules Through Study Day 85	**Day 85 and beyond:** If dose is adjusted upward or downward for any reason at Day 85 or during the extended treatment period the subject will return approximately 2 weeks later for blood draws to assess PK (AUC_{0-6}) and will return 2 weeks after assessment of PK to assess safety and	**Day 85 and beyond:** If dose is adjusted upward or downward for any reason at Day 85 or during the extended treatment period the subject will return approximately 2 weeks later for blood draws to assess PK (AUC_{0-6}). Subjects will return 2 weeks after the PK assessment to evaluate the safety and need for further dose	Administrative change

Section(s)	Original Text	Revised Text	Rationale for Change
	need for further dose adjustment.	adjustment.	
Synopsis: Extended Treatment Period	Subjects who are not Treatment Failures as of Week 12 may continue extended treatment under any of the following conditions • Have achieved and have sustained Partial or Complete Remission by Week 12 • Have achieved a significant response of at least 30% decline in proteinuria by Week 12 and, in the opinion of the Investigator, remain candidates for investigational treatment • No longer have nephrotic syndrome, independent of the % reduction in proteinuria and, in the opinion of the Investigator, remain candidates for investigational treatment	Subjects are eligible for the extended treatment period under the following conditions: 1. Not considered treatment failures as of Week 12 2. And, in the opinion of the Investigator, remain candidates for investigational treatment 3. And any of the conditions below apply: • Partial or Complete Remission by Week 12 • Response with ≥20% reduction in UPCR by Week 12 • No longer have nephrotic syndrome	Clarifications & Adjustment from at least 30% to ≥20% reduction in UPCR. This is in alignment with lead investigators and previously observed treatment effects in patients with diabetic nephropathy.
Synopsis: Extended Treatment Period	Subjects who are receiving a dose that is less than 15 mg twice daily at Week 12 can be considered for further dose escalation if all of the following are true: • Subject has not previously required dose reduction due to toxicity or adverse event • Subject has not achieved complete	Subjects can be considered for dose escalation if all of the following are true: • Subject is not already treated with 15 mg twice daily and Subject did not require previous downward dose adjustment and • Subject is not a Treatment Failure, and • Meets all criteria for continuation: - Subject has not achieved and	Clarifications and standardization of all titration requirements in extended treatment period with the initial treatment period.

Section(s)	Original Text	Revised Text	Rationale for Change
	remission • The next dose has not been determined to be above the maximally tolerated dose • Based on PK analysis the exposure (AUC_{0-12}) at the next dose is not projected to exceed 240 µg•h/mL. • Subject is not a Treatment Failure	maintained at least a Partial Remission, and - Projected AUC_{0-12} on the next higher planned dose level does not exceed 240 µg•h/mL and - The next higher dose does not exceed the Maximum Tolerated Dose (MTD)	
Synopsis: Dose Modification Rules	**Dose Modification Rules <u>for individual subjects</u>** Discontinue treatment with CCX140-B when a subject experiences any of the following events confirmed by repeat measurement after 2 weeks: 50% increase from baseline in serum creatinine value, confirmed by repeat measurement after 2 weeks If baseline UPCR < 6.0 g/g and increase of >3.0 g/g; if UPCR ≥6.0 g/g an increase of 50%	**Dose Modification Rules <u>for individual subjects</u>** Discontinue treatment with CCX140-B when a subject experiences any of the following events confirmed by repeat measurement after 2 weeks: • Progression of renal disease, defined as eGFR that is both below 60 ml/min/1.73 m^2 and is confirmed to represent at least 30% decline in eGFR from baseline • Requirement for rescue with glucocorticoids, other new immunomodulatory or immunosuppressive therapy, plasmapheresis or dialysis • Pre-specified adverse event or laboratory abnormality that, per Protocol, requires permanent discontinuation of study CCX140-B Any other treatment-related adverse event, laboratory evidence of toxicity or intolerance that in the judgment of the investigator, warrants permanent discontinuation of	Added per recommendation from FDA

Section(s)	Original Text	Revised Text	Rationale for Change
		CCX140-B Consider discontinuation of treatment when a subject experiences any of the following events: An increase of serum ALT to >3xULN should be followed by repeat testing within 48 to 72 hours of all four of the usual serum measures (ALT, AST, ALP, and TBL) to confirm the abnormalities and to determine if they are increasing or decreasing. Discontinuation of treatment should be considered if: • ALT or AST >8xULN • ALT or AST >5xULN for more than 2 weeks • ALT or AST >3xULN and (TBL >2xULN or INR >1.5) • ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
Synopsis (Inclusion and Exclusion criteria)	See body text of the protocol	See body text of the protocol	
Synopsis (Efficacy Assessment) and Time & Events Table	• Urine protein:creatinine ratio (UPCR) and urine:albumin ratio (UACR), assessed in a sample drawn from a 24 hour collection is required at baseline and Study Week 12 (see schedule). At other time points defined in the Time and Events table, 24 hour collection is preferred. However, at these visits, a first morning void sample	• Urine protein:creatinine ratio (UPCR) and urine:albumin ratio (UACR), assessed in a sample drawn from a 24 hour collection is required at baseline and Study Week 12 (see schedule). At other time points defined in the Time and Events table, 24 hour collection is preferred. However, at these visits, a midstream first morning void sample may be used for assessments if a 24hr urine sample is not available	Emphasize importance of 24h urine collection. Allow for collection of midstream urine during visit on days when 24h urine is not mandatory and therefore not available.

Section(s)	Original Text	Revised Text	Rationale for Change
	may be used for assessments.		
Synopsis (Efficacy Assessment)	eGFR calculated from serum creatinine usingby the chronic kidney disease-epidemiology collaboration (CKD-EPI equation based on cystatin C; Levey et al, 2009)	Change from baseline in eGFR calculated by the CKD-EPI Cystatin C equation, CKD-EPI Creatinine equation, CKD-EPI Creatinine-Cystatin C equation and MDRD Creatinine equation	To allow calculating eGFR by several equations including creatinine instead of Cystatin C only, based on FDA recommendation in study CL011_140
Time and Events Table: Dose	(Days1-14) 5 mg bid (Days 15 -29) 10 mg bid	(Days1-14) 5 mg bid (Days 15 -43) 10 mg bid	Although PK blood draws will occur on Day 29 the dose modification is not scheduled to occur until Day 43. This was an error in the Time and Events Table
Time and Events Table: ACTG-BPNST	blank	Added to study days 1- 52	ACTG-BPNST evaluation was inadvertently omitted in Section 6 and the Time and Events table
Time and Events Table: Footnote 1	Organ transplantation including renal transplantation should be captured in medical history.	Removed	Since organ transplants are exclusionary, subjects that have had transplants will not enroll. Therefore, this footnote is not applicable.
Section 2.1 Primary Efficacy Objective	The Primary Efficacy Objective is to evaluate the effect of CCX140-B on proteinuria in subjects with primary FSGS with nephrotic syndrome, assessed as achievement of partial or complete remission of urine protein to creatinine ratio (UPCR) through Study Week 12, where partial and complete remission are defined as follows: Partial Remission (includes all of the following)	The Primary Efficacy Objective is to evaluate the effect of CCX140-B on proteinuria in subjects with primary FSGS with nephrotic syndrome, assessed as a median reduction from baseline of urine protein to creatinine ratio (UPCR) of at least 20%, i.e. ≥ 20%, by week 12.	Move partial and complete remission from primary to secondary objective and evaluate median reduction of UPCR as primary efficacy. This change is based on discussions with lead investigators of the study and is aligned with previously observed treatment effects with CCX140-B in subjects with diabetic nephropathy.

Section(s)	Original Text	Revised Text	Rationale for Change
	Reduction from baseline by ≥50 percent in UPCR Reduction in UPCR to a level that is <3.5 g/g Serum albumin within normal range Subject may not be a treatment failure (e.g. has not received rescue therapy, has not required discontinuation of study drug) Complete Remission (includes all of the following) Reduction in UPCR to <0.3 g/g Serum albumin within normal range Subject may not be a treatment failure (e.g. has not received rescue therapy and has not required discontinuation of study drug)		
Section 2.2 Secondary Efficacy Objective	None	The secondary efficacy objectives of this study will be assessed at Study Week 12 and through End of Treatment and include: 1. Achievement of partial or complete remission of urine protein to creatinine ratio (UPCR) through Study Week 12, where partial and complete remission are defined as follows: Partial Remission (includes all of the following) • reduction from baseline by ≥50	Move partial and complete remission from primary to secondary efficacy objective and evaluate median reduction of UPCR as primary efficacy instead. This change is based on discussions with lead investigators of the study and is aligned with previously observed treatment effects with CCX140-B in subjects with diabetic nephropathy.

Section(s)	Original Text	Revised Text	Rationale for Change
		percent in UPCR • reduction in UPCR to a level that is < 3.5 g/g • subject may not be a treatment failure (e.g. has not received rescue therapy, has not required discontinuation of study drug) Complete Remission (includes all of the following) • reduction in UPCR to < 0.3 g/g • serum albumin within normal range • For patients with abnormal serum creatinine levels at baseline, return to normal levels for that age group • For patients with normal serum creatinine levels at baseline, final value within 20% of baseline levels • subject may not be a treatment failure (e.g. has not received rescue therapy and has not required discontinuation of study drug)	Redefined partial and complete remission based on expert input from investigators
Section 2.2: Secondary Efficacy Objective	eGFR, calculated by the CKD EPI equation, based on cystatin C	eGFR, calculated by the CKD-EPI Cystatin C equation, CKD-EPI Creatinine equation, CKD-EPI Creatinine-Cystatin C equation and MDRD Creatinine equation.	To allow calculating eGFR by several equations including creatinine instead of solely Cystatin C, based on FDA recommendation in study CL011_140
Section 2.3 Safety Objectives	4. AIDS Clinical Trials Group Brief Peripheral Neuropathy Screen (ACTG BPNS)	4. AIDS Clinical Trials Group Brief Peripheral Neuropathy Screening Tool (ACTG BPNST): To assess potential signs and symptoms of peripheral neuropathy the ACTG BPNST will be completed by study personnel or the study investigator as specified in the Time and Events table.	The acronym ACTG-BPNS was changed to ACTG-BPNST as this was a typographical error. Further specification was added that the study personnel or study investigator will complete the ACTG-BPNST.

Section(s)	Original Text	Revised Text	Rationale for Change
Section 3.1: Initial Treatment Phase	During the initial 12 weeks of treatment, dose will be escalated from 5 mg twice daily to 10 mg twice daily on Study Day 15, then to 15 mg twice daily on Study Day 43, unless dose escalation is stopped or reversed due to any of the following: 1. Achievement of Partial Response 2. Exposure that exceeds, or is projected to exceed, the maximal allowable exposure defined for the study 3. Safety	During the initial 12 weeks of treatment, dose will be escalated from 5 mg twice daily to 10 mg twice daily on Study Day 15, then to 15 mg twice daily on Study Day 43, if subjects are not considered treatment failures and who otherwise meet criteria for continuation (Table 1, Figure 1).	Clarifications and standardization of all titration requirements.
Section 3.1: Initial Treatment Phase	After 12 weeks, dose may be escalated further if escalation was previously halted prior to 15 mg twice daily solely due to achievement of Partial Response, and if Complete Response has not been achieved.	If planned dose escalation to 10 mg (on day 15) or 15 mg twice daily (on day 43) was previously halted the dose may be escalated further if subjects are not considered treatment failures and who otherwise meet criteria for continuation (Table 1, Figure 1). In such case the subject will return approximately 2 weeks later for blood draws to assess PK (AUC_{0-6}). Subjects will return 2 weeks after the PK assessment to evaluate the safety and need for further dose adjustment.	Language was missing in this section although synopsis allowed for later dose escalation. Previous text referring to the period ("after 12 weeks…") applies to the extended treatment phase and was therefore deleted from Section 3.1.1
Section 3.1: Table 2: Dose Modification Schedule and Rules Through Study Day 85	Table 2 was deleted as duplication from Table 1.	Reference is made to table 1 in various sections of the main body of the protocol.	Delete Duplication
Section 3.1.1: Day 85 and beyond	Blank	If dose is adjusted upward or downward for any reason at Day 85 or during the extended treatment period the subject will return approximately 2 weeks later for blood draws to assess PK (AUC_{0-6}). Subjects will return 2 weeks after the PK	Section 3.1.2 was added to make synopsis consistent with main body text of protocol.

Section(s)	Original Text	Revised Text	Rationale for Change
		assessment to evaluate the safety and need for further dose adjustment.	
Section 3.1.2: Extended Treatment Period	Subjects who are not Treatment Failures as of Week 12 may continue extended treatment under any of the following conditions: • Have achieved and have sustained Partial or Complete Remission by Week 12 • Have achieved a significant response of at least 30% decline in proteinuria by Week 12 and, in the opinion of the Investigator, remain candidates for investigational treatment • No longer have nephrotic syndrome, independent of the % reduction in proteinuria and, in the opinion of the Investigator, remain candidates for investigational treatment	Subjects are eligible for the extended treatment period under the following conditions: 1) Not considered treatment failures as of Week 12 2) And, in the opinion of the Investigator, remain candidates for investigational treatment 3) And any of the conditions below apply: • Partial or Complete Remission by Week 12 • Response with ≥20% reduction in UPCR by Week 12 • No longer have nephrotic syndrome	Clarifications & Adjustment from at least 30% to ≥20% reduction in UPCR. This is in alignment with lead investigators and previously observed treatment effects in patients with diabetic nephropathy.
Section 3.1.2: Extended Treatment Period	Subjects who are receiving a dose that is less than 15 mg twice daily at Week 12 (Day 85) can be considered for further dose escalation if all of the following are true: • Subject has not previously required dose reduction due to toxicity or adverse event • Subject has not	Subjects can be considered for dose escalation if all of the following are true: • Subject is not already treated with 15 mg twice daily and • Subject did not require previous downward dose adjustment • Subject is not a Treatment Failure, and • Meets all criteria for	Clarifications and standardization of all titration requirements in extended treatment period with the initial treatment period.

Section(s)	Original Text	Revised Text	Rationale for Change
	achieved complete remission • The next dose has not been determined to be above the maximally tolerated dose • Based on PK analysis the exposure (AUC_{0-12}) at the next dose is not projected to exceed 240 µg•h/mL. • Subject is not a Treatment Failure	continuation: - Subject has not achieved and maintained at least a Partial Remission, and - Projected AUC_{0-12} on the next higher planned dose level does not exceed 240 µg•h/mL and - The next higher dose does not exceed the Maximum Tolerated Dose (MTD)	
Section 3.2: Dose Modification Based on PK Exposure	Blank	If planned dose escalation to 10 mg (on day 15) or 15 mg twice daily (on day 43) was previously halted the dose may be escalated further if subjects are not considered treatment failures and who otherwise meet criteria for continuation (Table 1, Figure 1). In such case the subject will return approximately 2 weeks later for blood draws to assess PK (AUC_{0-6}). Subjects will return 2 weeks after the PK assessment to evaluate the safety and need for further dose adjustment.	Language was missing in this section although synopsis allowed for later dose escalation
Synopsis and Section 4.2: Inclusion criteria	2. Renal biopsy findings consistent with diagnosis of primary focal segmental glomerulosclerosis (FSGS), including all histologic subtypes; subjects with genetic risk factors with presentations that are otherwise consistent with primary FSGS may be enrolled	2. Renal biopsy findings consistent with diagnosis of focal segmental glomerulosclerosis (FSGS), and consistent with primary FSGS based on presentation of histopathology, medical history, and clinical course; subjects with genetic risk factors with presentations that are otherwise consistent with primary FSGS may also be enrolled	Clarification of primary FSGS
Synopsis and Section 4.2: Inclusion criteria	2. Renal biopsy findings consistent with diagnosis of primary focal segmental glomerulosclerosis	2. Renal biopsy findings consistent with diagnosis of focal segmental glomerulosclerosis (FSGS), and consistent with primary FSGS based on presentation of	Clarification of primary FSGS

Section(s)	Original Text	Revised Text	Rationale for Change
	(FSGS), including all histologic subtypes; subjects with genetic risk factors with presentations that are otherwise consistent with primary FSGS may be enrolled	histopathology, medical history, and clinical course; subjects with genetic risk factors with presentations that are otherwise consistent with primary FSGS may also be enrolled	
Synopsis and Section 4.2: Inclusion criteria	4. Estimated glomerular filtration rate (eGFR, calculated using the CKD-EPI creatinine equation) >30 mL/min/1.73m2	4. Estimated glomerular filtration rate (eGFR) >30 mL/min/1.73m2, as calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD_EPI) equation (using creatinine or cystatin C)	Specify equation source for the calculation of eGFR
Synopsis & Section 4.3: Exclusion Criteria #4	Blank	4. Histological FSGS subtype of collapsing variant	Added exclusion per discussion with lead investigator as these patients will not respond to any medical therapy.
Synopsis & Section 4.3: Exclusion Criteria #5 and #6 related to rituximab and other anti-CD20 monoclonal antibodies	4. Use of rituximab within 20 weeks prior to screening with recovery of CD20+ B cell population; if rituximab was used between 20 and 52 weeks prior to screening, recovery of CD20 positive B cell population must be confirmed; where recovery is defined as within normal limits or within 70% of pre-treatment baseline, whichever is least	5. Subjects who initiated, discontinued or changed dose of rituximab or other anti-CD20 monoclonal antibodies within 16 weeks (4 months) prior to screening are excluded. Patients who initiated treatment with rituximab or other anti-CD20 monoclonal antibodies >16 weeks (4 months) prior to screening are permitted if deemed safe by the investigator and only if they are intended to remain on continued, unchanged therapy at a dosing interval that has been documented to achieve continuous B cell depletion for the given patient. UPCR assessments up to 1 year prior to screening (if available) that were performed in these patients as part of the clinical routine should be documented in the medical history. 6. Subjects who discontinued Rituximab or other anti-CD20 monoclonal antibodies >16	Exclusion #4 became #5 and addition of #6 due to additional exclusion criteria. Specify exclusion/use Rituximab and other anti-CD20 monoclonal antibodies. Added exclusion per discussion with lead investigator as these patients will not respond to any medical therapy. Per discussion with lead investigators a subgroup treated chronically with anti-CD20 monoclonal antibodies should be included in the study target population as these patients have a high unmet medical need despite antibody treatment.

Section(s)	Original Text	Revised Text	Rationale for Change
		weeks (4 months) prior to screening without confirmed recovery of CD20+ B cell population to within normal range are excluded. Patients who discontinued rituximab or other anti-CD20 monoclonal antibodies >16 weeks (4 months) prior to screening with confirmed recovery of CD20+ B cell population to within normal range are permitted in the study. UPCR and other urine protein assessments up to 1 year prior to screening (if available) that were performed in these patients as part of the clinical routine should be recorded in the medical history.	
Synopsis & Section 4.3: Exclusion Criteria - #7 related to calcineurin inhibitors, or other immunotherapy	5. Increase in dose or introduction of new calcineurin inhibitors, or other immunotherapy, within 12 weeks prior to screening; dose reductions to maintain calcineurin inhibitors at optimal safe levels are permitted	7. Subjects who initiated or increased the dose of calcineurin inhibitors, or other immunotherapy, within 12 weeks prior to screening are excluded; dose reductions to maintain calcineurin inhibitors at optimal safe levels are permitted. Patients who initiated a treatment with calcineurin inhibitors, or other immunotherapy >12 weeks are permitted. UPCR and other urine protein assessments up to 1 year prior to screening (if available) that were performed in these patients as part of the clinical routine should be recorded in the medical history.	Further clarification on intended exclusion/use of calcineurin inhibitors, or other immunotherapy.
Synopsis & Section 4.3: Exclusion Criteria - #8 related to Glucocorticoids	6. Glucocorticoids at dose greater than 10 mg/day prednisone equivalent within 4 weeks prior to screening	8. Subjects taking glucocorticoids at dose greater than 10 mg/day prednisone equivalent within 4 weeks prior to screening are excluded.	Clarification
Synopsis & Section 4.3: Exclusion Criteria - #16	14. Evidence of hepatic disease; AST, ALT, alkaline phosphatase, or bilirubin > 2 x the upper limit of normal (unless due to Gilbert's	16. Evidence of hepatic disease; AST, ALT, alkaline phosphatase >2x ULN, or total bilirubin > 2x ULN or INR > 1.5 x ULN at baseline with the exception that isolated INR elevation in the	Change based on FDA recommendation to include INR.

Section(s)	Original Text	Revised Text	Rationale for Change
	disease) at baseline (baseline = within 24 hours prior to dosing)	absence of other significant liver enzyme abnormalities is explained by anticoagulant therapy, (e.g. warfarin).	
Synopsis & Section 4.3: Exclusion Criteria and Section 7.5.1: Dose Modification / Stopping Rules	QTc	QTcF	Changed all references of QTc to QTcF to clarify that the Fridericia equation will be used to calculate the QTc interval.
Synopsis & Section 4.3: Exclusion Criteria	Evidence of hepatic disease; AST, ALT, alkaline phosphatase >2x ULN, or total bilirubin > 2x ULN or INR > 1.5 x ULN at baseline with the exception that isolated INR elevation in the absence of other significant liver enzyme abnormalities is explained by anticoagulant therapy, (e.g. warfarin).	Evidence of hepatic disease; AST, ALT, alkaline phosphatase >2x ULN, or total bilirubin > 2x ULN or INR > 1.5 x ULN at screening with the exception that isolated INR elevation in the absence of other significant liver enzyme abnormalities is explained by anticoagulant therapy, (e.g. warfarin).	Day 1 blood draws will be evaluated by a central laboratory and therefore won't be available in time for Day 1 dosing. Therefore, the screening assessments should be used.
Synopsis & Section 4.3: Exclusion Criteria - #20 and #27	23. History of alcohol or illicit drug abuse or of lithium, pamidronate, interferon or prescribed NSAIDS. Recreational use of cannabis is not excluded where legal.	20. History of alcohol or illicit drug abuse. Recreational use of cannabis is not excluded where legalized. 27. Subjects taking lithium, pamidromate or interferon; subjects taking non-steroidal anti-inflammatory agents (NSAIDS) chronically (intermittent, i.e. occasional NSAIDS for pain or fever is discouraged, but is not excluded).	Clarify drug exclusion and medication exclusion with two separate exclusion criteria
Synopsis & Section 4.3: Exclusion Criteria - #21	None	21. History of gastrointestinal conditions that may interfere with study medication compliance, e.g., severe gastroparesis, with regurgitation of food or oral medication	Added to make consistent with other CCXI protocols
Synopsis & Section 4.3: Exclusion Criteria - #26	22. Subject is taking strong CYP3A4 inducers (e.g., phenytoin, rifampicin,	26. Subjects taking strong CYP3A4 inducers (e.g., phenytoin, rifampicin, carbamazepine, St. John's Wort)	Strong CYP3A4 inhibitors are additionally excluded as concomitant medication due to

Section(s)	Original Text	Revised Text	Rationale for Change
	carbamazepine, St. John's Wort)	or strong CYP3A4 inhibitors (e.g., boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole) within two weeks prior to screening.	CYP3A4 metabolism of CCX_140-B.
Section. 5.2: Rationale for Dose Range	Pre-existing language in the synopsis only. Was inadvertently not included in section 5.2.	In all subjects, treatment at the selected dose will be continued through 12 weeks or until declaration of Treatment Failure, where Treatment Failure is defined as any of the following: 1) Progression of renal disease, defined as eGFR that is both below 60 ml/min/1.73 m2 and is confirmed to represent at least a 30% decline in eGFR from baseline; 2) Requirement for rescue with glucocorticoids, other new immunomodulatory or immunosuppressive therapy, plasmapheresis, or dialysis, per the judgment of the Investigator; 3) Pre-specified adverse event or laboratory abnormality that, per Protocol, requires permanent discontinuation of study CCX140-B 4) Any other treatment-related adverse event, laboratory evidence of toxicity, or intolerance that, in the judgment of the Investigator, warrants permanent discontinuation of CCX140-B.	Pre-existing language from the synopsis was inadvertently omitted in main body of the protocol.
Section 6: Study procedures and Time and Events table	Blank	The following item was added to sections 6.1 through 6.17 (day 1 through week 52): AIDS Clinical Trials Group	ACTG-BPNST evaluation was inadvertently omitted in Section 6 and the Time and Events table

Section(s)	Original Text	Revised Text	Rationale for Change
		Brief Peripheral Neuropathy Screening Tool (ACTG BPNST).	
Synopsis and Section 6.1: Screening Assessments (Day -28 to Day 0) (and Time and Events Table where applicable)	10. Concomitant medications including medications taken for up to 12 weeks prior to screening Day 1 should be captured on the eCRF. Rituximab within 52 weeks of screening must be captured on the eCRF (note that there must be documented evidence of CD20+ B cells when subject has history of use or Rituximab)	10. Concomitant medications including medications taken for up to 12 weeks prior to screening Day 1 should be captured on the eCRF. Prior treatment with rituximab or other anti-CD20 monoclonal antibodies and corresponding levels of CD20+ B cells need to be recorded up to 1 year prior to screening Day 1. Eligible patients who have entered the study on a continuous cycle therapy of rituximab or other anti-CD20 monoclonal antibodies need to remain on an unchanged therapy throughout the study at a dosing interval that has been documented to achieve continuous B cell depletion for the given patient unless prohibited due to safety considerations. Record UPCR and urine protein assessments up to 1 year prior to screening (if available) in the medical history if patients were treated with Rituximab, other CD20+ monoclonal antibodies or calcineurin inhibitors, or other immunotherapy.	To record CD20+ monoclonal antibodies levels or urine protein levels in the medical history in conjunction with prior medications
Section 6.2: Study Day 1 and Section 6.8: Study Week 12	Blank	Please be reminded that a 24 hr urine collection at baseline (study day 1) and week 12 are mandatory	Highlighting the importance of 24 hr. urine collection for study days 1 and week 12 as the defined efficacy endpoints
Section 6.5 and Section 6.6 and Time and Events table	**Day 43:** no PK collection **Day 57:** Pharmacokinetics (C_{min}) – sample is to be collected at time 0 (just prior to taking the first	**Day 43:** 4. Pharmacokinetics (C_{min}) – sample is to be collected at time 0 (just prior to taking the next) **Day 57:**	

Section(s)	Original Text	Revised Text	Rationale for Change
	dose of CCX140-B). However, if there was a dose increase in the prior 2 weeks, PK AUC (time 0, 0.5, 1, 2, 3, 4 & 6 hours post dose) is to be collected instead. The time 0 sample is to be collected just prior to administration of the first dose of CCX140-B. Subjects must fast prior to the time 0, 0.5 and 1 hour PK and can consume food immediately after the 1 hour PK blood draw.	8. Pharmacokinetics (time 0, 0.5, 1, 2, 3, 4 & 6 hours post dose), the time 0 sample is to be collected just prior to administration of the next dose of CCX140-B. Subjects must fast prior to the time 0, 0.5 and 1 hour PK and can consume food immediately after the 1 hour PK blood draw.	
Section 7.3.1: Adverse Event Severity Reporting	The severity of each adverse event will be determined by the investigator using CTCAE v4.0. If and event is not defined in the CTCAE criteria, use the following scale:	The severity of each adverse event will be determined by the investigator using the following scale:	Removed references to the CTCAE per feedback from the FDA
Section 7.3.5: Pregnancies	Any pregnancies that occur in female subjects or partners of male study subjects must be reported to the Safety team within 24 hours of awareness as indicated in Section 7.3.3. All pregnancies must be followed up until conclusion and the outcome of the pregnancy reported within 24 hours of awareness to the Safety team as indicated in Section 7.3.3	Any pregnancies that occur in female subjects or partners of male study subjects must be reported to [redacted] Clinical Safety within 2 hours of awareness to the contacts details outlined in Section 7.3.3. An exposure in Utero form will then be forwarded for completion as soon as possible. All pregnancies must be followed up until conclusion and the outcome of the pregnancy reported within 24 hours of awareness to [redacted] Clinical Safety. Should the outcome of the pregnancy meet criteria for an SAE, this should be reported as indicated in Section 7.3.3	Updated guidelines for reporting of pregnancies and special situation reporting
Section 7.3.6: Special Situation Reporting	Blank	Special situation reports include reports of overdose, misuse and abuse of the IMP: • Overdose: refers to the administration of a quantity of a	Updated guidelines for reporting of pregnancies and special situation reporting

Section(s)	Original Text	Revised Text	Rationale for Change
		medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol. Clinical Judgment should always be applied. In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the subject has taken excess dose(s) or the investigator has reason to suspect that the subject has taken additional dose (s). • Misuse: refers to situations where the medicinal product is intentionally and inappropriately used not in a way that is not in accordance with the protocol instructions or local prescribing information and may be accompanied by harmful physical or psychological effects. • Abuse: is defined as persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical and/or psychological effects. • Medication Error: Medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product by a healthcare professional, patient or consumer, respectively. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors, cases of subjects missing doses of investigational product are not considered reportable as medication error • All special situation reports must be reported on the special situations report form and	

Section(s)	Original Text	Revised Text	Rationale for Change
		forwarded to [redacted] within 24 hour All adverse events (AEs) associated with these special situation reports should be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management and outcome will be reported, when available.	
Section 7.3.7 Serious Adverse Event Reporting	Contact details are as follows: [redacted] New Zealand: Telephone: [redacted] Facsimile: [redacted] e-mai [redacted] [redacted] SAE hotline – Europe: Te ph ne: [redacted] Fax: [redacted] e-mail [redacted]	[redacted] Telephone: [redacted] **or** [redacted] Fac m e: [redacted] e-mail: [redacted]	Updated contact information [redacted] for SAE repor n

Section(s)	Original Text	Revised Text	Rationale for Change
Section 7.5 Dose Modification Rules Table 2 Dose Modifications for Individual Subjects (was table 3 before)	Assessment ALT, AST Event ALT or AST ≥ 3x ULN Timing Halt treatment then alert Sponsor (who will alert the DMc) and reassess after 1 week Response If ALT or AST and Total bilirubin normalize discuss next steps for resumption of treatment with Medical Monitor	Assessment ALT, AST Event ALT or AST ≥ 8x ULN Timing Confirmed within 72 hours (ALT, ASP, ALT and Total Bilirubin should all be re-tested) Response Consider Discontinuation of Treatment	Added and modified per FDA recommendation
Section 7.5 Dose Modification Rules Table 2 Dose Modifications for Individual Subjects (was table 3 before)	New Information	Assessment ALT, AST Event ALT or AST ≥ 5x ULN Timing Confirmed within 2 weeks (ALT, ASP, ALT and Total Bilirubin should all be re-tested) Response Consider Discontinuation of Treatment	Added per recommendation from the FDA
Section 7.5 Dose Modification Rules Table 2 Dose Modifications for	New Information	Assessment ALT, AST , Total Bilirubin and INR	Added per recommendation from the FDA

Section(s)	Original Text	Revised Text	Rationale for Change
Individual Subjects (was table 3 before)		Event ALT or AST ≥ 3x ULN and Total Bilirubin > 2 x ULN or INR > 1.5 Timing Confirmed within 72 hours (ALT, ASP, ALT and Total Bilirubin and INR should all be re-tested) Response Consider Discontinuation of Treatment	
Section 7.5 Dose Modification Rules Table 2 Dose Modifications for Individual Subjects (was table 3 before)	New Information	Assessment ALT, AST Event ALT or AST ≥ 3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and / or eosinophilia (>5%) Timing Confirmed within 72 hours (ALT, ASP, ALT and Total Bilirubin should all be re-tested) Response Consider Discontinuation of Treatment	Added per recommendation from the FDA
Section 7.5.1 Dose modification / Stopping Rules for overall studies	A Safety Review Committee (SRC) comprising the Study Director, Medical Monitor, at least one external expert nephrologist, and Study Statistician will review all safety events …	A Safety Review Committee (SRC) comprising the Study Director, Medical Monitor, Clinical Pharmacologist, at least one external expert nephrologist, and Study Statistician will review all safety events …	Addition of Clinical Pharmacologist to SRC to advise on pharmacokinetic findings and projections
Section 7.7 Concomitant	Blank	In addition, subjects taking strong CYP3A4 inhibitors (e.g	Exclusion of CYP3A4 inhibitors due to

Section(s)	Original Text	Revised Text	Rationale for Change
Medications and Restrictions (and Time and Events table where applicable)	Also, rituximab should be recorded up to 52 weeks prior to screening Day 1 with evidence for recovery of CD20+ B cell population.	boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil,nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole) will be excluded as these drugs may substantially increase the CCX140-B plasma Prior treatment with rituximab or other anti-CD20 monoclonal antibodies and corresponding levels of CD20+ B cells need to be recorded up to 1 year prior to screening Day 1. Eligible patients who have entered the study on a continuous cycle therapy of rituximab or other anti-CD20 monoclonal antibodies need to remain on an unchanged therapy throughout the study at a dosing interval that has been documented to achieve continuous B cell depletion for the given patient unless prohibited due to safety considerations. Their levels of CD20+ B cells that are routinely evaluated per standard of care with anti-CD20 monoclonal antibody therapy need to be recorded throughout the study. Record UPCR and urine protein assessments up to 1 year prior to screening (if available) in the medical history if patients were treated with Rituximab, other CD20+ monoclonal antibodies or calcineurin inhibitors, or other immunotherapy.	metabolism of CCX140-B Additional instructions needed because not all patients treated with rituximab or other anti-CD20 monoclonal antibodies are excluded per revised exclusion criteria Additional instructions for the collection of levels of CD20+ B cells, UPCR and urine protein assessments due to revised exclusion criteria.
Section 7.7 Concomitant Medications and Restrictions (and Time and Events table where	Blank	**Rescue Therapy:** If the investigator decides that a subject needs to receive rescue therapy the subject will be	Added per feedback from the FDA

Section(s)	Original Text	Revised Text	Rationale for Change
applicable)		considered a treatment failure. Rescue therapy is considered any new therapy or required dose increase of an existing concomitant therapy (other than allowed per section 7.7. Concomitant Medications and Restrictions) that is required for the safety of the patient and to treat the underlying disease of FSGS. This would include but is not limited to the initiation of high dose glucocorticoid therapy, new immunosuppressive agents such as calcineurin inhibitors, cyclophosphamide, MMF, monoclonal antibodies, or other major treatments (e.g. plasmapheresis, dialysis).	
Section 8.2.1: Primary Endpoint Analysis	The primary efficacy endpoint is the proportion of subjects with partial or complete remission at any time during the treatment period. Partial Remission is defined as … Figure 1…. The number and percent of subjects with partial and complete response as of week 12 will be summarized including 2-sided 90% and 95% confidence intervals (CIs). Statistical inference will be made based off of decision rules of the Fleming two-stage design.	The Primary Efficacy endpoint is to evaluate the effect of CCX140-B on proteinuria in subjects with primary FSGS with nephrotic syndrome, assessed as a median reduction from baseline of urine protein to creatinine ratio (UPCR) of at least 20%, i.e. ≥ 20%, by week 12. The assumed treatment effect for this study is based on efficacy findings with 5 and 10 mg CCX140 once daily in study CL005_140 in patients with diabetic nephropathy and proteinuria. In a pre-specified subset analysis, the greatest percentage improvement of UACR at approximately 12 weeks from baseline was observed in subjects who presented with the highest baseline UACR (801-3000 mg/g) and eGFR of at least 60 mL/min/1.73m^2. This subgroup receiving 5 (N=10) or 10 mg (N=13) of CCX140 once daily showed a median reduction in UACR of approximately 20%-30% receiving CCX140 while	Change primary endpoint "partial and complete remission" to secondary endpoint and evaluate "median reduction of UPCR" as primary efficacy instead. Existing text is modified or deleted accordingly. This change is based on discussions with lead study investigators and is based on previously observed treatment effects of CCX140-B for the reduction of proteinuria in subjects with diabetic nephropathy.

Section(s)	Original Text	Revised Text	Rationale for Change
		patients receiving placebo (N=12) showed an increase of approximately 12%. Based on these data, it is assumed that the median reduction from baseline UPCR is at least 20% by week 12 in the planned study CL012_140. If the final observed data are consistent with this assumption, i.e. the previous positive study results are replicated in the FSGS population, the study will be considered positive in assessing the efficacy of CCX140. Otherwise, if the observed data are consistent with the median reduction of below 20%, the study would not be considered positive.	
Section 8.2.2: Secondary Endpoint	Secondary endpoints include: • Change from baseline of UPCR in subjects treated with CCX140-B over time …	Secondary endpoints include: • Partial Remission (includes all of the following) - reduction from baseline by ≥50 percent in UPCR - reduction in UPCR to a level that is < 3.5 g/g at week 12 - subject may not be a treatment failure (e.g. has not received rescue therapy, has not required discontinuation of study drug) • Complete Remission (includes all of the following) at week 12 - reduction in UPCR to < 0.3 g/g - serum albumin within normal range - for patients with abnormal serum creatinine levels at baseline, return to normal levels for that age group	The definition of previous primary endpoint "partial and complete remission" was moved to secondary endpoint section because the primary endpoint was changed as described above.

Section(s)	Original Text	Revised Text	Rationale for Change
		- for patients with normal serum creatinine levels at baseline, final value within 20% of baseline levels - subject may not be a treatment failure (e.g. has not received rescue therapy and has not required discontinuation of study drug) • Change from baseline of UPCR in subjects treated with CCX140-B over time … • The proportion of patients with partial remission at any time during the treatment period • The proportion of patients with complete remission at any time during the treatment period	Deleted inconsistencies within definitions of partial and complete remission
	The proportion with partial remission defined as reduction from baseline by ≥50 percent in UPCR, normalization of serum albumin and subject may not be a treatment failure (e.g. has not received rescue therapy, has not required discontinuation of study drug) • The proportion with complete remission at any time during the treatment period, defined as achievement of UPCR ≤ 0.3 g/g and normal eGFR or no progression of renal failure		
Section 8.2.2: Secondary Endpoint Analysis	Change from baseline in renal function, based on eGFR (calculated with the CKD EPI equation using the CKD-EPI Cystatin C equation, CKD-EPI Creatinine equation, CKD-EPI Creatinine-Cystatin C equation and MDRD Creatinine equation over time	Change from baseline in renal function, based on eGFR (calculated using the CKD-EPI Cystatin C equation (Dharnidharka VR, et al, 2002), the CKD-EPI Creatinine equation (Schwartz GJ, et al. 2016, Selistre L et al 2016), CKD-EPI Creatinine-Cystatin C equation (Stevens et al., 2008) and MDRD Creatinine equation (Levey et al. 1999, Levey et al. 2006) over time	Added references for each of the 4 eGFR equations

Section(s)	Original Text	Revised Text	Rationale for Change
Section 8.4: Sample Size Assumptions	Six (6) male or female adult subjects with biopsy-proven primary FSGS and nephrotic syndrome will be enrolled into the first stage of this study. Analysis of data in this study will follow the Fleming's two-stage design. The null hypothesis that the true response (partial or complete remission) rate is 0.25 will be tested against a one-sided alternative assuming a true response rate of 0.65. In the first stage, 6 subjects will be treated. After all of the initial 6 subject have completed their 12-week of treatment the study will be paused and assessed safety and efficacy. If the overall study results are deemed safe and the subjects' responses to treatment are considered clinically meaningful seven additional subjects will be treated for a total of 13 subjects. The null hypothesis will be rejected if 6 or more responses are observed in 13 subjects. This design yields a one-sided type I error rate of 0.05 and 80% power.	Six (6) male or female adult subjects with biopsy-proven primary FSGS and nephrotic syndrome will be enrolled into the first stage of this study, which is followed by another seven subjects after the data review of the initial 6 patients. The relatively small sample size is selected based on the exploratory safety and efficacy nature of the study. After all of the initial 6 subject have completed their 12-week of treatment the study will be paused and assessed safety and efficacy. If the overall study results are deemed safe and the subjects' responses to treatment are considered clinically meaningful seven additional subjects will be treated for a total of 13 subjects.	This section was updated to reflect changes in the primary and secondary endpoints and to allow for the exploration of safety and efficacy in the study more appropriately.
Section 10.8: Case Report Form Completion	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.	It is the policy of the Sponsor that study data must be verifiable to the source data, which necessitates access to all relevant source documents, laboratory reports, and subjects' records.	Although original documentation is the primary source, certified copies from an EMR captured in each subject's printed chart can be utilized for SDV.

Section(s)	Original Text	Revised Text	Rationale for Change
References	Blank	Added reference #s 13 (Dharnidharka VR, et al. (2002) 22 Levey AS, et al. (1999) 23 Levey AS, et al. (2006) 26 Schwartz GJ, et al. (2009) 27 Selistre L, et al. (2016)	Added references for the 4 different eGFR calculations utilized for this study
Appendix A	Statement of Obligations of Sponsor, Monitor and Clinical Investigator,	Removed	The Statement of Obligations is redundant with language on FDA Form 1572 and is therefore not required as an appendix in the protocol

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

I. STUDY SYNOPSIS

<table>
<tr><td>Name of Sponsor
ChemoCentryx, Inc.</td><td>Name of Active Ingredient
CCX140-B</td><td>Study number
CL012_140</td></tr>
<tr><td colspan="3">Title
An Open-Label, Intra-Subject Dose Escalation Study of CCX140-B in Subjects with Primary Focal Segmental Glomerulosclerosis (FSGS) and Nephrotic Syndrome</td></tr>
<tr><td colspan="3">Investigators
TBD</td></tr>
<tr><td colspan="3">Study centers
Up to 10 sites planned in North America and Europe</td></tr>
<tr><td colspan="2">Primary Study Period
• Participation time for each subject:
o Up to 4 weeks screening
o Up to 12 weeks initial treatment
o 4 weeks follow-up after last dose administered
Extended Study Period
• Subjects who meet pre-defined response criteria at 12 weeks may enter an extended treatment period for up to an additional 40 weeks</td><td>Phase of development
Phase 2</td></tr>
<tr><td colspan="3">Efficacy Objectives and Endpoints
The Primary Efficacy Objective is to evaluate the effect of CCX140-B on proteinuria in subjects with primary FSGS with nephrotic syndrome, assessed as a median reduction from baseline of urine protein to creatinine ratio (UPCR) of at least 20%, i.e. ≥ 20%, by week 12.
Secondary efficacy endpoints of this study will be assessed through Study Week 12 and through End of Treatment and include:
• Achievement of partial or complete remission of urine protein to creatinine ratio (UPCR):
Partial Remission (includes all of the following)
• reduction from baseline by ≥50 percent in UPCR
• reduction in UPCR to a level that is < 3.5 g/g
• subject may not be a treatment failure
Complete Remission (includes all of the following)</td></tr>
</table>

- reduction in UPCR to < 0.3 g/g
- Serum albumin within normal range
- For patients with abnormal serum creatinine levels at baseline, return to normal levels for that age group
- For patients with normal serum creatinine levels at baseline, final value within 20% of baseline levels
- subject may not be a treatment failure
- Change from baseline in UPCR over time
- Time to and proportion with achievement of partial remission during the treatment period
- Time to and proportion with achievement of complete remission during the treatment period
- Time to rescue therapy, based on Investigator or physician initiation of glucocorticoids or new immunosuppressive agents or new major treatment modalities (e.g. plasmapheresis, dialysis)
- Changes over time in other laboratory and other parameters related to renal function, including:
  - Serum albumin
  - Creatinine
  - Cystatin C
  - eGFR, calculated by the CKD-EPI Cystatin C equation, CKD-EPI Creatinine equation, CKD-EPI Creatinine-Cystatin C equation and MDRD Creatinine equation.
  - urine albumin to creatinine ratio (UACR)
  - total 24 hour urine protein excretion

Quality of Life endpoints include:

- Change in factors associated with quality of life from baseline over time as assessed using the SF-36 v2
- Change in factors associated with quality of life from baseline over time as assessed using the EQ-5D-5L

Safety will be evaluated via the following endpoints:

- Adverse events
- Vital signs
- Electrocardiograms
- AIDS Clinical Trials Group Brief Peripheral Neuropathy Screening Tool (ACTG BPNST)
- Changes in laboratory parameters including:

- hematology, including complete blood count, reticulocyte count, smear evaluation
- serum haptoglobin, lactate dehydrogenase
- serum chemistry, expanded to include serum transaminases, CPK
- urinalysis
- coagulation factors

Pharmacokinetics will be evaluated based on:
Exposure (AUC, C_{max}, C_{min})

Exploratory objectives include:

- Assessment of biomarkers associated with disease activity over time, including blood lipid profile, urinary MCP-1, and potentially other biomarkers of renal inflammation, fibrosis and injury;
- Assessment of biomarkers associated with risk of severity of disease, which may include allelic variations associated with the pathogenesis and/or prognosis of FSGS such as NPHS1, NPHS2, WT-1, LAMB2, CD2AP, TRPC6, ACTN4, INF2, APOL1.
- Assessment of blood and/or urinary biomarkers associated with CCR2 biology, which may include peripheral blood leukocyte subsets and selected cytokines and chemokines
- Assessment of mechanisms by which nephrotic syndrome may potentially impact pharmacokinetics of CCX140, including assessment of CCX140 in urine
- Assessment of edema as measured by physical examination, leg circumference and body weight
- Assessment of concentration of CCX140-B in urine

Background

Focal segmental glomerulosclerosis (FSGS) may present with nephrotic syndrome, with marked proteinuria, reduced plasma albumin, edema, hyperlipidemia and a high risk for progression to end stage renal disease. Current therapeutic recommendations include supportive measures and consideration of a trial of high dose glucocorticoids. Glucocorticoid treatment for durations of 4 to 24 months has been reported to achieve partial remission in 28% to 74% of patients, but is associated with significant morbidity, incomplete response in most patients, and a high risk of recurrence following withdrawal (Korbet et al., 2012; Banfi et al., 1991; Cattran and Rao, 1998; Rydel et al., 1995; Gipson et al., 2016).

CCR2 has emerged as a potential target for treatment of FSGS based on (a) expression of CCR2 in diseased kidney, (b) association between disease activity and elevated urinary levels of macrophage chemo-attractant protein-1 (MCP-1, ligand of CCR2), and (c) efficacy of CCR2 blockade in animal models with features of FSGS.

CCX140-B is an orally administered, selective antagonist of CCR2, which has exhibited efficacy in murine models of renal injury. In patients with diabetic nephropathy, administration

of CCX140-B at 5 mg daily or 10 mg daily for up to 52 weeks was associated with a favorable safety profile and a significant reduction from baseline in proteinuria (Study CL005_140; de Zeeuw, et al., 2015).

Based on the preclinical rationale, favorable safety profile, and signals of efficacy in diabetic subjects with marked proteinuria, ChemoCentryx plans to assess CCX140-B in FSGS.

Methodology

This is an open label clinical trial to test the efficacy, safety, pharmacokinetics and tolerability of ascending doses of CCX140-B in subjects with primary FSGS and nephrotic syndrome. Throughout the treatment period, any changes in background medications should be limited to settings in which the Investigator deems it to be necessary for the safety of the subject.

Eligibility requirements are detailed in the inclusion and exclusion criteria.

The screening period will be up to 28 days.

Dose and Dose Adjustments

Eligible subjects will start treatment with CCX140-B at 5 mg twice daily. CCX140-B will be taken orally without food, at least one hour before a meal. The dose may be increased in a stepwise manner to 10 mg twice daily on day 15, then to 15 mg twice daily on day 43 while monitoring efficacy, PK and safety. Dose escalations will occur in accordance with the rules and schedule detailed in Table 1, Figure 1 and Section 7.5.1. Dose may be adjusted downward in the event of intolerance, laboratory evidence of toxicity, or a measured or projected steady state exposure that exceeds the pre-specified maximum safe exposure based on the No Observed Adverse Event Level (NOAEL) established in the non-clinical toxicology program.

In all subjects, treatment at the selected dose will be continued through 12 weeks or until declaration of Treatment Failure, where Treatment Failure is defined as any of the following:

1) Progression of renal disease, defined as eGFR that is both below 60 ml/min/1.73 m^2 and is confirmed to represent at least a 30% decline in eGFR from baseline;
2) Requirement for rescue with glucocorticoids, other new immunomodulatory or immunosuppressive therapy, plasmapheresis, or dialysis, per the judgment of the Investigator;
3) Pre-specified adverse event or laboratory abnormality that, per Protocol, requires permanent discontinuation of study CCX140-B
4) Any other treatment-related adverse event, laboratory evidence of toxicity, or intolerance that, in the judgment of the Investigator, warrants permanent discontinuation of CCX140-B.

If planned dose escalation to 10 mg (on day 15) or 15 mg twice daily (on day 43) was previously halted the dose may be escalated further if subjects are not considered treatment failures and who otherwise meet criteria for continuation. In such case the subject will return approximately 2 weeks later for blood draws to assess PK (AUC_{0-6}). Subjects will return 2 weeks after the PK assessment to evaluate the safety and need for further dose adjustment.

Subjects who completed 12 weeks of treatment are not considered treatment failures and who otherwise meet criteria for continuation may be extended for up to an additional 40 weeks to assess degree and duration of response. During the extension period the dose may be adjusted if indicated based on assessment of safety, PK and efficacy. (see Table 1 and Figure 1 for

guidelines).

Starting with the extended treatment period (Day 85 and beyond) if the dose is adjusted upward or downward for any reason at Day 85 or during the extended treatment period the subject will return approximately 2 weeks later for blood draws to assess PK (AUC_{0-6})

Table 1: Dose Modification Schedule and Rules Through Study Day 85

Study Day	Dose and Requirements for Dose Modification
1	Initiate dosing at 5 mg twice daily
15	At Day 15, dose will be increased to 10 mg twice daily if all of the following are true: • Subject has not achieved and maintained at least Partial Remission *and* • Subject is not a Treatment Failure
29	At Day 29, PK samples will be collected to measure AUC_{0-6} and enable projection of AUC_{0-12} at both the current dose level and the next higher planned dose level AUC_{0-12}
43	At Day 43 based on results of the Day 29 PK, the dose may be adjusted to the next higher planned dose level (15 mg twice daily for subjects receiving 10 mg twice daily; 10 mg twice daily for subjects receiving 5 mg twice daily) if all of the following are true: • Subject is not a Treatment Failure, *and* • Meets all criteria for continuation: o Subject has not achieved and maintained at least a Partial Remission, *and* o Projected AUC_{0-12} on the next higher planned dose level does not exceed 240 µg•h/mL *and* o The next higher dose does not exceed the Maximum Tolerated Dose (MTD) NOTE: If the projected AUC_{0-12} on the <u>current dose</u> exceeds 240 µg•h/mL, dose will be de-escalated to the next lower dose level
57	At Day 57, PK samples will be collected to measure AUC_{0-6} and enable projection of AUC_{0-12}
Day 71	Based on results of Day 57 PK, subjects can be considered for dose escalation if all of the following are true: • Subject is not already treated with 15 mg twice daily and • Subject did not require previous downward dose adjustment *and* • Subject is not a Treatment Failure, *and* • Meets all criteria for continuation: o Subject has not achieved and maintained at least a Partial

	Remission, *and* o Projected AUC_{0-12} on the next higher planned dose level does not exceed 240 µg•h/mL *and* o The next higher dose does not exceed the Maximum Tolerated Dose (MTD) NOTE: If the projected AUC_{0-12} on the current dose exceeds 240 µg•h/mL, dose will be de-escalated to the next lower dose level
Day 85 and beyond	If dose is adjusted upward or downward for any reason at Day 85 or during the extended treatment period the subject will return approximately 2 weeks later for blood draws to assess PK (AUC_{0-6}). Subjects will return 2 weeks after the PK assessment to evaluate the safety and need for further dose adjustment.

Blood will be drawn to evaluate trough exposure in accordance with the Time and Events Schedule. In addition, blood will be drawn to assess exposure (AUC_{0-12}), extrapolated from measured AUC_{0-6}), at the following times to guide dosing decisions:

- Study Day 1 prior to first dose of CCX140, and at intervals through 6 hours following the initial dose
- On study Day 29, two weeks following initiation of 10 mg twice daily, to assess exposure at steady state, and to confirm that exposure is within the safety margins based on non-clinical NOAEL
- If dose was adjusted on Day 43, blood will be collected on study Day 57 to assess AUC_{0-6}
- Additional assessments of exposure may be scheduled if indicated. Indications may include:
    - Subjects receiving a total dose greater than 10 mg daily who have experienced at least 50% reduction in proteinuria since the previous PK assessment, to assess impact of change in proteinuria on exposure and to ensure exposure is within safety margins
    - Subjects who experienced a potentially dose-limiting safety event
    - Subjects who required a dose reduction for higher than planned exposure; PK will be assessed approximately 2 weeks after reduction
    - Subjects for whom dose is adjusted for any other reason; PK will be assessed approximately 2 weeks after reduction

If measured or projected steady state PK exposure (AUC_{0-12}) exceeds 240 µg•h/mL, which is approximately half of the rat NOAEL AUC_{0-24}, the dose will be reduced to the dose projected to provide exposure within the target range.

Extended Treatment Period

- Subjects are eligible for the extended treatment period under the following conditions:
    1. Not considered treatment failures as of Week 12 *and*
    2. In the opinion of the Investigator, remain candidates for investigational treatment *and*
    3. Any of the conditions below apply:

- Partial or Complete Remission by Week 12
- Response with ≥20% reduction in UPCR by Week 12
- No longer have nephrotic syndrome

These subjects will return to clinic for safety, PK and efficacy measurements every 4-8 weeks. Subjects taking CCX140-B at 15 mg twice daily will be maintained at that dose unless de-escalation is required based on safety signal or steady state PK exposure (AUC_{0-12}) exceeds 240 µg•h/mL.

Subjects can be considered for dose escalation if all of the following are true:

- Subject is not already treated with 15 mg twice daily and
- Subject did not require previous downward dose adjustment *and*
- Subject is not a Treatment Failure, *and*
- Meets all criteria for continuation:
  - Subject has not achieved and maintained at least a Partial Remission, *and*
  - Projected AUC_{0-12} on the next higher planned dose level does not exceed 240 µg•h/mL *and*
  - The next higher dose does not exceed the Maximum Tolerated Dose (MTD)

Subjects who undergo dose escalation will return to clinic approximately 2 weeks after initiation of the increase for assessment of PK.

Dose modification rules that applied during the initial dose escalation period also apply to dose escalation after 12 weeks.

Follow-Up

Following completion of treatment or early termination of treatment all subjects should be encouraged to return for the termination visit, and 7 and 14 days after their last dose for blood draws to assess elimination pharmacokinetics, and 28 days after their last dose for follow-up and End of Study visit assessments. The subject's condition will be evaluated by the Investigator at the end of study drug administration and again during the post 4 week follow-up visit. Appropriate standard of care medical treatment should be provided to all subjects as needed.

Subjects will be discharged from the study when all the visit procedures have been completed.

Rationale for Dose Range

Safety:

A dose of 15 mg twice daily in humans is projected to produce a steady state AUC_{0-12} of 72 µg•hr/mL, based on modeling from Phase 1 PK data. The safety margin associated with this exposure is approximately 3-fold below the NOAEL exposure in rats, and 5-8-fold below the NOAEL exposure established in dogs.

Efficacy:

This study is designed to test CCX140-B at doses ranging from 5 mg twice daily through 15 mg twice daily, a dose projected to provide continuous high level receptor engagement and

antagonism.

The targeted dose was projected from observations in a murine model with features of FSGS, the adriamycin-induced nephropathy mouse model (Lee, et al., 2011). CCX140-B does not bind murine CCR2 and human CCR2 with the same potency, therefore the model was established in a CCR2 knockout and human CCR2 knock-in (hCCR2-KI) mouse. Mice were treated with 10, 30, and 90 mg/kg of CCX140-B once daily for 9 days. The 24 hour post last dose blood samples from 90 mg/kg dosing resulted in close to 100% receptor coverage. The mean CCX140-B concentration at trough was 3.3 µg/mL (6.6 µM).

In the absence of proteinuria, the human trough concentration with 15 mg twice daily dosing is projected to be ~5.5 µg/mL, which is higher than the 3.3 µg/mL required for 100% CCR2 blockade in the above described hCCR2 mouse model. However, the projected exposures and safety margins were established for humans without proteinuria. Because CCX140-B is highly protein bound, subjects with nephrotic-level proteinuria may have a lower exposure at a given dose due to potential drug loss with protein in urine or impact of disease on metabolism. A post-hoc analysis of PK in diabetic nephropathy subjects of trial CL005_140 who entered in study with albuminuria of 2 – 3 grams indicated that exposure was approximately 30% below the mean for the treatment group as a whole (~0.8 µg/mL versus ~1.2 µg/mL).

Therefore 15 mg twice daily was selected as the upper limit for dose ranging for subjects with nephrotic level proteinuria.

Dose Modification Rules

Dose Modification Rules <u>for individual subjects</u>

Discontinue treatment with CCX140-B when a subject experiences any of the following events confirmed by repeat measurement after 2 weeks:

- Progression of renal disease, defined as eGFR that is both below 60 ml/min/1.73 m^2 and is confirmed to represent at least 30% decline in eGFR from baseline
- Requirement for rescue with glucocorticoids, other new immunomodulatory or immunosuppressive therapy, plasmapheresis or dialysis
- Pre-specified adverse event or laboratory abnormality that, per Protocol, requires permanent discontinuation of study CCX140-B
- Any other treatment-related adverse event, laboratory evidence of toxicity or intolerance that in the judgment of the investigator, warrants permanent discontinuation of CCX140-B

Halt treatment then alert sponsor and reassess after 1 week when there is a Clinical diagnosis of hemolysis in the judgment of the investigator, based on elevation of LDH, elevation of reticulocyte count, elevation of bilirubin and or other laboratory indications.

Consider discontinuation of treatment when a subject experiences any of the following events:

An increase of serum ALT to >3xULN should be followed by repeat testing within 48 to 72 hours of all four of the usual serum measures (ALT, AST, ALP, and TBL) to confirm the abnormalities and to determine if they are increasing or decreasing.

Discontinuation of treatment should be considered if:

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

Halt treatment then alert sponsor and reassess after 2 weeks whenever a subject has either

- Hemoglobin reduced from baseline by ≥ 2 g/L and deemed clinically significant by the PI
- An increase in reticulocyte count by ≥ 2% (absolute) from baseline that is not otherwise explained
- ≥ moderate symptoms limiting instrumental activities of daily living or asymptomatic (based on diagnostic evaluation only) and deemed clinically significant by the investigator
- Any adverse events assessed as moderate, related to study drug, and clinically significant

Dose Modification / Stopping Rules <u>for the overall study</u>

A dose will be considered as potentially exceeding the maximum tolerated dose should any of the following events occur:

- 2 or more subjects with confirmed QTcF prolongation ≥ 450 msec and an increase from baseline of ≥ 30 msec, based on triplicate 12-lead ECGs that is not otherwise explained
- 2 or more subjects with clinically significant hemolytic anemia, defined as hemoglobin that has declined from baseline by at least 2 grams/deciliter and is less than or equal to 8 g/dL and is assessed by the investigator and is not otherwise explained
- 2 or more subjects with bilirubin greater than 3 times upper limit of normal, and not ascribable to Gilbert's disease
- 2 or more subjects with new motor neuropathy or sensory neuropathy that limits instrumental activities of daily living and is assessed by the Investigator as clinically significant
- 2 or more subjects who require dose reduction or discontinuation due to adverse events assessed as possibly related to Study Drug, where the adverse events are medically similar events in the same System Organ Class based on MedDRA criteria

If a dose is assessed to be above the maximum tolerated dose, dosing will be reduced to the next lower dose.

A Safety Review Committee (SRC) comprising the Sponsor Study Director, Medical Monitor, at least one external expert nephrologist, and the Study Statistician will review all safety events described in the dose modification rules and all serious adverse events as they occur. The SRC will periodically review all adverse events and all laboratory abnormalities. The SRC may declare a dose to be above the maximally tolerated dose based either on the defined rules or on other considerations.

Number of Subjects

Six (6) male or female adult subjects with biopsy-proven primary FSGS and nephrotic syndrome will be enrolled in the first stage of this study. An additional 7 subjects may be enrolled in the second stage of this study based on observations in the first 6 subjects, as described in the sample size section of this protocol.

Main Criteria for Inclusion

1. Male or female subjects aged 18 years and older
2. Renal biopsy findings consistent with diagnosis of primary focal segmental glomerulosclerosis (FSGS) and consistent with primary FSGS based on presentation of histopathology, medical history and clinical course; subjects with genetic risk factors with presentations that are otherwise consistent with primary FSGS may also be enrolled.
3. Urinary total protein:creatinine ratio (UPCR) ≥3.5 g protein/g creatinine at screening, based on sample drawn from a 24-hour collection
4. Hypoalbuminemia of less than 3.5 g/dL
5. Estimated glomerular filtration rate (eGFR) >30 mL/min/1.73m^2, as calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (using creatinine or cystatin C)
6. If used, RAAS inhibitor dose, including doses of angiotensin converting enzyme inhibitor and/or angiotensin II receptor antagonist, must have been started at least 4 weeks prior to Study Day 1, and projected to remain stable throughout the course of the study unless adjustment is required for management of hypertension
7. Female subjects of childbearing potential may participate if adequate contraception is used during, and for at least 5 half-lives after last dose of study drug. 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 one month after the last dose of study drug. 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). In addition, a barrier method (i.e. cervical cap, diaphragm or condom) must be used during intercourse between a male subject and a female of child-bearing potential.
8. Willing and able to give written Informed Consent and to comply with the requirements of the study protocol.
9. Judged to be otherwise fit for the study 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. Pregnant or nursing
2. History of organ transplantation, including renal transplantation
3. Currently on an organ transplant waiting list or there is a reasonable possibility of getting an

organ transplant within 6 months of screening.
4. Histological FSGS subtype of collapsing variant
5. Subjects who initiated, discontinued or changed dose of rituximab or other anti-CD20 monoclonal antibodies within 16 weeks (4 months) prior to screening are excluded. Subjects who initiated treatment with rituximab or other anti-CD20 monoclonal antibodies **>16 weeks (4 months)** prior to screening are permitted if deemed safe by the investigator and only if they are intended to remain on continued, unchanged therapy at a dosing interval that has been documented to achieve continuous B cell depletion for the given patient. UPCR and other urine protein assessments up to 1 year prior to screening (if available) that were performed in these patients as part of the clinical routine should be recorded in the medical history.
6. Subjects who discontinued Rituximab or other anti-CD20 monoclonal antibodies **>16 weeks (4 months) prior to screening** *without* confirmed recovery of CD20+ B cell population to within normal range are excluded. Subjects who discontinued rituximab or other anti-CD20 monoclonal antibodies >16 weeks (4 months) prior to screening *with* confirmed recovery of CD20+ B cell population to within normal range are permitted in the study. UPCR and other urine protein assessments up to 1 year prior to screening (if available) that were performed in these patients as part of the clinical routine should be recorded in the medical history.
7. Subjects who initiated or increased the dose of calcineurin inhibitors, or other immunotherapy, within 12 weeks prior to screening are excluded; dose reductions to maintain calcineurin inhibitors at optimal safe levels are permitted. Subjects who initiated a treatment with calcineurin inhibitors, or other immunotherapy >12 weeks are permitted. UPCR and other urine protein assessments up to 1 year prior to screening (if available) that were performed in these patients as part of the clinical routine should be recorded in the medical history.
8. Subjects taking glucocorticoids at dose greater than 10 mg/day prednisone equivalent within 4 weeks prior to screening are excluded.
9. Plasmapheresis within 12 weeks prior to screening
10. Body Mass Index (BMI) ≥40
11. Participated in any clinical study of an investigational product within 12 weeks prior to screening or within 5 half-lives after taking the last dose
12. Currently on dialysis or likely to require dialysis during the study.
13. History or presence of any form of cancer within the 5 years prior to screening, with the exception of excised basal cell or squamous cell carcinoma of the skin, or carcinoma *in situ* such as cervical or breast carcinoma *in situ* that has been excised or resected completely and is without evidence of local recurrence or metastasis
14. Positive HBV, HCV, or HIV viral screening test. Subjects who have received highly effective therapy for HCV demonstrated to have negative viral titers for at least 6 months following discontinuation of treatment, will be considered to have a negative HCV screening test weeks prior to screening
15. Evidence of tuberculosis based on interferon γ release assay (IGRA), tuberculin purified protein derivative (PPD) skin test, or chest radiography done during screening or within 6 weeks prior to screening
16. Evidence of hepatic disease; AST, ALT, alkaline phosphatase >2x ULN, or total bilirubin > 2x ULN or INR > 1.5 x ULN at screening with the exception that isolated INR elevation in

the absence of other significant liver enzyme abnormalities is explained by anticoagulant therapy, (e.g. warfarin).
17. Clinically significant peripheral neuropathy
18. Hematologic abnormalities as follows: Hb <8 g/dL, platelets <50,000, ANC <1000 cells/μL) at baseline
19. Abnormality of ECG at screening, assessed by the Investigator as clinically significant (e.g. QTcF greater than 450 msec).
20. History of alcohol or illicit drug abuse. Recreational use of cannabis is not excluded where legalized.
21. History of gastrointestinal conditions that may interfere with study medication compliance, e.g., severe gastroparesis, with regurgitation of food or oral medication
22. Known hypersensitivity to CCX140-B or inactive ingredients of the CCX140-B tablets (including microcrystalline cellulose, starch, crospovidone, magnesium stearate, or silicon dioxide)
23. Renal disease associated with disorders other than FSGS (e.g. lupus nephritis, C3 glomerulonephropathy) that is active, or has significant risk of progressing to end stage renal disease during the 12-week initial treatment phase of the study
24. History or presence of systemic disorder other than FSGS that requires, or is expected to require, systemic glucocorticoids or immune modulators; topical or inhaled corticosteroids and immune modulators are not excluded
25. 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
26. Subjects taking strong CYP3A4 inducers (e.g., phenytoin, rifampicin, carbamazepine, St. John's Wort) or strong CYP3A4 inhibitors (e.g., boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole) within two weeks prior to screening.
27. Subjects taking lithium, pamidronate or interferon; subjects taking non-steroidal anti-inflammatory agents (NSAIDS) chronically (intermittent, i.e. occasional NSAIDS for pain or fever is discouraged, but is not excluded).

Study Medication

CCX140-B will be administered as 5 mg CCX140-B tablets

Duration of Treatment and Observation

Subjects will be screened within a period not to exceed 28 days prior to Day 1.

The initial treatment period, including dose escalation, will be up to 12 weeks. Subjects who are not Treatment Failures and who otherwise meet criteria for continuation may continue treatment for up to an additional 40 weeks to assess achievement of remission and duration of response. All subjects will be followed for 4 weeks (28 days) after the last CCX140-B dose administered.

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, ECGs, clinical laboratory tests (including blood chemistry, hematology, and urinalysis), and the AIDS Clinical Trials Group Brief Peripheral Neuropathy Screening Tool (ACTG BPNST), a validated assessment tool for early detection of peripheral neuropathy.

Efficacy Assessments

Primary and Secondary Efficacy assessments include:

- Urine protein:creatinine ratio (UPCR) and urine:albumin ratio (UACR), assessed in a sample drawn from a 24 hour collection is required at baseline and Study Week 12 (see schedule). At other time points defined in the Time and Events table, 24 hour collection is preferred. However, at these visits, a midstream void sample may be used for assessments if a 24hr urine sample is not available.
- 24 hour urine protein excretion to be collected at baseline (pre-dose on Day 1), Day 15, Day 29, Day 57 and Day 85 (12 weeks) (same as previous)
- Change from baseline in eGFR calculated by the CKD-EPI Cystatin C equation, CKD-EPI Creatinine equation, CKD-EPI Creatinine-Cystatin C equation and MDRD Creatinine equation
- Serum albumin level
- Health-related quality of life based on the SF-36 v2 and EQ-5D-5L

Exploratory Assessments

MCP-1 excreted in urine and biomarker analysis including genetic mutations associated with the pathogenesis and/or prognosis of FSGS, biomarkers associated with CCR2 biology and biomarkers of renal inflammation, fibrosis and injury and leg circumference measurements.

Pharmacokinetic Assessments and Analysis

Plasma samples will be collected according to the Time and Events Table to determine the PK profile of CCX140. Individual plasma concentrations of CCX140 will be listed, plotted, and summarized descriptively and graphically. PK parameters will be calculated based on plasma CCX140 concentrations at the time of sample collection in relation to time of administration of the most recent dose of study medication. The following parameters will be determined, where possible:

Concentrations of CCX140 (neutral form of CCX140-B which is a sodium salt) will be determined in plasma according to the Time and Events Table. 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 for all subjects, after the first dose of 5 mg QD, two weeks after 10 mg BID, and four weeks after 15 mg BID

AUC_{0-12} Area under the plasma concentration-time curve from Time 0 to Hour 12, two weeks after 10 mg BID and four weeks after 15 mg BID, will be extrapolated for all subjects.

C_{min} Trough level plasma concentrations at visits when AUC_{0-6} is not collected

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

The relationships among PK parameters, UPCR and renal function based on eGFR will be evaluated. The data may also be used to evaluate the PK/PD relationship of CCX140-B treatment. To this end, the change and/or percent change from baseline in UPCR, eGFR, and other biomarkers may be used as PD markers.

If there are sufficient data, population PK analysis will be performed.

Pharmacodynamic Markers and Analysis

- Blood will be collected according to Time and Event Table for leukocyte absolute counts and percentage as well as lymphocyte subsets. Gene mutations associated with prevalence and prognosis of FSGS may be evaluated as well.
- Plasma/serum samples will be collected according to the Time and Events Table for pharmacodynamic marker measurements, which may include, for example, inflammatory cytokine and chemokine levels
- Urine samples will be collected according to the Time and Events Table for biomarker analysis including, for example, markers for renal inflammation, fibrosis and injury.

The change and/or percent change from baseline in UPCR, eGFR, and other biomarkers may be used as PD markers.

Statistical Methods

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

All continuous study assessments will be summarized by visit (as applicable) and change from baseline (baseline is typically defined as pre-dose evaluation on day 1 unless otherwise specified) to each post-baseline visit using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). All categorical study assessments will be summarized by visit (as applicable) using frequency counts and percentages.

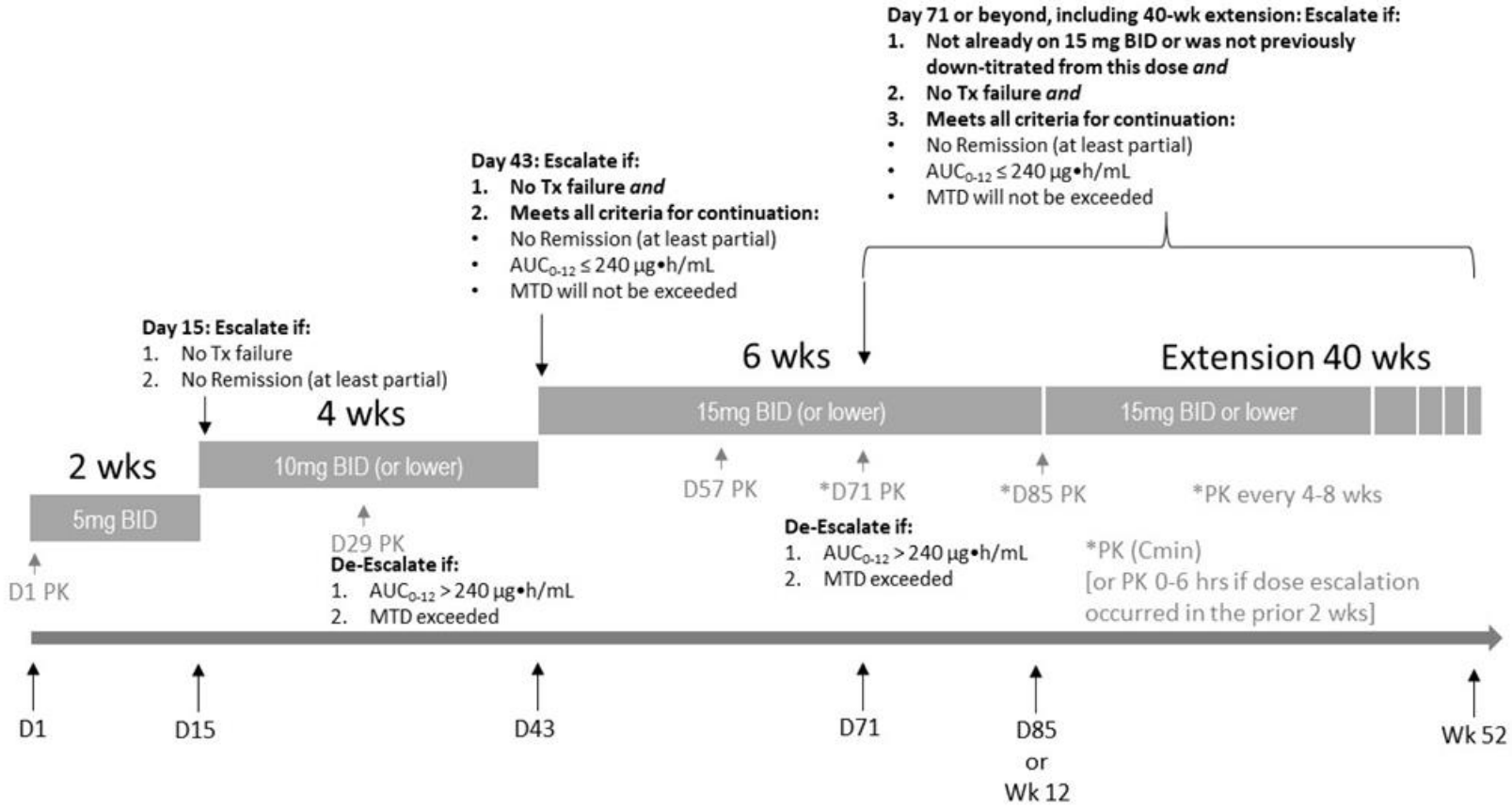
Figure 1: Study Schematic

Treatment failure = Tx failure:

1. Progression of renal disease, defined as eGFR that is both below 60 ml/min/1.73 m2 and is confirmed to represent at least a 30% decline in eGFR from baseline;
2. Requirement for rescue with glucocorticoids, other new immunomodulatory or immunosuppressive therapy, plasmapheresis, or dialysis, per the judgment of the Investigator;
3. Pre-specified adverse event or laboratory abnormality that, per Protocol, requires permanent discontinuation of study CCX140-B
4. Any other treatment-related adverse event, laboratory evidence of toxicity, or intolerance that, in the judgment of the Investigator, warrants permanent discontinuation of CCX140-B.

Eligibility Criteria for Extended Treatment Period:

1. Not considered treatment failures as of Week 12
2. And, in the opinion of the Investigator, remain candidates for investigational treatment
3. And any of the conditions below apply:
   - Partial or Complete Remission by Week 12
   - Response with ≥20% reduction in UPCR by Week 12
   - No longer have nephrotic syndrome



II. TIME AND EVENTS TABLE

Visit **D(ays) +/-3 days &** **W(eeks) +/- 1 week**	**Scr**	**D 1**	**D 15**	**D 29**	**D 43**	**D 57**	**D 71**	**D 85 or wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 52 or Early Term Visit (for any reason)**	**7 and 14 days post final dose**	**Follow up Visit (4 wks post final dose)**
Dose		(Days1-14) 5 mg bid (Days 15 -43) 10 mg bid			Starting on D43, dose modifications based on PK and safety results in accordance with Table 1. Dose will not exceed 15 mg bid					During the extended treatment period, further dose modifications may be made based on efficacy, PK and safety results, in accordance with Table 1. Dose will not exceed 15 mg bid[2]									Single blood draw to assess elimination	
Informed consent	X																			
Demog, Med Hx[1]	X																			
Screening for TB, HIV,HBV, HCV	X																			
Renal biopsy to confirm FSGS if not done prior to entry	X																			
Enroll Eligible Subject		**X**																		
PE & Vital signs,	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Neuropathy Screening Tool (ACTG BPNST)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Assessment of body fluid via measurement of leg circumference & bio-impedance	X	X				X		X				X			X			X		X

Visit D(ays) +/-3 days & W(eeks) +/- 1 week	**Scr**	**D 1**	**D 15**	**D 29**	**D 43**	**D 57**	**D 71**	**D 85 or wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 52 or Early Term Visit (for any reason)**	**7 and 14 days post final dose**	**Follow up Visit (4 wks post final dose)**
Triplicate 12-lead ECGs (triplicates, performed within a 5 minute interval). All ECGs must be performed prior to any IV access or blood draws.	X[3]	X		X		X		X	X	X	X	X	X	X	X	X	X	X		X
PG test	X	X		X		X		X	X	X	X	X	X	X	X	X	X	X		X
Hematology, serum chemistry, lipids,	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X		X
Urinalysis	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X		X
24-hour urine for UPCR, UACR & total protein[4]		X	X	X		X		X				X			X			X		
Midstream spot urine void for UPCR during site visit	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X		X
SF-36 v2 & EQ-5D-5L		X				X	X	X	X	X	X	X	X	X	X	X	X	X		
Dispense CCX140-B		→		→		→		→	→	→	→	→	→	→	→	→	→			
CCX140-B accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Whole blood for DNA		X																		
PD plasma/serum/urine sample collection[5]		X	X	X		X		X		X		X			X			X		X
Lymphocyte Subset[6]		X	X	X		X		X		X		X			X			X		X

Visit D(ays) +/-3 days & W(eeks) +/- 1 week	**Scr**	**D 1**	**D 15**	**D 29**	**D 43**	**D 57**	**D 71**	**D 85 or wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 52 or Early Term Visit (for any reason)**	**7 and 14 days post final dose**	**Follow up Visit (4 wks post final dose)**
PK AUC plasma sample [7]		X		X		X	Pharmacokinetics (C_{min}) – sample is to be collected. However, if there was a dose increase in the prior 2 weeks, PK AUC sample is to be collected instead.														
PK C_{min} sample			X		X															
PK concentration sample																		X	X	
Concomitant medications[8]	X	X	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	X		X

1. Record UPCR and urine protein assessments up to 1 year prior to screening (if available) in the medical history if patients were treated with Rituximab, other CD20+ monoclonal antibodies or calcineurin inhibitors, or other immunotherapy. Plasmapheresis within 12 weeks of screening should be captured in medical history.
2. The decision to modify the dose (i.e.: either to maintain, reduce or increase) will be made 2 weeks after each subject escalates to the 15 mg bid dose. This time point could vary for each subject.
3. Only the Screening 12-lead ECG can be single. The remainder should be triplicate 12 lead ECGs
4. 24 hr UPCR is be required for each dose escalation, and to confirm response at current dose. Total volume should be recorded and a 2 ml aliquot samples should be collected for PK assessment. Sites need to contact the patient prior to the visit day as a reminder to start the 24 hr urine collection. In the rare event that a patient does not bring in a 24-hour sample, a 24 hour sample needs to be started on the visit day and returned to the site upon completed collection. Urine protein:creatinine ratio (UPCR) and urine:albumin ratio (UACR), assessed in a sample drawn from a 24 hour collection is required at baseline and Study Week 12 (see schedule). At other time points defined in the Time and Events table, 24 hour collection is preferred. However, at these visits, a midstream void sample may be used for assessments if a 24hr urine sample is not available.
5. PD samples must be collected before administration of the morning dose. Include urine samples for MCP-1 and MCP-1/creatinine ratio
6. Whole blood for analysis of absolute count and percentages of T cells, B cells and Natural Killer Cells.
7. PK samples are to be collected from time 0 through 6 hours (0, 0.5, 1, 2, 3, 4 & 6) on study day 1 and on the relevant study day for each dose escalation (time 0 occurs immediately before the 1st dose and subsequent samples are collected at 0.5, 1, 2, 3, 4 & 6 hours after dosing and at least 2 weeks after the subject has completed dose escalation/adjustment and is receiving a continuous stable dose. Subjects can eat 1 hour after the time 0 blood draws have been completed (immediately after the 1 hour blood draw).
8. Medications taken up to 12 weeks prior to screening should be captured as concomitant medications. Prior treatment with rituximab or other anti-CD20 monoclonal antibodies and corresponding levels of CD20+ B cells need to be recorded up to 1 year prior to screening. Eligible patients who have entered the study on a continuous cycle therapy of rituximab or other anti-CD20 monoclonal antibodies need to remain on an unchanged therapy at a dosing interval that has been documented to achieve continuous B cell depletion for the given patient unless prohibited due to safety considerations. Their levels of CD20+ B cells that are routinely evaluated per standard of care with anti-CD20 monoclonal antibody therapy need to be recorded throughout the study.

III. LIST OF ABBREVIATIONS AND ACRONYMS

ACTG-BPNST	AIDS Clinical Trials Group – Brief Peripheral Neuropathy Screening Tool
ADLs	Activities of Daily Living
ADR	Adriamycin
ARB	angiotensin receptor II blocker
AUC	area under the curve
AUC_{0-6}	area under the curve, from time of dosing to 6 hours post-dose
BID	two doses per day; also represented as b.i.d.
BMI	Body mass index
CCL2	CC Chemokine Ligand 2 (also known as MCP-1), main chemokine for CCR2
CCR2	CC Chemokine Receptor 2
CCX140-B	sodium salt of CCX140
CKD-EPI	chronic kidney disease epidemiology collaboration
C_{min}	Minimum (minimal) plasma concentration
C_{max}	maximum (maximal) plasma concentration
CR	Complete remission
CTCAE	Common Terminology (or Toxicity) Criteria for Adverse Events
CYP	cytochrome P450
DN	Diabetic nephropathy
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EQ-5D-5L	EuroQo1-5 Dimensions-5 Levels
ESRD	End Stage Renal Disease
FDA	Food and Drug Administration
FSGS	Focal Segmental Glomerulosclerosis
GI	Gastrointestinal
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
hERG	potassium channel encoded by the human ether-à-gogo related gene
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IgG	Immunoglobulin G
IgM	Immunoglobulin M

IGRA	Interferon γ Release Assay
IMP	Investigational medicinal product
IND	Investigational New Drug Application
INR	International Normalized Ratio
KDIGO	Kidney Disease Improving Global Outcomes
LLN	Lower Limit of Normal
LOCF	Last observation carried forward
MCP-1	monocyte chemoattractant protein 1, also known as CCL2
mITT	Modified Intent to treat
MMRM	Mixed-effects model for repeated measures
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
PK	pharmacokinetic(s)
PO	oral (per os); also represented as “p.o.”
PPD	Protein purified derivative
PR	Partial remission
PT	Preferred Term
PT	Prothrombin time
PTT	Partial thromboplastin time
QD	one dose per day; also represented as “q.d.”
RAAS	Renin-angiotensin-aldosterone system
RBC	red blood cell(s)
SAE	Serious adverse event
SF-36	Short form (36) Health Survey
SOC	System Organ Class
$t_{1/2}$	half-life
T2DM	type 2 diabetes mellitus
TEAE	Treatment emergent adverse event
T_{max}	time of maximal concentration
UACR	urinary albumin:creatinine ratio
UAER	urinary albumin excretion rate
ULN	Upper Limit of Normal
UPCR	Urinary protein:creatinine ratio
µM	Micromolar

1. INTRODUCTION

1.1. Background Information

Focal segmental glomerulosclerosis (FSGS) describes a group of disorders that present clinically with proteinuria and progressive renal insufficiency and share a common histologic lesion characterized by scarring that appears on light microscopy to occur in a subset of glomeruli and to affect only part of the involved glomeruli.

Primary FSGS comprises a subset that is currently defined by ruling out other forms of FSGS, where the latter include genetic, adaptive, viral, and medication-associated or toxin-associated disease. Clinically, primary FSGS commonly presents with nephrotic-range proteinuria, reduced plasma albumin levels, and hyperlipidemia. Electron microscopy often reveals generalized effacement of podocytes, despite the focal and segmental appearance of lesions with light microscopy. Current therapeutic recommendations include a trial of high dose glucocorticoids; treatment for durations of 4 to 24 months has been reported to achieve complete or partial remission in 28% to 74% of patients (Korbet et al., 2012; Banfi et al., 1991; Cattran and Rao, 1998; Rydel et al., 1995; Gipson et al., 2016).

Limitations of current therapy include inadequate control for a significant proportion of subjects, high risk of relapse, and toxicity associated with treatment; the latter includes metabolic, cardiovascular, neuropsychiatric and bone toxicity with glucocorticoids, nephrotoxicity with calcineurin inhibitors and increased risk of infection and/or neoplasm associated with immune suppression. There is a need for therapeutic approaches that induce a more rapid response in a greater proportion of subjects with less toxicity, and for well-tolerated agents that can be used chronically to reduce the risk of relapse.

CCR2 has emerged as a potential target for treatment of FSGS based on expression of CCR2 in diseased kidney, association between disease activity and efficacy of CCR2 blockade in animal models with features of FSGS.

CCX140-B is an orally administered, selective antagonist of CCR2, which has exhibited efficacy in murine models of renal injury as assessed by reduction in proteinuria and improvement in renal histology. In patients with diabetic nephropathy, administration of CCX140-B at 5 mg daily or 10 mg daily for up to 52 weeks was associated with and favorable safety profiled and significant reduction from baseline in proteinuria (Study CL005_140; de Zeeuw, et al., 2015).

Based on the preclinical rationale, favorable safety profile, and signals of efficacy in diabetic subjects with marked proteinuria, ChemoCentryx plans to assess CCX140-B in subjects with FSGS. The present study will evaluate the effect of ascending doses of CCX140-B in subjects with nephrotic syndrome who are assessed to be sufficiently stable to delay initiation of high dose glucocorticoids and other immunosuppressant therapy This population has a high unmet medical need for new therapeutic options.

1.2. Potential Role of CCR2 in Pathogenesis of FSGS

A potential role for CCR2 in the pathogenesis of FSGS is supported by clinical and histopathologic observations in subjects with renal disease, and findings with *in vitro* studies and *in vivo* mouse models of FSGS.

CCR2 is a major driver of monocyte migration and activation, and has been shown to mediate renal interstitial inflammation and tubular atrophy in chronic renal diseases by recruiting monocytes to the renal interstitium (Yadav et al; 2010). Increased urinary levels of MCP-1, the ligand for CCR2, is associated with increased interstitial macrophage infiltration in subjects with chronic kidney disease (Eardley et al, 2006) and with increased degree of proteinuria in children with FSGS (Wasilewska, et al, 2011). There is a well-characterized DNA polymorphism (MCP1 2518 A/G) that has been associated with elevated MCP-1 levels and greater risk for development of renal failure in FSGS, as well as in IgA nephropathy, diabetic nephropathy and lupus nephritis (Besbas et al, 2015).

In vitro experiments support a role for the CCR2/MCP-1 pathway in the purported disease acceleration role ascribed to proteinuria. Specifically, it is reported that tubular epithelial cells release MCP-1 (CCL2) when exposed to serum proteins on the apical side (Burton et al, 1999).

In vivo, targeting the MCP-1/CCR2 system in preclinical models of CKD demonstrates benefit. MCP-1 deficient mice are resistant to the development of albuminuria following diabetes induction by streptozotocin and this protective phenotype is marked by a lack of monocyte recruitment into the glomeruli (Chow et al., 2006). MCP-1 deficiency also prevents diabetic *db/db* mice from developing albuminuria (Chow et al., 2007). Pharmacological treatment with a CCR2 antagonist prevents the onset of albuminuria in *db/db* mice and this benefit correlates with a lack of monocyte recruitment to the glomeruli and amelioration of histological damage (Kang et al., 2010). ChemoCentryx conducted an extensive series of preclinical efficacy studies with CCX140-B and surrogate CCR2 antagonists. Efficacy was observed in mouse models of diabetic, non-diabetic nephropathy and in models with features of FSGS induced by partial nephrectomy or by exposure to Adriamycin (ADR). Rapid and significant reduction in proteinuria as assessed by measurements of urinary albumin excretion rate (UAER) and urinary albumin:creatinine ratio (UACR) was observed in all animal models, the reduction in proteinuria are sustained throughout the duration of the studies. Histological parameters were also improved by treatment with CCR2 inhibitors and in combination with RAAS blockade. These histological parameters include reduced glomerular hypertrophy, mesangial expansion, glomerular sclerosis, and increased tubular and glomerular integrity. In addition, histopathology reveals preservation of glomerular architecture and restoration of normal tubular appearance with CCR2 blockade in the 5/6 nephrectomy mouse model. The presence of intra-glomerular CCR2 positive cells has been demonstrated in the animal models (PC0684_140). Moreover, renal protective effects are associated with CCR2 inhibition in the FSGS models. Notably, the number of podocytes per glomerulus is significantly higher with CCR2 inhibitor therapy than in vehicle-treated matched controls (See Investigator's Brochure).

Ex vivo, evidence for a role for CCR2 in FSGS in humans comes from unpublished studies conducted by ChemoCentryx. Expression of CCR2 protein was assessed using immunohistochemistry methods in renal biopsies from normal kidney and from subjects with primary FSGS. Both showed expression of CCR2 in cells implicated in pathogenesis, including parietal epithelial cells, tubular epithelial cells and infiltrating macrophages.

Difference in expression between healthy and diseased kidney was observed in the tubular epithelium, consistent with prior data showing that proteinuria induces CCL2 (MCP-1, the ligand for CCR2) expression in tubules (Burton et al; 1999).

Finally, support derives from the demonstration that CCX140-B was associated with clinically meaningful reduction in proteinuria in a Phase 2 study in subjects with diabetic nephropathy (de Zeeuw, et al., 2015). The pathogenic mechanisms that contribute to proteinuria and progressive renal dysfunction in diabetic nephropathy are shared, at least in part, with mechanisms in FSGS (Jefferson et al., 2008). Specifically, a decrease in podocyte number has been shown in subjects with both type I and type II diabetes mellitus, reduced podocyte number may precede the onset of clinically detectable albuminuria and/or proteinuria by several years, foot process effacement is observed, and experimental and clinical studies have shown a direct correlation between the magnitude of proteinuria and the extent of effacement and decrease in podocyte number. Further, as in FSGS, increased glomerular proteinuria leads to enhanced tubular cell uptake of protein, leading to complement activation, tubulointerstitial inflammation and release of fibrogenic growth factors and inflammatory cytokines.

These observations support the rationale that selective CCR2 inhibition with CCX140-B may provide therapeutic benefit in subjects with FSGS.

1.3. CCR2 Inhibitor CCX140-B: Non-Clinical Safety

The nonclinical safety of CCX140-B was studied in vitro and in vivo in mice, rats, dogs and Cynomolgus monkeys.

In repeat dose toxicity studies (up to 26 weeks in rats and 39 weeks in dogs) two adverse nonclinical findings of concern were revealed:

- Anemia (red blood cell [RBC] parameter findings, with reticulocytosis) was observed across all species studied; rapid recovery of the RBC findings and reticulocytosis was observed following discontinuation of treatment.
- Peripheral axonopathy was observed at high exposures only in dogs; histological findings showed a likely cessation of active damage with decreased immune cell infiltrates following discontinuation of treatment; however, recovery was incomplete during the observation period.

The NOAEL in the 26-week rat studies of 15 mg/kg/day (based on reversible anemia) was associated with systemic $AUC_{0\text{-}24}$ total plasma exposures to CCX140 of 464.6 and 493.7 µg•hr/mL, for males and females, respectively, and the C_{max} concentrations was 32 µg/mL. The NOAEL in the dog studies (based on neuropathy) is higher than the NOAEL established in rat. Thus, for dose escalation in human subjects, the more sensitive rat-based NOAEL will be used: total plasma $AUC_{0\text{-}24}$ exposures of 465 µg•hr/mL, with total C_{max} exposures of 32 µg/mL. These exposures are approximately 3- to 4-fold higher than the predicted human exposures with a 15 mg twice daily (b.i.d.), the highest dose of CCX140-B to be tested in the current study.

Anemia findings are likely translatable to humans, but are verifiable, reversible, and there was an acceptable safety margin across all species (see below). To ensure early detection of anemia in the Phase 2 clinical trial, blood samples will be drawn at baseline, at 6 hours following administration of the first dose, at Study Days 8, 15 and 29, then at every 4 week intervals throughout the treatment and follow up period for assessment of complete blood count, reticulocyte count and bilirubin.

Neuronal findings were observed only in dogs, and may not be translatable to humans. Specifically, in the 39-week dog study, the highest tested dose of CCX140-B was associated with slight to mild neuronal cell changes on histology, with no clinically-observable changes. Off-target binding assays, in vivo immune mechanism assessments, and immunohistochemistry evaluations did not reveal a mechanism, but may rule out direct CCR2 receptor inhibition. In in vitro assessments, there were no metabolites that were unique to dogs, but there was a higher percentage of free CCX140 in plasma in dogs which was unique among studied species, including humans. Thus a threshold effect of free drug concentration cannot be ruled out. Subjects in the Phase 2 study will be monitored for adverse events related to the nervous system, and will be evaluated for early symptoms using a questionnaire validated for early detection of peripheral neuropathy in studies of patients with HIV infection.

1.4. CCR2 Inhibitor CCX140-B: Clinical Experience

CCX140-B has been assessed in 4 Phase 1 clinical trials in healthy volunteers, one Phase 2 trial in subjects with diabetes, and two Phase 2 trials in subjects with diabetic nephropathy. A tabular summary of clinical studies conducted with CCX140-B and submitted to IND 114469 are provided in the Investigator's Brochure.

Efficacy findings in study CL005_140 in patients with diabetic nephropathy and proteinuria provide support for exploring CCX140-B in FSGS. In that trial, 192 subjects with diabetic nephropathy received uninterrupted dosing for up to 52 weeks with placebo, 5 mg daily of CCX140-B or 10 mg daily of CCX140-B. Compared to placebo, CCX140-B was associated with greater reduction in albuminuria. Specifically, changes from baseline in the ratio of urinary albumin to creatinine (UACR) averaged -2% in the placebo group (95% CI -11% to +9%), -18% in the CCX140-B 5 mg group (95% CI -26% to -8%), and -11% in the CCX140-B 10 mg group (95% CI -20% to -1%). The decrease in UACR was observed at the earliest measured time point (Day 15) and reached a maximum decrease by the Day 85 visit (de Zeeuw et al., 2015). Of note, subjects entering the study were stratified based on the level of proteinuria at baseline. In a pre-specified subset analysis, the greatest percentage improvement in UACR from baseline was observed in subjects who presented with the highest baseline UACR (801-3000 mg/g) and eGFR of at least 60 mL/min/1.73m^2. In this subset mean changes in UACR from baseline were +45 % in the placebo group (95% CI -6% to +121%, n=8), -23% in the CCX140-B 5 mg group (95% CI -55% to +32%, n=5; p = 0.03 vs control), and -39% in the CCX140-B 10 mg group (95% CI -61% to -7%; n=8; p = 0.004 vs control).

The pathogenic mechanisms that contribute to proteinuria and progressive renal dysfunction in diabetic nephropathy are shared, at least in part, with mechanisms in FSGS (Jefferson et al., 2008). Specifically, a decrease in podocyte number has been shown in subjects with both type I and type II diabetes mellitus, reduced podocyte number may precede the onset of clinically detectable albuminuria and/or proteinuria by several years, foot process effacement is observed, and experimental and clinical studies have shown a direct correlation between the magnitude of proteinuria and the extent of effacement and decrease in podocyte number. Further, as in FSGS, increased glomerular proteinuria leads to enhanced tubular cell uptake of protein, leading to complement activation, tubulointerstitial inflammation and release of fibrogenic growth factors and inflammatory cytokines.

When taken together with results from the pre-clinical studies, and a favorable clinical safety profile (see Investigator's Brochure), these observations further support evaluation of CCX140-B in highly proteinuric renal diseases, including FSGS.

1.5. Rationale for Study in FSGS: Unmet Medical Need

Supportive management for FSGS includes renin-angiotensin aldosterone system inhibitors (RAAS) blockers for management of proteinuria and hypertension when indicated, and statins for management of dyslipidemia. For patients presenting with primary FSGS and proteinuria, glucocorticoids at doses equivalent to 0.3 to 1.5 mg/kg/d prednisone for durations of 4 to 24 months have been reported to achieve complete or partial remission in 28% to 74% of patients (Korbet et al., 1994; Banfi et al., 1991; Cattran and Rao, 1998; Rydel et al., 1995; Gipson et al., 2016; Cattran et al., 2008).

Limitations of current treatment include inadequate response in a significant proportion of patients, frequent recurrence of disease is responders, and progression of renal insufficiency in most patients over time. The most informative published data on rate of progression derives from the Toronto Glomerulonephritis Registry (Cattran et al, 2008). Among 370 patients with FSGS, eGFR declined by 5 to 18 g/ml/1.75m^2/year in the subset with nephrotic level proteinuria. Among patients with high levels of proteinuria at the time of presentation, 50% progressed to ESRD within 3 to 8 years (D'Agati, 2011). In the US, the estimated incidence of newly-recognized FSGS, and the reported incidence end stage renal disease (ESRD) due to FSGS, are both approximately 7/million/year (Sim et al., 2016). Thus current therapies may be delaying but not preventing, renal failure (Troyanov et al., 2005).

Additional limitations of current therapy include significant morbidity and premature mortality ascribable to the neurologic, metabolic and bone toxicity associated with high dose glucocorticoids, renal toxicity associated with calcineurin inhibitors, and to immunosuppression. There is a need for therapeutic approaches that induce and maintain response in a greater proportion of subjects with less toxicity.

1.6. Risk-Benefit Assessment

For subjects with primary FSGS who do not achieve sustained response with immunosuppression, as assessed by reduction in proteinuria there are no effective therapies available. Histologic recurrence in renal transplants is very high, with high levels of proteinuria portending a poor renal prognosis (Besbas et al, 2015). For subjects who do achieve response, the increased risk of infection associated with corticosteroids is a significant concern, as are the metabolic and neurologic toxicities associated with corticosteroids; these toxicities become increasingly concerning for subjects who require continuous treatment to maintain control (corticosteroid/ immunosuppressant dependent) or who experience frequent relapses and require recurrent treatment.

To date, CCX140-B has been well-tolerated in the 7 completed clinical studies with administered doses ranging from 0.05 mg to 15 mg QD for 12 days and 10 mg QD for 52 weeks.

The rationale for exploring this agent in FSGS is strong. Blockade of CCR2 in murine models of FSGS is associated with reduced proteinuria, improved renal function, and more normal histology. In subjects with diabetic nephropathy, treatment with CCX140-B was associated with

rapid and sustained reduction in proteinuria. If similar findings are observed in clinical trials, CCX140-B may comprise a novel podocyte protective agent to reduce morbidity associated with nephrotic syndrome and sustain renal function, with a favorable safety profile compared to current best standards of care.

2. OBJECTIVES

2.1. Primary Efficacy Objective

The Primary Efficacy Objective is to evaluate the effect of CCX140-B on proteinuria in subjects with primary FSGS with nephrotic syndrome, assessed as a median reduction from baseline of urine protein to creatinine ratio (UPCR) of at least 20%, i.e. ≥ 20%, by week 12.

2.2. Secondary Efficacy Objectives

The secondary efficacy objectives of this study will be assessed at Study Week 12 and through End of Treatment and include:

1. Achievement of partial or complete remission of urine protein to creatinine ratio (UPCR) through Study Week 12 and through the end of treatment, where partial and complete remission are defined as follows:

   Partial Remission (includes all of the following)

   - reduction from baseline by ≥50 percent in UPCR
   - reduction in UPCR to a level that is < 3.5 g/g
   - subject may not be a treatment failure

   Complete Remission (includes all of the following)

   - reduction in UPCR to < 0.3 g/g
   - serum albumin within normal range
   - For patients with abnormal serum creatinine levels at baseline, return to normal levels
   - For patients with normal serum creatinine levels at baseline, final value within 20% of baseline levels
   - subject may not be a treatment failure
2. Assessment of change from baseline in UPCR over time
3. Assessment of time to, and proportion of subjects with achievement of partial remission
4. Assessment of time to, and proportion of subjects with achievement of complete remission
5. Assessment of time to rescue therapy, based on Investigator or physician initiation of glucocorticoids or new immunosuppressive agents or new major treatment modalities (e.g. plasmapheresis, dialysis)

6. Changes over time in other laboratory parameters related to renal function, including:
    - Serum albumin
    - Creatinine
    - Cystatin C
    - eGFR, calculated by the CKD-EPI Cystatin C equation, CKD-EPI Creatinine equation, CKD-EPI Creatinine-Cystatin C equation and MDRD Creatinine equation.
    - urine albumin to creatinine ratio (UACR)
    - total 24 hour urine protein excretion
7. Quality of Life endpoints include:
    - Change in factors associated with quality of life from baseline over time as assessed using the SF-36 v2
    - Change in factors associated with quality of life from baseline over time as assessed using the EQ-5D-5L

2.3. Safety Objectives

The safety objectives of CCX140-B will be assessed via the following endpoints:

1. Adverse events
2. Vital signs
3. Electrocardiograms
4. AIDS Clinical Trials Group Brief Peripheral Neuropathy Screening Tool (ACTG BPNST): To assess potential signs and symptoms of peripheral neuropathy the ACTG BPNST will be completed by study personnel or the study investigator as specified in the Time and Events table.
5. Changes in laboratory parameters including:
    - Hematology including complete blood count, reticulocyte count, smear evaluation
    - Serum haptoglobin, lactate dehydrogenase
    - Serum chemistry including serum transaminases and CPK
    - Urinalysis
    - Coagulation factors (Prothrombin Time [PT], Partial Thromboplastin Time [PTT], International Normalization Ratio [INR])

2.4. Exploratory Objectives

Whole blood, plasma, serum and urine will be collected at baseline and at intervals over the course of the treatment period for exploratory analyses. Parameters will include:

1. Assessment of biomarkers associated with disease activity over time, including blood lipid profile, MCP-1 excreted in urine, and potentially other biomarkers of renal inflammation, fibrosis and injury
2. Assessment of biomarkers associated with risk of severity of disease, which may include allelic variations associated with the pathogenesis and/or prognosis of FSGS such as NPHS1, NPHS2, WT-1, LAMB2, CD2AP, TRPC6, ACTN4, INF2, APOL1

3. Assessment of blood and/or urinary biomarkers associated with CCR2 biology, which may include peripheral blood leukocyte subsets and selected cytokines and chemokines
4. Assessment of mechanisms by which nephrotic syndrome may potentially impact pharmacokinetics of CCX140, including assessment of CCX140 in urine.
5. Assessment of edema as measured by physical examination, leg circumference and body weight
6. Assessment of concentration of CCX140-B in urine

3. STUDY DESIGN AND DOSING REGIMEN

3.1. Initial Treatment Phase

This is an open label clinical trial to test the efficacy, safety, pharmacokinetics and tolerability of ascending doses of CCX140-B in subjects with primary FSGS and nephrotic syndrome.

The screening period will be up to 28 days. Subjects will visit the study center during Screening and on Day 1 (baseline), weekly throughout Dose Escalation, then every 2 weeks through Study Week 12.

Eligible subjects will start treatment with CCX140-B at 5 mg twice daily. CCX140-B will be taken orally without food, at least one hour before meal. The dose will be increased in a stepwise manner to 15 mg twice daily while monitoring safety, in accordance with the rules (Table 1 and Figure 1) and schedule detailed in the Time and Events Table. Treatment at the selected dose will be continued up to Week 12 or until declaration of Treatment Failure.

This study incorporates intra-subject dose escalation and dose modification. Four factors guide dose modification including:

1. Time
2. Response
3. Exposure
4. Safety

During the initial 12 weeks of treatment, dose will be escalated from 5 mg twice daily to 10 mg twice daily on Study Day 15, then to 15 mg twice daily on Study Day 43, if subjects are not considered treatment failures and who otherwise meet criteria for continuation (Table 1, Figure 1).

If planned dose escalation to 10 mg (on day 15) or 15 mg twice daily (on day 43) was previously halted the dose may be escalated further if subjects are not considered treatment failures and who otherwise meet criteria for continuation (Table 1, Figure 1). In such case the subject will return approximately 2 weeks later for blood draws to assess PK (AUC_{0-6}). Subjects will return 2 weeks after the PK assessment to evaluate the safety and need for further dose adjustment.

At any time during the study dose may be de-escalated for safety, or if projected exposure exceeds the maximum allowable exposure defined for the study. Because exposure may be impacted by changes in proteinuria, the protocol requires assessment of exposure if proteinuria declines significantly.

Blood will be drawn to evaluate trough exposure in accordance with the Time and Events Schedule. In addition, as detailed in Table 1, blood will be drawn to assess exposure (AUC_{0-12}, extrapolated from measured AUC_{0-6}), at the following times to guide dosing decisions:

- Study Day 1 prior to first dose of CCX140, and at intervals through 6 hours following the initial dose
- On study Day 29, two weeks following initiation of 10 mg twice daily, to assess exposure at steady state, and to confirm that exposure is within the safety margins based on non-clinical NOAEL
- If dose was adjusted on Day 43, blood will be collected on study Day 57 to assess exposure
- Additional assessments of exposure may be scheduled if indicated. Indications may include:
    - Subjects receiving a total dose greater than 10 mg daily who have experienced at least 50% reduction in proteinuria since the previous PK assessment, to assess impact of change in proteinuria on exposure and to ensure exposure is within safety margins
    - Subjects who experienced a potentially dose-limiting safety event
    - Subjects who required a dose reduction for higher than planned exposure; PK will be assessed approximately 2 weeks after reduction
    - Subjects for whom dose is adjusted for any other reason; PK will be assessed approximately 2 weeks after reduction

If measured or projected steady state PK exposure (AUC_{0-12}) exceeds 240 µg•h/mL, which is approximately half of the rat NOAEL AUC_{0-24}, the dose will be reduced to the dose projected to provide exposure within the target range.

3.1.1. Day 85 and Beyond

If dose is adjusted upward or downward for any reason at Day 85 or during the extended treatment period the subject will return approximately 2 weeks later for blood draws to assess PK (AUC_{0-6}). Subjects will return 2 weeks after the PK assessment to evaluate the safety and need for further dose adjustment.

3.1.2. Extended Treatment Period

Subjects are eligible for the extended treatment period under the following conditions:

1) Not considered treatment failures as of Week 12 *and*
2) In the opinion of the Investigator, remain candidates for investigational treatment *and*
3) Any of the conditions below apply:
    - Partial or Complete Remission by Week 12
    - Response with ≥20% reduction in UPCR by Week 12
    - No longer have nephrotic syndrome

These subjects will return to the clinic for safety, PK and efficacy measurements every 4 weeks. Subjects taking CCX140-B at 15 mg twice daily will be maintained at that dose unless de-escalation is required based on safety signal or steady state PK exposure (AUC_{0-12}) that exceeds 240 µg•h/mL.

Subjects can be considered for dose escalation if all of the following are true:

- Subject is not already treated with 15 mg twice daily *and*
- Subject did not require previous downward dose adjustment ***and***
- Subject is not a Treatment Failure, *and*
- Meets all criteria for continuation:
    - Subject has not achieved and maintained at least a Partial Remission, *and*
    - Projected AUC_{0-12} on the next higher planned dose level does not exceed 240 µg•h/mL *and*
    - The next higher dose does not exceed the Maximum Tolerated Dose (MTD)

Subjects who undergo dose escalation will return to clinic approximately 2 weeks after initiation of the increase for assessment of PK.

Dose modification rules that applied during the initial dose escalation period also apply to dose escalation after 12 weeks.

3.1.3. Follow-Up

Following completion of treatment, or early termination of treatment, all subjects should be urged to return for the termination visit and again 7 and 14 days after their last dose for blood draws to assess elimination pharmacokinetics, and 28 days after their last dose for follow-up and End of Study visit assessments. Appropriate standard of care medical treatment should be provided to all subjects as needed.

After Study Day 43, dose escalation can occur by not more than one step monthly. Within 2 weeks following each dose escalation, PK must be assessed to ensure that the projected AUC_{0-12} does not exceed 240 µg•h/mL. Unscheduled visits for assessment of PK may be required. Stopping rules and dose reduction rules that applied during the 12 week initial dose escalation period also apply during dose escalation after 12 weeks (See Table 2).

Throughout the treatment period, any changes in background medications should be limited to settings in which the Investigator deems it to be necessary for the safety of the subject.

Subjects will be discharged from the study when all the visit procedures have been completed.

3.2. Dose Modification Based on PK Exposure

Blood will be drawn to evaluate trough exposure in accordance with the Time and Events Schedule. In addition, blood will be drawn to assess exposure (AUC_{0-12}, extrapolated from measured AUC_{0-6}) at the following times to guide dosing decisions:

- Study Day 1 prior to first dose of CCX140-B, and at intervals through 6 hours following the initial dose
- Two weeks (Day 29) following initiation of 10 mg twice daily, to assess exposure at steady state, and to confirm that exposure is within the safety margins based on non-clinical NOAEL
- Approximately 2 weeks following initiation of 15 mg twice daily (Day 57, if dose was increased at Day 43), to assess exposure at steady state, and to confirm that exposure is

within the safety margins (projected AUC_{0-12} less than or equal to 240 µg•h/mL) based on non-clinical NOAEL

- At Study Day 85 PK will be assessed to guide dosing beyond Week 12.
- Additional assessments of exposure may be scheduled if indicated. Indications may include:
    - Subjects receiving a total dose greater than 10 mg daily who have experienced at least 50% reduction in proteinuria since the previous PK assessment, to assess impact of change in proteinuria on exposure and to ensure exposure is within safety margins
    - Subjects who experienced a potentially dose-limiting safety event
    - Subjects who required a dose reduction for higher than planned exposure; PK will be assessed approximately 2 weeks after reduction
    - Subjects for whom dose is adjusted for any other reason; PK will be assessed approximately 2 weeks after reduction

If planned dose escalation to 10 mg (on day 15) or 15 mg twice daily (on day 43) was previously halted the dose may be escalated further if subjects are not considered treatment failures and otherwise meet criteria for continuation (Table 1, Figure 1). In such cases the subject will return approximately 2 weeks later for blood draws to assess PK (AUC_{0-6}). Subjects will return 2 weeks after the PK assessment to evaluate the safety and need for further dose adjustment.

3.3. Dose Modifications During the Extended Treatment Period

If measured or projected exposure steady state PK exposure (AUC_{0-12}) exceeds 240 µg•h/mL, which is approximately half of the rat NOAEL AUC_{0-24}, the dose will be reduced to the dose projected to provide exposure within the target range.

For subjects who escalate dose to 10 mg twice daily on Study Day 15, PK samples from the dose two weeks after 10 mg BID dosing (planned for Day 29) will be analyzed expeditiously and the PK data will be used for projecting the steady state PK exposure. If the projected steady state PK exposure (AUC_{0-12}) is higher than 240 µg•h/mL, which is half of the rat NOAEL steady state AUC_{0-24}, the dose will be reduced to 5 mg BID for the remainder of the study (Table 2).

If the projected steady state PK exposure (AUC_{0-12}) is lower than 240 µg•h/mL, the steady PK exposure at 15 mg BID will be projected from the 10 mg BID Day 43 PK data. If the projected PK exposure (AUC_{0-12}) at 15 BID is lower than 240 µg•h/mL, the dose will be escalated to 15 BID. If the projected PK exposure (AUC_{0-12}) is higher than 240 µg•h/mL, the dose will not escalate to 15 mg BID but will stay at 10 mg BID for the remainder of the study.

4. STUDY POPULATION

4.1. Size of Population

Approximately 13 male or female adult subjects with biopsy-proven primary FSGS and nephrotic syndrome will be enrolled in the study. In the first stage 6 subjects will be treated.

After all of the initial 6 subjects have completed their 12-weeks of treatment the study will be paused and assessed. If the overall study results are deemed safe and the subjects' responses to

treatment are considered clinically meaningful, seven additional subjects will be treated for a total of 13 subjects.

4.2. Inclusion Criteria

1. Male or female subjects aged 18 years and older
2. Renal biopsy findings consistent with diagnosis of focal segmental glomerulosclerosis (FSGS), and consistent with primary FSGS based on presentation of histopathology, medical history, and clinical course; subjects with genetic risk factors with presentations that are otherwise consistent with primary FSGS may also be enrolled.
3. Urinary total protein:creatinine ratio (UPCR) ≥ 3.5 g protein/g creatinine at screening, based on sample drawn from a 24-hour collection
4. Hypoalbuminemia of less than 3.5 g/dL
5. Estimated glomerular filtration rate (eGFR) >30 mL/min/1.73m^2, as calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD_EPI) equation (using creatinine or cystatin C)
6. If used, RAAS inhibitor dose, including doses of angiotensin converting enzyme inhibitor and/or angiotensin II receptor antagonist must have been started at least 4 weeks prior to Study Day 1, and projected to remain stable throughout the course of the study unless adjustment is required for management of hypertension.
7. Female subjects of childbearing potential may participate if adequate contraception is used during, and for at least 5 half- lives after last dose of study drug. 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 one month after the last dose of study drug. 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). In addition, a barrier method (i.e. cervical cap, diaphragm or condom) must be used during intercourse between a male subject and a female of child-bearing potential.
8. Willing and able to give written Informed Consent and to comply with the requirements of the study protocol
9. Judged to be otherwise fit for the study 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. Pregnant or nursing
2. History of organ transplantation, including renal transplantation

3. Currently on an organ transplant waiting list or there's a reasonable possibility of getting an organ transplant within 6 months of screening
4. Histological FSGS subtype of collapsing variant
5. Subjects who initiated, discontinued or changed dose of rituximab or other anti-CD20 monoclonal antibodies **within 16 weeks (4 months)** prior to screening are excluded. Subjects who initiated treatment with rituximab or other anti-CD20 monoclonal antibodies >16 weeks (4 months) prior to screening are permitted if deemed safe by the investigator and only if they are intended to remain on continued, unchanged therapy at a dosing interval that has been documented to achieve continuous B cell depletion for the given patient. UPCR and other urine protein assessments up to 1 year prior to screening (if available) that were performed in these patients as part of the clinical routine should be recorded in the medical history.
6. Subjects who discontinued Rituximab or other anti-CD20 monoclonal antibodies **>16 weeks (4 months)** prior to screening *without* confirmed recovery of CD20+ B cell population to within normal range are excluded. Subjects who discontinued rituximab or other anti-CD20 monoclonal antibodies >16 weeks (4 months) prior to screening *with* confirmed recovery of CD20+ B cell population to within normal range are permitted in the study. UPCR and other urine protein assessments up to 1 year prior to screening (if available) that were performed in these patients as part of the clinical routine should be recorded in the medical history.
7. Subjects who initiated or increased the dose of calcineurin inhibitors, or other immunotherapy, within 12 weeks prior to screening are excluded; dose reductions to maintain calcineurin inhibitors at optimal safe levels are permitted. Subjects who initiated a treatment with calcineurin inhibitors, or other immunotherapy >12 weeks are permitted. UPCR and other urine protein assessments up to 1 year prior to screening (if available) that were performed in these patients as part of the clinical routine should be recorded in the medical history.
8. Subjects taking glucocorticoids at dose greater than 10 mg/day prednisone equivalent within 4 weeks prior to screening are excluded.
9. Plasmapheresis within 12 weeks prior to screening
10. Body Mass Index (BMI) ≥ 40
11. Participated in any clinical study of an investigational product within 12 weeks prior to screening or within 5 half-lives after taking the last dose
12. Currently on dialysis or likely to require dialysis during the study
13. History or presence of any form of cancer within the 5 years prior to screening, with the exception of excised basal cell or squamous cell carcinoma of the skin, or carcinoma *in situ* such as cervical or breast carcinoma *in situ* that has been excised or resected completely and is without evidence of local recurrence or metastasis
14. Positive HBV, HCV, or HIV viral screening test. Subjects who have received highly effective therapy for HCV demonstrated to have negative viral titers for at least 6 months

following discontinuation of treatment, will be considered to have a negative HCV screening test weeks prior to screening

15. Evidence of tuberculosis based on interferon γ release assay (IGRA), tuberculin purified protein derivative (PPD) skin test, or chest radiography done during screening or within 6 weeks prior to screening
16. Evidence of hepatic disease; AST, ALT, alkaline phosphatase >2x ULN, or total bilirubin > 2x ULN or INR > 1.5 x ULN at screening with the exception that isolated INR elevation in the absence of other significant liver enzyme abnormalities is explained by anticoagulant therapy, (e.g. warfarin).
17. Clinically significant peripheral neuropathy
18. Hematologic abnormalities as follows: Hb <8 g/dL, platelets <50,000, ANC <1000 cells/μL) at baseline
19. Abnormality of ECG at screening, assessed by the Investigator as clinically significant (e.g. QTcF greater than 450 msec).
20. History of alcohol or illicit drug abuse. Recreational use of cannabis is not excluded where legalized.
21. History of gastrointestinal conditions that may interfere with study medication compliance, e.g., severe gastroparesis, with regurgitation of food or oral medication
22. Known hypersensitivity to CCX140-B or inactive ingredients of the CCX140-B tablets (including microcrystalline cellulose, starch, crospovidone, magnesium stearate, or silicon dioxide)
23. Renal disease associated with disorders other than FSGS (e.g. lupus nephritis, C3 glomerulonephropathy) that is active, or has significant risk of progressing to end state renal disease during the 12-week initial treatment phase of the study
24. History or presence of systemic disorder other than FSGS that requires, or is expected to require, systemic corticosteroids or immune modulators; topical or inhaled corticosteroids and immune modulators are not excluded
25. 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
26. Subjects taking strong CYP3A4 inducers (e.g., phenytoin, rifampicin, carbamazepine, St. John's Wort) or strong CYP3A4 inhibitors (e.g., boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole) within two weeks prior to screening.
27. Subjects taking lithium, pamidronate or interferon; subjects taking non-steroidal anti-inflammatory agents (NSAIDS) chronically (intermittent, i.e. occasional NSAIDS for pain or fever is discouraged, but is not excluded).

5. STUDY TREATMENTS

5.1. Product Characterizations

The investigational medicinal products (IMP) are oral film coated tablets containing 5 mg of CCX140-B. The tablets are manufactured under current good manufacturing practice. The clinical trial material is packaged in high density polyethylene (HDPE) bottles containing 30 tablets.

5.2. Rationale for Dose Range

5.2.1. Safety

The three active treatment doses proposed for the study are 5 mg administered twice daily, 10 mg administered twice daily and 15 mg administered twice daily.

Five (5) mg twice daily is selected as the lowest dose for exploration of dose response. The projected exposure at this dose is well below the NOAEL established in non-clinical toxicology studies. Specifically, using the rat as the more sensitive species based on exposure, the NOAEL in the 26-week rat study was 15 mg/kg/day. The NOAEL in the 13-week and 26-week rat studies were associated with systemic exposures to CCX140 which were about 18-20 times higher than the projected human exposure associated with a daily 5 mg dose, and about 8-10 fold a 10 mg BID dose.

Ten (10) mg twice daily is selected as an intermediate dose for exploration of dose response and to guard against losing the efficacious dose if 15 mg twice daily is associated with unexpected or intolerable toxicity. Using the rat as the more sensitive species based on exposure, the NOAEL in the 26-week rat study was 15 mg/kg/day. The NOAEL in the 13-week and 26-week rat studies were associated with systemic exposures to CCX140 which were about 9-10 times higher than the human exposure associated with a daily 10 mg dose, and about 4-5 fold a 10 mg BID dose.

Fifteen (15) mg twice daily is selected as the highest dose for this protocol, which is projected to provide exposure at both peak and trough that is within the safety margins established in the toxicology program, and that is projected to maintain a high level of target engagement, as summarized below and detailed in the Investigator's Brochure. The projected clinical exposure with 15 mg twice daily dosing is 3-fold below the NOAEL exposure established in the most sensitive species tested in the nonclinical toxicity studies (rat 26-week, PO, QD) The safety margin associated with this exposure is approximately 3-fold below the NOAEL established in rat, and 5-8-fold below the exposure established in dog.

The projected exposures and safety margins were established for humans without proteinuria. Because CCX140-B is highly protein bound, nephrotic subjects may have a lower exposure at a given dose due to potential drug loss with protein in urine.

In humans, CCX140-B has been administered and was well tolerated at 15 mg administered once daily for up to 10 days in healthy volunteers, and at 10 mg administered once daily for up to 52 weeks in subjects with Diabetic Nephropathy (DN). Administration of 15 mg twice daily in humans without proteinuria is projected to achieve a peak concentration of ~6.5 µg/mL (~13 µM) and a trough concentration of ~5.5 µg/mL (~11µM) at steady state. Total exposure with 15 mg twice daily is projected to be ~2-fold higher than that achieved with 15 mg daily

administration in healthy volunteers and 3.07-fold higher than that observed with 10 mg daily exposure in subjects with DN. Trough exposure with 15 mg twice daily is projected to be 2.4-fold higher than trough exposure achieved in DN.

The projected clinical exposure with 15 mg BID dosing is 3-fold below the NOAEL exposure established in the most sensitive species tested in the nonclinical toxicity studies (rat 26-week, PO, QD), as detailed in the Investigator's Brochure.

Rationale for selection of 15 mg twice daily is to ensure adequate exposure margin to address:

1. Loss of albumin-bound drug through proteinuria; a post-hoc analysis PK in subjects of trial #CL005_140 who entered in study with albuminuria >1 gram indicated exposure was approximately 30% below the mean for the treatment group as a whole
2. Increased binding competition from endogenous ligand; MCP-1 is reported to be increased in serum and urine in subjects with FSGS

Rationale for administration of the highest dose as a divided dose (15 mg twice daily), as opposed to a single dose (30 mg once daily) include:

1. Ease of administration (3 tablets twice daily vs 6 tablets once daily)
2. 15 mg administered as a single daily dose has previously been tested and tolerated in healthy volunteers, while 30 mg has not been previously dosed
3. 15 mg twice daily will result in a lower C_{max} than 30 mg once daily, mitigating the potential for C_{max}-driven safety concerns

To ensure early detection of dose-related safety signals, the proposed protocol will incorporate:

1. Frequent clinical visits and safety laboratory assessments, including application of a standard health assessment and a questionnaire to detect symptoms of neuropathy at regular intervals as detailed in the Time and Events Table.
2. Safety monitoring by a Safety Review Committee throughout the study.

In all subjects, treatment at the selected dose will be continued through 12 weeks or until declaration of Treatment Failure, where Treatment Failure is defined as any of the following:

1. Progression of renal disease, defined as eGFR that is both below 60 ml/min/1.73 m^2 and is confirmed to represent at least a 30% decline in eGFR from baseline;
2. Requirement for rescue with glucocorticoids, other new immunomodulatory or immunosuppressive therapy, plasmapheresis, or dialysis, per the judgment of the Investigator;
3. Pre-specified adverse event or laboratory abnormality that, per Protocol, requires permanent discontinuation of study CCX140-B
4. Any other treatment-related adverse event, laboratory evidence of toxicity, or intolerance that, in the judgment of the Investigator, warrants permanent discontinuation of CCX140-B.

5.2.2. Efficacy

This study is designed to test CCX140-B at doses ranging from 5 mg twice daily, through 15 mg bid, a dose projected to provide continuous high level receptor engagement and antagonism.

The targeted dose was derived from observations in a murine model with features of FSGS, the Adriamycin-induced nephropathy mouse model (Lee, et al., 2011). CCX140 does not bind murine CCR2 and human CCR2 with the same potency. Therefore the model was established in a CCR2 knockout and human CCR2 knock-in (hCCR2-KI) mouse. Mice were treated with 10, 30, and 90 mg/kg of CCX140 once daily for 9 days. The 24 hour blood samples from 90 mg/kg dosing resulted in close to 100% receptor coverage. The mean CCX140 concentration at trough was 3.3 µg/mL.

In the absence of proteinuria, the human trough concentration with 15 mg twice daily dosing is projected to be ~5.5 µg/mL, which is higher than the 3.3 µg/mL required for 100% CCR2 blockade in the above described hCCR2 mouse model. However, the projected exposures and safety margins were established for humans without proteinuria. Because CCX140-B is highly protein bound, subject with nephrotic-level proteinuria may have a lower exposure at a given dose due to potential drug loss with protein in urine or impact of disease on metabolism. A post-hoc analysis of PK in diabetic nephropathy subjects of trial CL005_140 who entered in study with albuminuria of 2 – 3 grams indicated that exposure was approximately 30% below the mean for the treatment group as a whole (~0.8 µg/mL versus ~1.2 µg/mL).

Therefore 15 mg twice daily was selected as the upper limit for dose ranging for subjects without nephrotic level proteinuria.

5.3. Drug Supply

5.3.1. Packaging and Labeling

The investigational medicinal products (IMP) are oral film coated tablets containing 5 mg of CCX140-B. The tablets are manufactured under current good manufacturing practice. The clinical trial material is packaged in high density polyethylene (HDPE) bottles containing 30 tablets.

5.3.2. Storage

CCX140-B tablets will be stored according to label instructions. Access should be restricted to pharmacy staff or to the designated responsible member of the Investigator's staff, and to the study monitor. The Investigator agrees that neither s/he nor any of the study staff will supply study medication to any persons other than those enrolled in the study.

5.3.3. Blinding

Since this study is open-label blinding guidelines are not applicable.

6. STUDY PROCEDURES

6.1. Screening Assessments (Day-28 to Day 0)

Prior to any study related assessments review the Informed Consent and have the subject acknowledge their understanding, then provide a copy to the subject

1. Demographics, Medical History (verify plasmapheresis status within 12 weeks of screening)
2. Screening for Tuberculosis, HIV, HBC & HCV if status is unknown
3. Full Physical Examination and Vital Signs including height, weight, heart rate, respiratory rate and body temperature
4. AIDS Clinical Trials Group Brief Peripheral Neuropathy Screening Tool (ACTG BPNST)
5. Leg circumference and bioimpedance to assess edema
6. Renal biopsy for FSGS confirmation if status is unknown
7. Hematology, Serum Chemistry, Urinalysis
8. Pregnancy Test for women of childbearing potential
9. 12-lead ECG (no triplicate ECG is necessary for screening)
10. Concomitant medications including medications taken for up to 12 weeks prior to screening Day 1 should be captured on the eCRF. Prior treatment with rituximab or other anti-CD20 monoclonal antibodies and corresponding levels of CD20+ B cells need to be recorded up to 1 year prior to screening Day 1. Eligible patients who have entered the study on a continuous cycle therapy of rituximab or other anti-CD20 monoclonal antibodies need to remain on an unchanged therapy throughout the study at a dosing interval that has been documented to achieve continuous B cell depletion for the given patient unless prohibited due to safety considerations. Their levels of CD20+ B cells that are routinely evaluated per standard of care with anti-CD20 monoclonal antibody therapy need to be recorded throughout the study. Record UPCR and urine protein assessments up to 1 year prior to screening (if available) in the medical history if patients were treated with Rituximab, other CD20+ monoclonal antibodies, calcineurin inhibitors, or other immunotherapy

6.2. Study Day 1 (After Confirmation of Eligibility)

All evaluations on day 1 (unless otherwise specified in the Day 1 section) will occur PRIOR to dosing to serve as baseline evaluations.

1. Enroll study subject and obtain enrollment ID code
2. Full Physical Examination and Vital Signs including height, weight, heart rate, respiratory rate and body temperature
3. 24 hour urine collection for UPCR, UACR and total protein. ***Subject starts 24hr. collection after the first void in the morning of the day prior to the visit day and should bring the 24hr collection (including first morning void on the visit day) to the visit. Sites need to contact the subject prior to the visit day as a reminder to start the 24 hr. urine collection***
4. AIDS Clinical Trials Group Brief Peripheral Neuropathy Screening Tool (ACTG BPNST)

5. Leg circumference and bioimpedance to assess edema
6. Triplicate 12-Lead ECG
7. Pregnancy Test for women of childbearing potential
8. Hematology, Serum Chemistry, Urinalysis
9. 24 hour urine collection for UPCR, UACR and total protein. ***Subject starts 24hr. collection after the first void in the morning of the day prior to the visit day and should bring the 24hr collection (including first morning void on the visit day) to the visit. Sites need to contact the subject prior to the visit day as a reminder to start the 24 hr. urine collection. Please be reminded that a 24 hr. urine collection at baseline (Study day 1) and at week 12 are mandatory.***
10. SF-36 v2 and EQ-5D-5L
11. Dispense diaries and *Directions for Use* along with a 30 day supply of CCX140-B bottles.
12. Pharmacokinetics (time 0, 0.5, 1, 2, 3, 4 & 6 hours post dose), the time 0 sample is to be collected just prior to administration of the first dose of CCX140-B. Subjects must fast prior to the time 0, 0.5 and 1 hour PK and can consume food immediately after the 1 hour PK blood draw.
13. PD (plasma, serum and urine and whole blood for the lymphocyte subset and DNA)
14. Concomitant medications- verify and document any new medications that subject has started since the previous visit.
15. Adverse Events- record all adverse events starting with first dose of study medication and serious adverse events starting after administration of Informed Consent.

6.3. Study Day 15 (Safety, Efficacy and PK)

1. Symptom directed abbreviated physical examination and vital signs including weight, heart rate, respiratory rate and body temperature.
2. AIDS Clinical Trials Group Brief Peripheral Neuropathy Screening Tool (ACTG BPNST).
3. Leg circumference and bioimpedance to assess edema
4. Hematology, Serum Chemistry, Urinalysis
5. 24 hour urine collection for UPCR, UACR and total protein. ***Subject starts 24hr. collection after the first void in the morning of the day prior to the visit day and should bring the 24hr collection (including first morning void on the visit day) to the visit. Sites need to contact the subject prior to the visit day as a reminder to start the 24 hr. urine collection***
6. Review diary and used study medication with each subject. Confirm dosing compliance.
7. Pharmacokinetics (C_{min}) – sample is to be collected at time 0 (just prior to taking the first dose of 10 mg CCX140-B)
8. PD (plasma, serum and urine and whole blood for the lymphocyte subset). Samples are to be collected at time 0.

9. Concomitant medications- verify and document any new medications that subject has started since the previous visit.
10. Adverse Events- record all adverse events starting with first dose of study medication.

6.4. Study Day 29 (Safety, Efficacy and PK)

1. Symptom directed abbreviated physical examination and vital signs including weight, heart rate, respiratory rate and body temperature.
2. AIDS Clinical Trials Group Brief Peripheral Neuropathy Screening Tool (ACTG BPNST)
3. Leg circumference and bioimpedance to assess edema
4. Triplicate 12-Lead ECG
5. Pregnancy Test for women of childbearing potential
6. Hematology, Serum Chemistry, Urinalysis
7. Review diary and used study medication with each subject. Confirm dosing compliance.
8. Dispense diaries and *Directions for Use* along with a 30 day supply of CCX140-B bottles. Discuss new potential dose when relevant.
9. 24 hour urine collection for UPCR, UACR and total protein. ***Subject starts 24 hr. collection after the first void in the morning of the day prior to the visit day and should bring the 24 hr collection (including first morning void on the visit day) to the visit. Sites need to contact the subject prior to the visit day as a reminder to start the 24 hr. urine collection***
10. PD (plasma, serum and urine and whole blood for the lymphocyte subset). Samples are to be collected at time 0.
11. Concomitant medications- verify and document any new medications that subject has started since the previous visit.
12. Adverse Events- record all adverse events.
13. Pharmacokinetics (time 0, 0.5, 1, 2, 3, 4 & 6 hours post dose), the time 0 sample is to be collected just prior to administration of the first dose of CCX140-B. Subjects must fast prior to the time 0, 0.5 and 1 hour PK and can consume food immediately after the 1 hour PK blood draw.

6.5. Study Day 43- evaluate results from Day 29 (modify dose per dose modification guidelines based on PK results)

1. Symptom directed abbreviated physical examination and Vital Signs including weight, heart rate, respiratory rate and body temperature. AIDS Clinical Trials Group Brief Peripheral Neuropathy Screening Tool (ACTG BPNST)
2. First morning void for UPCR measurement
3. Review diary and used study medication with each subject. Confirm dosing compliance.
4. Pharmacokinetics (C_{min}) – sample is to be collected at time 0 (just prior to taking the next)

5. Dispense diaries and *Directions for Use* along with CCX140-B bottles. Discuss new potential dose when relevant.
6. Concomitant medications- verify and document any new medications that subject has started since the previous visit.
7. Adverse Events- record all adverse events.

6.6. Study Day 57(+/- 3 Days)-Safety, Efficacy, PK

1. Symptom directed abbreviated physical examination and Vital Signs including weight, heart rate, respiratory rate and body temperature.
2. AIDS Clinical Trials Group Brief Peripheral Neuropathy Screening Tool (ACTG BPNST)
3. Leg circumference and bioimpedance to assess edema
4. Triplicate 12-Lead ECG
5. Pregnancy Test for women of childbearing potential
6. Review diary and used study medication with each subject. Confirm dosing compliance.
7. Dispense diaries and *Directions for Use* along with a 30 day supply of CCX140-B bottles. Discuss new potential dose when relevant.
8. Hematology, Serum Chemistry, Urinalysis
9. Pharmacokinetics (time 0, 0.5, 1, 2, 3, 4 & 6 hours post dose), the time 0 sample is to be collected just prior to administration of the next dose of CCX140-B. Subjects must fast prior to the time 0, 0.5 and 1 hour PK and can consume food immediately after the 1 hour PK blood draw.
10. PD (plasma, serum and urine and whole blood for the lymphocyte subset). Samples are to be collected at time 0.
11. 24 hour urine collection for UPCR, UACR and total protein. ***Subject starts 24 hr. collection after the first void in the morning of the day prior to the visit day and should bring the 24 hr collection (including first morning void on the visit day) to the visit. Sites need to contact the subject prior to the visit day as a reminder to start the 24 hr. urine collection***
12. SF-36 V2 and EQ-5D-5L
13. Concomitant medications- verify and document any new medications that subject has started since the previous visit.
14. Adverse Events- record all adverse events.

6.7. Study Day 71(+/- 3 Days)-Safety, Efficacy, PK

1. Symptom directed abbreviated physical examination and Vital Signs including weight, heart rate, respiratory rate and body temperature.
2. AIDS Clinical Trials Group Brief Peripheral Neuropathy Screening Tool (ACTG BPNST)
3. Review diary and used study medication with each subject. Confirm dosing compliance.

4. Pharmacokinetics (C_{min}) – sample is to be collected at time 0 (just prior to taking the first dose of CCX140-B). However, **if there was a dose increase in the prior 2 weeks,** PK AUC (time 0, 0.5, 1, 2, 3, 4 & 6 hours post dose) is to be collected instead. The time 0 sample is to be collected just prior to administration of the first dose of CCX140-B. Subjects must fast prior to the time 0, 0.5 and 1 hour PK and can consume food immediately after the 1 hour PK blood draw.
5. First morning void for UPCR measurement
6. SF-36 V2 and EQ-5D-5L
7. Concomitant medications- verify and document any new medications that subject has started since the previous visit.
8. Adverse Events- record all adverse events.

6.8. Study Week 12 or Day 85 (+/- 3 days) (Safety & Efficacy)- See Section 6.19 for PK elimination visit guidelines

1. Symptom directed abbreviated physical examination and Vital Signs including weight, heart rate, respiratory rate and body temperature.
2. AIDS Clinical Trials Group Brief Peripheral Neuropathy Screening Tool (ACTG BPNST)
3. Leg circumference and bioimpedance to assess edema
4. Triplicate 12-Lead ECG
5. Pregnancy Test for women of childbearing potential
6. Hematology, Serum Chemistry, Urinalysis
7. 24 hour urine collection for UPCR, UACR and total protein. ***Subject starts 24 hr. collection after the first void in the morning of the day prior to the visit day and should bring the 24 hr collection (including first morning void on the visit day) to the visit. Sites need to contact the subject prior to the visit day as a reminder to start the 24 hr. urine collection. Please be reminded that a 24 hr. urine collection at baseline (study day 1) at week 12 are mandatory.***
8. Pharmacokinetics (C_{min}) – sample is to be collected at time 0 (just prior to taking the first dose of CCX140-B). However, **if there was a dose increase in the prior 2 weeks,** PK AUC (time 0, 0.5, 1, 2, 3, 4 & 6 hours post dose) is to be collected instead. The time 0 sample is to be collected just prior to administration of the first dose of CCX140-B. Subjects must fast prior to the time 0, 0.5 and 1 hour PK and can consume food immediately after the 1 hour PK blood draw.
9. SF-36 V2 and EQ-5D-5L
10. PD (plasma, serum and urine and whole blood for the lymphocyte subset). Samples are to be collected at time 0.
11. Review diary and used study medication with each subject. Confirm dosing compliance.
12. Dispense diaries and *Directions for Use* along with a 30 day supply of CCX140-B bottles.

13. Concomitant medications- verify and document any new medications that subject has started since the previous visit.
14. Adverse Events- record all adverse events.

6.9. Week 16 (+/- 1 week) (See Section 6.19 for PK elimination visit guidelines)

1. Symptom directed abbreviated physical examination and Vital Signs including weight, heart rate, respiratory rate and body temperature.
2. AIDS Clinical Trials Group Brief Peripheral Neuropathy Screening Tool (ACTG BPNST)
3. Triplicate 12-Lead ECG
4. Pregnancy Test for women of childbearing potential
5. Hematology, Serum Chemistry, Urinalysis
6. Pharmacokinetics (C_{min}) – sample is to be collected at time 0 (just prior to taking the first dose of CCX140-B). However, **if there was a dose increase in the prior 2 weeks,** PK AUC (time 0, 0.5, 1, 2, 3, 4 & 6 hours post dose) is to be collected instead. The time 0 sample is to be collected just prior to administration of the first dose of CCX140-B. Subjects must fast prior to the time 0, 0.5 and 1 hour PK and can consume food immediately after the 1 hour PK blood draw.
7. First morning void for UPCR measurement
8. SF-36 V2 and EQ-5D-5L
9. Review diary and used study medication with each subject. Confirm dosing compliance.
10. Dispense diaries and *Directions for Use* along with a 30 day supply of CCX140-B bottles.
11. Concomitant medications- verify and document any new medications that subject has started since the previous visit.
12. Adverse Events- record all adverse events.

6.10. Week 20 (+/- 1 week)

1. Symptom directed abbreviated physical examination and Vital Signs including weight, heart rate, respiratory rate and body temperature.
2. AIDS Clinical Trials Group Brief Peripheral Neuropathy Screening Tool (ACTG BPNST)
3. Triplicate 12-Lead ECG
4. Pregnancy Test for women of childbearing potential
5. Hematology, Serum Chemistry, Urinalysis
6. First morning void for UPCR measurement
7. Pharmacokinetics (C_{min}) – sample is to be collected at time 0 (just prior to taking the first dose of CCX140-B). However, **if there was a dose increase in the prior 2 weeks,** PK AUC (time 0, 0.5, 1, 2, 3, 4 & 6 hours post dose) is to be collected instead. The time 0 sample is to

be collected just prior to administration of the first dose of CCX140-B. Subjects must fast prior to the time 0, 0.5 and 1 hour PK and can consume food immediately after the 1 hour PK blood draw.

8. SF-36 V2 and EQ-5D-5L
9. PD (plasma, serum and urine and whole blood for the lymphocyte subset). Samples are to be collected at time 0.
10. Review diary and used study medication with each subject. Confirm dosing compliance.
11. Dispense diaries and *Directions for Use* along with a 30 day supply of CCX140-B bottles.
12. Concomitant medications- verify and document any new medications that subject has started since the previous visit.
13. Adverse Events- record all adverse events.

6.11. Week 24 (+/- 1 week) (See Section 6.19 for PK elimination visit guidelines)

1. Symptom directed abbreviated physical examination and Vital Signs including weight, heart rate, respiratory rate and body temperature.
2. AIDS Clinical Trials Group Brief Peripheral Neuropathy Screening Tool (ACTG BPNST)
3. Triplicate 12-Lead ECG
4. Pregnancy Test for women of childbearing potential
5. Hematology, Serum Chemistry, Urinalysis
6. Pharmacokinetics (C_{min}) – sample is to be collected at time 0 (just prior to taking the first dose of CCX140-B). However, **if there was a dose increase in the prior 2 weeks,** PK AUC (time 0, 0.5, 1, 2, 3, 4 & 6 hours post dose) is to be collected instead. The time 0 sample is to be collected just prior to administration of the first dose of CCX140-B. Subjects must fast prior to the time 0, 0.5 and 1 hour PK and can consume food immediately after the 1 hour PK blood draw.
7. First morning void for UPCR measurement
8. SF-36 V2 and EQ-5D-5L
9. Review diary and used study medication with each subject. Confirm dosing compliance.
10. Dispense diaries and *Directions for Use* along with a 30 day supply of CCX140-B bottles.
11. Concomitant medications- verify and document any new medications that subject has started since the previous visit.
12. Adverse Events- record all adverse events.

6.12. Week 28 (+/- 1 week) (See Section 6.19 for PK elimination visit guidelines)

1. Symptom directed abbreviated physical examination and Vital Signs including weight, heart rate, respiratory rate and body temperature.
2. AIDS Clinical Trials Group Brief Peripheral Neuropathy Screening Tool (ACTG BPNST)
3. Leg circumference and bioimpedance to assess edema
4. Triplicate 12-Lead ECG
5. Pregnancy Test for women of childbearing potential
6. Hematology, Serum Chemistry, Urinalysis
7. 24 hour urine collection for UPCR, UACR and total protein. ***Subject starts 24hr. collection after the first void in the morning of the day prior to the visit day and should bring the 24hr collection (including first morning void on the visit day) to the visit. Sites need to contact the subject prior to the visit day as a reminder to start the 24 hr. urine collection***
8. Pharmacokinetics (C_{min}) – sample is to be collected at time 0 (just prior to taking the first dose of CCX140-B). However, **if there was a dose increase in the prior 2 weeks,** PK AUC (time 0, 0.5, 1, 2, 3, 4 & 6 hours post dose) is to be collected instead. The time 0 sample is to be collected just prior to administration of the first dose of CCX140-B. Subjects must fast prior to the time 0, 0.5 and 1 hour PK and can consume food immediately after the 1 hour PK blood draw.
9. SF-36 V2 and EQ-5D-5L
10. PD (plasma, serum and urine and whole blood for the lymphocyte subset). Samples are to be collected at time 0.
11. Review diary and used study medication with each subject. Confirm dosing compliance.
12. Dispense diaries and *Directions for Use* along with a 30 day supply of CCX140-B bottles.
13. Concomitant medications- verify and document any new medications that subject has started since the previous visit.
14. Adverse Events- record all adverse events.

6.13. Week 32 (+/- 1 week) (See Section 6.19 for PK elimination visit guidelines)

1. Symptom directed abbreviated physical examination and Vital Signs including weight, heart rate, respiratory rate and body temperature.
2. AIDS Clinical Trials Group Brief Peripheral Neuropathy Screening Tool (ACTG BPNST)
3. Triplicate 12-Lead ECG
4. Pregnancy Test for women of childbearing potential
5. Hematology, Serum Chemistry, Urinalysis

6. Pharmacokinetics (C_{min}) – sample is to be collected at time 0 (just prior to taking the first dose of CCX140-B). However, **if there was a dose increase in the prior 2 weeks,** PK AUC (time 0, 0.5, 1, 2, 3, 4 & 6 hours post dose) is to be collected instead. The time 0 sample is to be collected just prior to administration of the first dose of CCX140-B. Subjects must fast prior to the time 0, 0.5 and 1 hour PK and can consume food immediately after the 1 hour PK blood draw.
7. First morning void for UPCR measurement
8. SF-36 V2 and EQ-5D-5L
9. Review diary and used study medication with each subject. Confirm dosing compliance.
10. Dispense diaries and *Directions for Use* along with a 30 day supply of CCX140-B bottles.
11. Concomitant medications- verify and document any new medications that subject has started since the previous visit.
12. Adverse Events- record all adverse events.

6.14. Week 36 (+/- 1 week) (See Section 6.19 for PK elimination visit guidelines)

1. Symptom directed abbreviated physical examination and Vital Signs including weight, heart rate, respiratory rate and body temperature.
2. AIDS Clinical Trials Group Brief Peripheral Neuropathy Screening Tool (ACTG BPNST)
3. Triplicate 12-Lead ECG
4. Pregnancy Test for women of childbearing potential
5. Hematology, Serum Chemistry, Urinalysis
6. Pharmacokinetics (C_{min}) – sample is to be collected at time 0 (just prior to taking the first dose of CCX140-B). However, **if there was a dose increase in the prior 2 weeks,** PK AUC (time 0, 0.5, 1, 2, 3, 4 & 6 hours post dose) is to be collected instead. The time 0 sample is to be collected just prior to administration of the first dose of CCX140-B. Subjects must fast prior to the time 0, 0.5 and 1 hour PK and can consume food immediately after the 1 hour PK blood draw.
7. First morning void for UPCR measurement
8. SF-36 V2 and EQ-5D-5L
9. Review diary and used study medication with each subject. Confirm dosing compliance.
10. Dispense diaries and *Directions for Use* along with a 30 day supply of CCX140-B bottles.
11. Concomitant medications- verify and document any new medications that subject has started since the previous visit.
12. Adverse Events- record all adverse events.

6.15. Week 40 (+/- 1 week) (See Section 6.19 for PK elimination visit guidelines)

1. Symptom directed abbreviated physical examination and Vital Signs including weight, heart rate, respiratory rate and body temperature.
2. AIDS Clinical Trials Group Brief Peripheral Neuropathy Screening Tool (ACTG BPNST)
3. Leg circumference and bioimpedance to assess edema
4. Triplicate 12-Lead ECG
5. Pregnancy Test for women of childbearing potential
6. Hematology, Serum Chemistry, Urinalysis
7. 24 hour urine collection for UPCR, UACR and total protein. ***Subject starts 24 hr. collection after the first void in the morning of the day prior to the visit day and should bring the 24 hr collection (including first morning void on the visit day) to the visit. Sites need to contact the subject prior to the visit day as a reminder to start the 24 hr urine collection.***
8. Pharmacokinetics (C_{min}) – sample is to be collected at time 0 (just prior to taking the first dose of CCX140-B). However, **if there was a dose increase in the prior 2 weeks,** PK AUC (time 0, 0.5, 1, 2, 3, 4 & 6 hours post dose) is to be collected instead. The time 0 sample is to be collected just prior to administration of the first dose of CCX140-B. Subjects must fast prior to the time 0, 0.5 and 1 hour PK and can consume food immediately after the 1 hour PK blood draw.
9. SF-36 V2 and EQ-5D-5L
10. PD (plasma, serum and urine and whole blood for the lymphocyte subset). Samples are to be collected at time 0.
11. Review diary and used study medication with each subject. Confirm dosing compliance.
12. Dispense diaries and *Directions for Use* along with a 30 day supply of CCX140-B bottles.
13. Concomitant medications- verify and document any new medications that subject has started since the previous visit.
14. Adverse Events- record all adverse events.

6.16. Week 44 (+/-1 week) (See Section 6.19 for PK elimination visit guidelines)

1. Symptom directed abbreviated physical examination and Vital Signs including weight, heart rate, respiratory rate and body temperature.
2. AIDS Clinical Trials Group Brief Peripheral Neuropathy Screening Tool (ACTG BPNST)
3. Triplicate 12-Lead ECG
4. Pregnancy Test for women of childbearing potential
5. Hematology, Serum Chemistry, Urinalysis

6. Pharmacokinetics (C_{min}) – sample is to be collected at time 0 (just prior to taking the first dose of CCX140-B). However, **if there was a dose increase in the prior 2 weeks,** PK AUC (time 0, 0.5, 1, 2, 3, 4 & 6 hours post dose) is to be collected instead. The time 0 sample is to be collected just prior to administration of the first dose of CCX140-B. Subjects must fast prior to the time 0, 0.5 and 1 hour PK and can consume food immediately after the 1 hour PK blood draw.
7. First morning void for UPCR measurement
8. SF-36 V2 and EQ-5D-5L
9. Review diary and used study medication with each subject. Confirm dosing compliance.
10. Dispense diaries and *Directions for Use* along with a 30 day supply of CCX140-B bottles.
11. Concomitant medications- verify and document any new medications that subject has started since the previous visit.
12. Adverse Events- record all adverse events.

6.17. Week 48 (+/- 1 week) (See Section 6.19 for PK elimination visit guidelines)

1. Symptom directed abbreviated physical examination and Vital Signs including weight, heart rate, respiratory rate and body temperature.
2. AIDS Clinical Trials Group Brief Peripheral Neuropathy Screening Tool (ACTG BPNST)
3. Triplicate 12-Lead ECG
4. Pregnancy Test for women of childbearing potential
5. Hematology, Serum Chemistry, Urinalysis
6. Pharmacokinetics (C_{min}) – sample is to be collected at time 0 (just prior to taking the first dose of CCX140-B). However, **if there was a dose increase in the prior 2 weeks,** PK AUC (time 0, 0.5, 1, 2, 3, 4 & 6 hours post dose) is to be collected instead. The time 0 sample is to be collected just prior to administration of the first dose of CCX140-B. Subjects must fast prior to the time 0, 0.5 and 1 hour PK and can consume food immediately after the 1 hour PK blood draw.
7. First morning void for UPCR measurement
8. SF-36 V2 and EQ-5D-5L
9. Review diary and used study medication with each subject. Confirm dosing compliance.
10. Dispense diaries and *Directions for Use* along with a 30 day supply of CCX140-B bottles.
11. Concomitant medications- verify and document any new medications that subject has started since the previous visit.
12. Adverse Events- record all adverse events.

6.18. Week 52 or Termination Visit (See Section 6.19 for PK elimination visit guidelines)

1. Full Physical Examination and Vital Signs including height, weight, heart rate, respiratory rate and body temperature.
2. AIDS Clinical Trials Group Brief Peripheral Neuropathy Screening Tool (ACTG BPNST)
3. Leg circumference and bioimpedance to assess edema
4. Triplicate 12-Lead ECG
5. Pregnancy Test for women of childbearing potential
6. Hematology, Serum Chemistry, Urinalysis.
7. 24 hour urine collection for UPCR, UACR and total protein. ***Subject starts 24hr. collection after the first void in the morning of the day prior to the visit day and should bring the 24 hr collection (including first morning void on the visit day) to the visit. Sites need to contact the subject prior to the visit day as a reminder to start the 24 hr urine collection***
8. SF-36 V2 and EQ-5D-5L
9. PD (plasma, serum and urine and whole blood for the lymphocyte subset). Samples are to be collected at time 0
10. PK concentration sample
11. Review diary and used study medication with each subject. Confirm dosing compliance.
12. Concomitant medications- verify and document any new medications that subject has started since the previous visit.
13. Adverse Events- record all adverse events that are ongoing at the time of this visit and determine if the subject needs to be further evaluated

6.19. Post Treatment Elimination Blood Draws

At the termination visit and again 7 and 14 days following the subject's final dose of study medication record the date/time of last dose and collect a blood sample for drug elimination assessment.

6.20. Follow-Up Visits - Four Weeks After Final Dose of Study Medication For Any Reason

1. Full Physical Examination and Vital Signs including height, weight, heart rate, respiratory rate and body temperature.
2. AIDS Clinical Trials Group Brief Peripheral Neuropathy Screening Tool (ACTG BPNST)
3. Leg circumference and bioimpedance to assess edema
4. Triplicate 12-Lead ECG
5. Pregnancy Test for women of childbearing potential

6. PD (plasma, serum and urine and whole blood for the lymphocyte subset). Samples are to be collected at time 0
7. Hematology, Serum Chemistry, Urinalysis
8. First morning void for UPCR measurement
9. Concomitant medications- verify and document any new medications that subject has started since the previous visit.
10. Adverse Events- record all adverse events that are ongoing at the follow up visit and determine if the subject needs to be further evaluated.

7. STUDY ASSESSMENTS

7.1. Physical Examinations, Vital Signs, and ECGs

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

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.

Vital signs and body weight will be measured during screening and on each scheduled study day as indicated in the Time and Events Table. Blood pressure, pulse rate, and body temperature will be measured. All vital signs assessments will be performed after the subject has rested for at least three minutes, while subject is seated. Body weight should be measured without shoes and the subject clothed in under garments or hospital gown only using a calibrated scale.

Leg circumference will be measured during screening, Day 1 and each scheduled visit as indicated in the Time and Events Table. A supplied measuring tape will be used to measure the leg circumference in each leg at the point of widest circumference. The measurement should be made with the subject standing with weight distributed equally on each foot.

The AIDS Clinical Trials Group Brief Peripheral Neuropathy Screening Tool (ACTG BPNST) will be used for the evaluation of peripheral neuropathy.

Bioimpedance will be measured during screening, Day 1 and each scheduled visit as indicated in the Time and Events Table.

A baseline 12-lead ECG, after resting for at least 3 minutes, will be performed at screening and assessed for any clinically significant abnormalities. When required (Time and Events Table), triplicate ECGs should be performed with a 1 minute interval between tracings. 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.

7.2. Clinical Safety Laboratory Assessments

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

Hematology: hemoglobin, hematocrit, RBC count, WBC count with differential, platelet count, mean cell hemoglobin, mean cell hemoglobin concentration, mean corpuscular volume, haptoglobin and schistocytes.

Serum Chemistry: liver panel (total and direct 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, coagulation panel (PT, PTT, INR), lipid panel (HDL, non-HDL LDL, Triglycerides, Total Cholesterol), uric acid, serum amylase, serum lipase, LDH and cystatin C.

Urinalysis: At the central laboratory, nitrite, blood, and protein, will be tested. If positive, microscopy will be performed.

Virology (measured only at screening and may be measured at the local laboratory): hepatitis B surface antigen, hepatitis C antibodies, HIV 1 and 2 antibodies; virology tests done within 6 weeks prior to screening are acceptable for eligibility assessment.

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

Pharmacodynamics: urinary MCP-1, and potentially other biomarkers of renal inflammation, fibrosis and injury. Assessment of blood and/or urinary biomarkers associated with CCR2. biology, which may include peripheral blood leukocyte subsets and selected cytokines and chemokines.

Genetic Markers: Assessment of biomarkers associated with risk of severity of disease, which may include allelic variations associated with the pathogenesis and/or prognosis of FSGS such as NPHS1, NPHS2, WT-1, LAMB2, CD2AP, TRPC6, ACTN4, INF2, APOL1.

7.3. Adverse Events

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

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

All adverse events occurring in subjects who have been treated with CCX140-B will be recorded in the EDC system and will be reported in accordance with regulatory requirements. Adverse events reported prior to commencement of administration of study medication will be considered

pre-treatment events. If subject stops taking CCX140-B, adverse event reporting should be continued as long as study is active.

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

7.3.1. Adverse Event Severity Assessment

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

- Mild (Grade 1): no limitation of usual activities
- Moderate (Grade 2): some limitation of usual activities
- Severe (Grade 3): inability to carry out usual activities
- Life-threatening (Grade 4): an immediate risk of death
- Death (Grade 5)

7.3.2. Causality Assessment

The relationship of CCX140-B 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 study drug CCX140-B.
- Possibly Related: there is evidence for a reasonable possibility that study drug CCX140-B administration caused the adverse event.

7.3.3. Serious Adverse Events

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

- Results in death;
- Is life-threatening (i.e., the subject 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 subject and/or may require medical or surgical intervention to prevent one of the other outcomes defining serious.

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

as SAEs. Hospital stays on the evening of Day 1 (or beyond) will also not be considered an SAE, unless other SAE criteria are met.

7.3.4. SARs and SUSARs

A serious adverse reaction (SAR) is defined as an SAE for which there is at least a reasonable possibility that the study drug CCX140-B caused the event.

A suspected unexpected serious adverse reaction (SUSAR) is defined as an SAE for which there is at least a reasonable possibility that the study drug CCX140-B caused the event, and the SAE is 'unexpected', i.e., not described in terms of nature, severity, or frequency in the Reference Safety Information within the current Investigator's Brochure.

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

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

Events related to the underlying disease, such as relapses or worsening of disease will not be considered as SUSARs, unless there is a reasonable possibility that CCX140-B use was associated with these events.

7.3.5. Pregnancies

Any pregnancies that occur in female subjects or partners of male study subjects must be reported to [redacted] Clinical Safety within 24 hours of awareness to the contacts details outlined in Section 7.3.3 An exposure in Utero form will then be forwarded for completion as soon as possible. All pregnancies must be followed up until conclusion and the outcome of the pregnancy reported within 24 hours of awareness to [redacted] Clinical Safety. Should the outcome of the pregnancy meet criteria for an SAE, th ould be reported as indicated in Section 7.3.3.

7.3.6. Special Situation Reporting

Special situation reports include reports of overdose, misuse and abuse of the IMP:

- Overdose: refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol. Clinical Judgment should always be applied. In cases of a discrepancy in the drug accountability, overdose will be established only when it is

clear that the subject has taken excess dose(s) or the investigator has reason to suspect that the subject has taken additional dose (s).

- Misuse: refers to situations where the medicinal product is intentionally and inappropriately used not in a way that is not in accordance with the protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.
- Abuse: is defined as persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- Medication Error: Medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product by a healthcare professional, patient or consumer, respectively. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors, cases of subjects missing doses of investigational product are not considered reportable as medication error.

All special situation reports must be reported on the special situations report form and forwarded to [redacted] Clinical Safety within 24 hours.

All adverse events (AEs) associated with these special situation reports should be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management and outcome will be reported, when available.

7.3.7. Serious Adverse Event Reporting

Any serious adverse event occurring from screening through the end of the treatment period, whether or not considered study related, will be reported immediately (within 24 hours) to the Safety team. Reporting is done by completing the SAE form in the EDC system. If it is not possible to access the EDC system, the Investigator will send an email to the appropriate regional clinical safety mailbox (see information below) or call their regional SAE hotline and fax the completed SAE report form within 24 hours of awareness. When access to the EDC system is resumed, the SAE information should be entered as soon as possible. Contact details are as follows:

[redacted] Clinical Safety
Telephone: [redacted] **or** [redacted] **or** [redacted]
Facsimile: [redacted] **or** [redacted] **or** [redacted]
e-mail: [redacted]

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

Follow-Up Reports

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

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

SAE reporting should continue for 90 days after stopping study drug. The Sponsor should be notified if the investigator becomes aware of any SAE that occurs after the end of the AE reporting period, if they believe that an event is related to the prior study drug treatment.

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

7.4. Study Completion and Withdrawal

The Week 12 visit will be the final treatment day and the week 16 visit will be the last Study Day for all subjects, except for those participating in the Open-Label Extension (last visit will be Week 52). Procedures for this day will be completed per the Time and Events Table. Each subject's condition will be evaluated by the Investigator at the end of the clinical trial and appropriate standard of care medical treatment will be provided to all subjects as needed. For early withdrawals from the study, the procedures for the Early Termination visit will be performed, including blood draws during the termination visit and again 7 & 14 days after the final dose, when possible. The clinical trial will be terminated early if there is a safety concern.

7.5. Dose Modification Rules

Table 2: Dose Modification Rules for Individual Subjects

Assessment	Event	Timing	Response
Serum Creatinine	50% increase from baseline value	If confirmed by repeat measurement after 2 weeks	If confirmed by repeat measurement after 2 weeks
Urine Protein:Creatinine ratio (UPCR)	If baseline UPCR < 6.0 g/g an increase of > 3.0 g/g; if UPCR ≥ 6.0 g/g an increase of 50%	If confirmed by repeat measurement after 2 weeks	If confirmed by repeat measurement after 2 weeks
ALT, AST	ALT or AST ≥ 8x ULN	Confirmed within 72 hours (ALT, ASP, ALP and Total Bilirubin should all be re-tested)	Consider Discontinuation of Treatment
ALT, AST	ALT or AST ≥ 5x ULN	Confirmed within 2 weeks (ALT, ASP, ALP and Total Bilirubin should all be re-tested)	Consider Discontinuation of Treatment
ALT, AST, Total	ALT or AST ≥ 3x	Confirmed within 72	Consider Discontinuation of

Bilirubin and INR	ULN and Total Bilirubin > 2 ULN or INR > 1.5	hours (ALT, ASP, ALP, Total Bilirubin and INR should all be re-tested)	Treatment
ALT, AST	ALT or AST ≥ 3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and /or eosinophilia (>5%)	Confirmed within 72 hours (ALT, ASP, ALP and Total Bilirubin should all be re-tested)	Consider Discontinuation of Treatment
Hemolysis	Clinical diagnosis of hemolysis in the judgment of the investigator, based on elevation of LDH, elevation of reticulocyte count, elevation of bilirubin and or other laboratory indications.	Halt treatment then reassess after 1 week	If normalized, continue to treat at reduced dose, defined as the next lower dose. Otherwise, contact Medical Monitor to discuss next steps
Anemia	Hemoglobin reduced from baseline by ≥ 2 g/L and deemed clinically significant by the PI	Halt treatment then reassess after 2 weeks	If normal, continue to treat at reduced dose, defined as next lower dose. Otherwise, contact Medical Monitor to discuss next steps
Reticulocyte Count	Increase in reticulocyte count by ≥2% (absolute) from baseline that is not otherwise explained	Halt treatment then reassess after 2 weeks	If within normal range for the hematocrit, continue to treat at reduced dose, defined as next lower dose. Otherwise, contact Medical Monitor to discuss next steps
Peripheral Neuropathy	≥ moderate symptoms limiting (limiting instrumental activities of daily living or asymptomatic (based on diagnostic evaluation only) and deemed clinically significant by the investigator	Halt treatment then reassess after 2 weeks	Contact Medical Monitor to discuss next steps
Other Clinically Significant Events	Any adverse events assessed as moderate, related to study drug, and clinically significant	Halt treatment then reassess after 2 weeks	Contact Medical Monitor to discuss next steps

7.5.1. Dose Modification / Stopping Rules for the Overall Study

A dose will be considered as potentially exceeding the maximum tolerated dose and consideration will be given for stopping the study should any of the following events occur:

- 2 or more subjects with QTcF prolongation ≥ 450 msec and an increase from baseline of ≥ 30 msec, based on triplicate 12-lead ECGs that is not otherwise explained
- 2 or more subjects with clinically significant hemolytic anemia, defined as hemoglobin that has declined from baseline by at least 2 grams/deciliter and is less than or equal to 8 g/dL and is assessed by the investigator and is not otherwise explained
- 2 or more subjects with bilirubin greater than 3 times upper limit of normal, and not ascribable to Gilbert's disease
- 2 or more subjects with new motor neuropathy or sensory neuropathy that limits instrumental activities of daily living and is assessed by the Investigator as clinically significant
- 2 or more subjects who require dose reduction or discontinuation due to adverse events assessed as possibly related to Study Drug, where the adverse events are medically similar in the same System Organ Class based on MedDRA criteria.

If a dose is assessed to be above the maximally tolerated dose, dosing and dose escalation will be limited to the next lower dose.

A Safety Review Committee (SRC) comprising the Study Director, Medical Monitor, Clinical Pharmacologist, at least one external expert nephrologist, and Study Statistician will review all safety events described in the stopping rules and all serious adverse events as they occur. The SRC will periodically review all adverse events and all laboratory abnormalities. The SRC may declare a dose to be above the maximally tolerated dose based on the defined rules, or based on other considerations.

7.5.2. 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.

7.6. Treatment Compliance

Subjects will be screened within a period not to exceed 28 days prior to Day 1.

The initial treatment period, including dose escalation, will be up to 12 weeks. Subjects who are not Treatment Failures and who otherwise meet criteria for continuation may continue treatment for up to an additional 40 weeks to assess achievement of remission and duration of response. All subjects should be followed for 4 weeks (28 days) after the last CCX140-B dose administered.

The CCX140-B tablets 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 Investigator or designee should review each subject's dosing diary at each relevant visit, reconcile them against the study medication that each subject returns, document reasons for any discrepancies and calculate the dosing compliance rate. This information will be recorded and entered into the electronic data capture (EDC) system. Subjects that do not take at least 85% of the study medication can be discontinued from the study for non-compliance.

7.7. Concomitant Medications and Restrictions

The doses of RAAS inhibitors must be stable prior to Day 1, and remain stable throughout the course of the study, unless adjustment is required for the safety of the subject. For eligible subjects willing to participate in the Open-Label Extension (after Week 12), the doses of RAAS inhibitors and other concomitant drugs may be modified per physician judgment. Subjects who require addition of a new immunosuppressive or immunomodulatory agent may continue treatment with CCX140-B if they have not met criteria for treatment failure, the case has been discussed with the study director and there is agreement to continue treatment. Plasmapheresis is not allowed at any point during the course of the study.

CCX140-B is primarily cleared through CYP3A4 metabolism. Subjects taking strong CYP3A4 inducers (e.g., phenytoin, rifampicin, carbamazepine, St. John's Wort) will be excluded from this clinical trial since these drugs may substantially reduce the CCX140-B plasma levels. In addition, subjects taking strong CYP3A4 inhibitors (e.g., boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole) will be excluded as these drugs may substantially increase the CCX140-B plasma levels.

All concomitant medications taken during the course and up to 12 weeks prior to screening Day 1 study should be recorded meticulously on the concomitant medication pages of the CRF.

Prior treatment with rituximab or other anti-CD20 monoclonal antibodies and corresponding levels of CD20+ B cells need to be recorded up to 1 year prior to screening.

Eligible patients who have entered the study on a continuous cycle therapy of rituximab or other anti-CD20 monoclonal antibodies need to remain on an unchanged therapy throughout the study at a dosing interval that has been documented to achieve continuous B cell depletion for the given patient unless prohibited due to safety considerations. Their levels of CD20+ B cells that are routinely evaluated per standard of care with anti-CD20 monoclonal antibody therapy need to be recorded throughout the study. Record UPCR and urine protein assessments up to 1 year prior to screening (if available) in the medical history if patients were treated with Rituximab, other CD20+ monoclonal antibodies, calcineurin inhibitors or other immunotherapy.

7.7.1. Rescue Therapy

If the investigator decides that a subject needs to receive rescue therapy the subject will be considered a treatment failure. Rescue therapy is considered any new therapy or required dose increase of an existing concomitant therapy (other than allowed per Section 7.7. Concomitant

Medications and Restrictions) that is required for the safety of the patient and to treat the underlying disease of FSGS.

This would include but is not limited to the initiation of high dose glucocorticoid therapy, new immunosuppressive agents such as calcineurin inhibitors, cyclophosphamide, MMF, monoclonal antibodies, or other major treatments (e.g. plasmapheresis, dialysis).

8. STATISTICAL METHODS

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

All continuous study assessments will be summarized by visit (as applicable) and change from baseline to each post-baseline visit using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). All categorical study assessments will be summarized by visit (as applicable) using frequency counts and percentages.

8.1. Demographics and Baseline Characteristics

All subject baseline characteristics and demographic data (age, sex, race, ethnicity, weight, height, body mass index, viral test results, serum creatinine, FSGS duration [from time of first diagnosis based on renal biopsy]), eGFR, proteinuria (UPCR), physical examination abnormalities, medical history, previous (within 6 months of screening) and concomitant medications (including other treatments for FSGS) at study entry will be listed by study center and subject number, and will also be summarized.

8.2. Efficacy Analysis

8.2.1. Primary Endpoint Analysis

The Primary Efficacy Objective is to evaluate the effect of CCX140-B on proteinuria in subjects with primary FSGS with nephrotic syndrome, assessed as a median reduction from baseline of urine protein to creatinine ratio (UPCR) of at least 20%, i.e. ≥ 20%, by week 12.

The assumed treatment effect for this study is based on efficacy findings with 5 and 10 mg CCX140-B once daily in study CL005_140 in patients with diabetic nephropathy and proteinuria. In a pre-specified subset analysis, the greatest percentage improvement of UACR at approximately 12 weeks from baseline was observed in subjects who presented with the highest baseline UACR (801-3000 mg/g) and eGFR of at least 60 mL/min/1.73m2. This subgroup receiving 5 (N=10) or 10 mg (N=13) of CCX140-B once daily showed a median reduction in

UACR of approximately 20%-30% receiving CCX140-B while patients receiving placebo (N=12) showed an increase of approximately 12%.

Based on these data, it is assumed that the median reduction from baseline UPCR is at least 20% by week 12 in the planned study CL012_140. If the final observed data are consistent with this assumption, i.e. the previous positive study results are replicated in the FSGS population, the study will be considered positive in assessing the efficacy of CCX140-B.

Otherwise, if the observed data are consistent with the median reduction of below 20%, the study would not be considered positive.

After all of the initial 6 subjects have completed their 12-week of treatment the study will be paused and assessed. If the overall study results are deemed safe and the subjects' responses to treatment are considered clinically meaningful seven additional subjects will be treated for a total of 13 subjects.

8.2.2. Secondary Endpoint Analysis

Secondary endpoints include:

- Achievement of Partial Remission (includes all of the following)
  - reduction from baseline by ≥50 percent in UPCR
  - reduction in UPCR to a level that is < 3.5 g/g at week 12
  - subject may not be a treatment failure
- Achievement of Complete Remission (includes all of the following) at week 12
  - reduction in UPCR to < 0.3 g/g
  - serum albumin within normal range
  - for patients with abnormal serum creatinine levels at baseline, return to normal levels for that age group
  - for patients with normal serum creatinine levels at baseline, final value within 20% of baseline levels
  - subject may not be a treatment failure
- Change from baseline of UPCR in subjects treated with CCX140-B over time
- The proportion of subjects with partial remission at any time during the treatment period.
- The proportion of subjects with complete remission at any time during the treatment period.
- Time to Partial Remission (PR) or Complete Remission (CR)
- Change from baseline in renal function, based on eGFR (calculated using the CKD-EPI Cystatin C equation (Dharnidharka VR, et al, 2002), the CKD-EPI Creatinine equation (Schwartz GJ, et al. 2016, Selistre L et al 2016), CKD-EPI Creatinine-Cystatin C equation (Stevens et al., 2008) and MDRD Creatinine equation (Levey et al. 1999, Levey et al. 2006) over time
- Change over time in total 24 hour urine protein excretion

- Change from baseline in serum albumin over time
- Change in UACR from baseline over time
- Time to investigator or physician initiation of rescue therapy including glucocorticoids, new immunosuppressive agents or new major treatment modalities (e.g. plasmapheresis, dialysis)
- Duration between achievement of remission and relapse or treatment failure
- Changes over time in Health Quality Assessment (SF-36 v2 and EQ-5D-5L)

Change from baseline will be summarized with descriptive statistics (mean, SD, median and range) and 95% confidence interval for the mean. Baseline is defined as the last assessment prior to the first dose of the study drug.

Time to PR or CR and duration between achievement of remission and relapse or treatment failure will be summarized with the Kaplan-Meier estimate for the median and quartiles.

The proportion of subjects who achieved either partial or complete remission and the proportion of subjects with treatment failures as of week 12 will be summarized separately similarly to the primary analysis. Formal statistical inference will not be made on these separate endpoints.

Serum albumin, proteinuria, eGFR, serum lipids, edema (body weight, leg circumference and bioimpedance), weight and albuminuria will be summarized by visit and for change from baseline to each visit using continuous summary statistics and 90% and 95% confidence intervals. [Timeframe: Baseline to week12 and Baseline through end of treatment]

Time to partial or complete remission will be summarized using Kaplan-Meier methods to estimate median time to remission as well as the 25^{th} and 75^{th} percentiles. Associated 95% confidence intervals, estimated using the method of Brookmeyer and Crowley (1982) will also be provided. Duration of remission will be summarized similarly. [Timeframe: Baseline to week 12 and Baseline through end of treatment]

Additionally, time to partial or complete remission will be summarized categorically by the first visit the subject showed partial or complete remission. [Timeframe: Baseline to week 12 and Baseline through end of treatment]

The Health Quality Assessment (SF-36 V2 and EQ-5D-5L) will be summarized by visit and for change from baseline to each visit using continuous summary statistics and 90% and 95% confidence intervals for the overall score and for each of the 8 domain scores: Vitality, Physical Functioning, Bodily Pain, General Health Perceptions, Physical Role Functioning, Emotional Role Functioning, Social Role Functioning, and Mental Health. [Timeframe: Baseline to week 12 and Baseline through end of treatment]

8.3. Safety Analysis

Safety endpoints include:

- Subject incidence of treatment-emergent serious adverse events, adverse events, and dose interruptions and / or withdrawals due to adverse events;
- Change from baseline and shifts from baseline in all safety laboratory parameters;
- Change from baseline in vital signs or clinically significant ECG changes.

All clinical safety and tolerability data will be listed by subject. [Timeframe: Baseline-week 12 and Day 85 through end of treatment]

Subject incidence of treatment-emergent adverse events (TEAE) will be tabulated by MedDRA System Organ Class (SOC) and preferred term (PT), by relatedness and by maximum severity. [Timeframe: Baseline-week 12 and Day 85 through end of treatment]

Treatment-emergent serious adverse events (TESAE) and TEAE leading to withdrawal will be listed. The listing will include MedDRA SOC, PT, and verbatim term, AE start/stop day, severity, relationship to study drug, action taken, and outcome. [Timeframe: Baseline-week 12 and Day 85 through end of treatment]

Individual vital signs and change from baseline in vital signs will be listed by subject and study visit, and summarized by visit. [Timeframe: Baseline-week 12 and Day 85 through end of treatment]

Individual abnormalities recorded on physical examination at baseline, and change from baseline, will be listed by subject and study visit, and summarized by visit. [Timeframe: Baseline-week 12 and Day 85 through end of treatment]

Individual ECG findings and change from baseline in ECG findings will be listed by subject and study visit, and summarized by visit. [Timeframe: Baseline-week 12 and Day 85 through end of treatment]

Laboratory data (actual values and change from baseline) will be listed by subject and study visit. Abnormal laboratory values will be flagged. Shift tables will be generated for shifts in laboratory parameters by study visit. [Timeframe: Baseline-week 12 and Day 85 through end of treatment]

8.4. Sample Size Assumptions

Six (6) male or female adult subjects with biopsy-proven primary FSGS and nephrotic syndrome will be enrolled into the first stage of this study, which is followed by another seven subjects after the data review of the initial 6 patients. The relatively small sample size is selected based on the exploratory safety and efficacy nature of the study. After all of the initial 6 subject have completed their 12-week of treatment the study will be paused and assessed safety and efficacy. If the overall study results are deemed safe and the subjects' responses to treatment are considered clinically meaningful seven additional subjects will be treated for a total of 13 subjects.

Further details will be specified in the SAP.

8.5. Subject Populations

8.5.1. Modified Intent-to-Treat Population

The modified Intent-to-Treat (mITT) Population will include all subjects who have received a dose of the study drug, and have at least one post-baseline efficacy assessment.

8.5.2. Per Protocol Population

The Per Protocol (PP) population will consist of all mITT subjects who do not have protocol deviations that could significantly affect the interpretation of the results for the primary endpoints. Subjects' inclusion/exclusion from the PP population will be determined and documented prior to the database lock. Subjects' inclusion into the PP population will also require drug compliance of ≥85%.

8.5.3. Safety Population

The safety population will include all subjects who have received at least one dose of study drug.

8.6. Demographics 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), physical examination abnormalities, medical history, previous (within 6 months of screening) and concomitant medications (including other treatments for FSGS) at study entry will be listed by study center and subject number, and will also be summarized.

8.7. Subject Disposition

The number of subjects who were screened, who screen failed (by reason), who completed Week 12, who completed the 52 week extension study, who withdrew early from the study, along with the reasons for withdrawal, will be presented.

8.8. Treatment Compliance

Exposure will be summarized by dose at each visit as well as total dose and average weekly dose.

CCX140-B plasma concentration measurements over the course of the study may also be used to assess subject compliance. Any events of non-compliance to the protocol will be documented in the study records. Non-compliant study subjects whose dosing compliance rate is less than 85% may be withdrawn from study.

8.9. Protocol Deviations

Significant protocol deviations (major and critical) will be listed and summarized by category. The effect of significant protocol deviations on the safety and efficacy outcomes will be assessed by conducting sensitivity analyses excluding subjects and/or study visits with significant protocol deviations.

Examples of major deviations may include but are not limited to:

- Failure to properly consent each study subject (i.e., using the correct version of the ICF in the appropriate language prior to initiation of study procedures, etc.)
- Enrollment of ineligible subjects
- Performance of procedures not defined in the approved protocol

- Study medication dispensing or dosing errors
- Failure of a study subject to return unused study medication after completing the trial
- Failure to report SAE to sponsor and/or regulatory agencies within specified timelines
- Use of recruitment procedures not approved by the IRB/EC
- Continuing research activities after IRB approval has expired
- Enrolling more subjects than the IRB has approved

The Sponsor will assess any protocol deviation and decide whether any of these should be reported to Competent Authorities as a serious breach of GCP and the protocol.

8.10. Prior and Concomitant Medications

Prior medication is defined as the medication started prior to the first administration of the study drug. Concomitant medication is defined as the medication with stop date on or after the first administration of the study drug. With the exception of Rituximab, which must be captured up to 1 year prior to screening, all other concomitant medications taken by study subjects must be captured starting 12 weeks prior to screening, throughout their participation in the study and through the follow-up visit, which should occur 4 weeks after each subject takes their final dose of study medication.

Subject incidence of the prior and concomitant medications will be tabulated by the WHODD Anatomical Therapeutic Chemical Classification and Preferred Term.

8.11. Pharmacokinetic and Pharmacodynamic marker analysis

Plasma samples will be collected according to the Time and Events Table to determine the PK profile of CCX140. Individual plasma concentrations of CCX140 will be listed, plotted, and summarized descriptively and graphically. PK parameters will be calculated based on plasma CCX140 concentrations at the time of sample collection in relation to time of administration of the most recent dose of study medication. 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 for all subjects, after the first dose of 5 mg BID, two weeks after 10 mg BID and four weeks after 15 mg BID
AUC_{0-12}	Area under the plasma concentration-time curve from Time 0 to Hour 12, two weeks after 10 mg BID and four weeks 15 mg BID, will be extrapolated for all subjects.
C_{min}	Trough level plasma concentrations at visits when AUC_{0-6} is not collected

If there are sufficient data, population PK analysis will be performed.

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

The relationships among PK parameters, UPCR and renal function based on eGFR will be evaluated. The data may also be used to evaluate the PK/PD relationship of CCX140-B treatment. To this end, the change and/or percent change from baseline in UPCR, eGFR, and other biomarkers may be used as PD markers.

9. STUDY COMPLETION AND TERMINATION

9.1. Study Completion

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

9.2. Study Termination

The end of study is defined as the last study visit of the last clinical trial subject. All subjects who took at least a single dose of CCX140-B should be urged to complete a study termination visit and to return 7 and 14 days after their final dose of study medication to have a blood draw to measure concentrations of CCX140 for the purpose of assessing its elimination characteristics. They should also be encouraged to complete a termination visit within 4 weeks of their final dose of study medication, for assessment of ongoing adverse events.

10. REGULATORY AND ADMINISTRATIVE REQUIREMENTS

10.1. Investigator Responsibilities

Prior to trial initiation, the Investigator will provide the Sponsor with a fully executed and signed FDA Form 1572, a Financial Disclosure Form, and a curriculum vitae. Financial Disclosure Forms also will be completed for all Sub-Investigators listed on the Form 1572 who will be involved directly in the treatment or evaluation of research 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 or his/her legal guardian will give his/her written Informed Consent before any protocol-specific tests or evaluations are performed.

10.2. Institutional Review Board or Ethics Committee

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

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

10.3. Informed Consent

A properly executed, written, and appropriately explained Informed Consent Form, in compliance with the Declaration of Helsinki, ICH GCP, and US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 46, Subpart A), will be signed by each subject or his/her legal guardian prior to entering the trial. Either the Investigator or the Investigator's designee will obtain the consent of the study 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.

10.4. Protocol Modifications

Only the Sponsor may modify the protocol. 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 competent authorities concerned of the reasons for, and content of, these amendments according to the European Directive "Detailed guidance on the request to the competent authorities for authorization of a clinical trial on a medical products for human use, the notification of substantial amendments and the declaration of the end of trial (CT-1)(2010/C 82/01)" and other regulatory guidance.

10.5. Regulatory Documentation

All regulatory documentation including regulatory submissions, 1572 forms, and correspondence regarding this study will be kept by the Sponsor. The CRO that will conduct the study on behalf

of the Sponsor will maintain all study documentation according to their SOPs. Clinical trial related documents will be archived for the longest of:

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

10.6. 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/or assigned number only.

10.7. Record Retention

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

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

10.8. Case Report Form Completion

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

It is the policy of the Sponsor that study data must be verifiable to the source data, which necessitates access to all relevant source documents, 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.

10.9. Monitoring

At intervals during the study, and 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 promptly recorded in EDC, reviewing source documentation and drug accountability records and reviewing all essential regulatory documents for accuracy and

completeness. The study will be conducted according to the principles of GCP as accepted in the United States and according to CPMP/ICH/135/95.

10.10. On-site Visits and Audits

The Sponsor's representatives will visit the study center prior to initiation of the study to provide on-site training of the center personnel and to provide information regarding the investigational agent, protocol requirements, monitoring requirements, requirements for maintenance of essential regulatory documentation 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 occur and will be advised as to the nature of the audit. Representatives of the Food and Drug Administration (FDA) and/or representatives of other regulatory authorities may also conduct an audit of the study. If informed of such an audit, the Investigator should notify the Sponsor immediately.

10.11. Use of Information and Publication

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

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

11. REFERENCES

1. Banfi G et al. (1991). The impact of prolonged immunosuppression on the outcome of idiopathic focal-segmental glomerulosclerosis with nephrotic syndrome in adults. A collaborative retrospective study. *Clin Nephrol, 36*(2), 53-59.
2. Beer A, Mayer G, Kronbichler A (2016) Treatment Strategies of Adult Primary Focal Segmental Glomerulosclerosis: A Systematic Review Focusing on the Last Two Decades. Biomed Res Int 2016:4192578.
3. Besbas N et al. (2015) MCP1 2518 A/G polymorphism affects progression of childhood focal segmental glomerulosclerosis. Ren Fail 37 (9):1435-1439.
4. Brookmeyer, R. and Crowley, J. (1982), "A Confidence Interval for the Median Survival Time," *Biometrics*, 38, 29–41.
5. Burton CJ et al. (1999) Secretion of chemokines and cytokines by human tubular epithelial cells in response to proteins. Nephrol Dial Transplant 14 (11):2628-2633.
6. Cattran and Appel (2016) in Treatment of Primary Focal Glomerulosclerosis
7. Cattran D, et al. (2008) The impact of sex in primary glomerulonephritis. Nephrol Dial Transplant 23(7):2247-53.
8. Cattran DC, Rao P (1998) Long-term outcome in children and adults with classic focal segmental glomerulosclerosis. Am J Kidney Dis 32(1):72-79.
9. Chen et al (2015) Focal segmental glomerulosclerosis: molecular genetics and targeted therapies. BMC Nephrol 16:101
10. Chow FY et al. (2006) Monocyte chemoattractant protein-1 promotes the development of diabetic renal injury in streptozotocin-treated mice. Kidney Int 69 (1):73-80.
11. Chow FY et al. (2007) Monocyte chemoattractant protein-1-induced tissue inflammation is critical for the development of renal injury but not type 2 diabetes in obese db/db mice. Diabetologia 50 (2):471-480.
12. D'Agati VD, Kaskel FJ, Falk RJ (2011) Focal segmental glomerulosclerosis. N Engl J Med 365(25):2398-2411.
13. de Zeeuw D et al. (2015) The effect of CCR2 inhibitor CCX140-B on residual albuminuria in subjects with type 2 diabetes and nephropathy: a randomised trial. Lancet Diabetes Endocrinol 3 (9):687-696.
14. Dharnidharka VR, Kwon C, Stevens G. (2002) Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. Am J Kidney Dis. 40:221–226.
15. Eardley KS et al. (2006) The relationship between albuminuria, MCP-1/CCL2, and interstitial macrophages in chronic kidney disease. Kidney Int 69 (7):1189-1197.
16. Gipson, D et al. (2016) Complete Remission in the Nephrotic Syndrome Study Network. *Clin J Am Soc Nephrol, 11*(1):81-89.

17. Investigators Brochure, Edition 9.0.
18. Jefferson JA (2008) Proteinuria in diabetic kidney disease: a mechanistic viewpoint. Kidney Int 74 (1):22-36.
19. Kang YS et al. (2010) CCR2 antagonism improves insulin resistance, lipid metabolism, and diabetic nephropathy in type 2 diabetic mice. Kidney Int 78 (9):883-894.
20. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group KDIGO Clinical Practice Guideline for Glomerulonephritis. Kidney Int Suppl. 2012; 2(Suppl 2):139–274.
21. Korbet SM (2012) Treatment of primary FSGS in adults. J Am Soc Nephrol 23 (11):1769-1776.
22. Korbet SM, Schwartz MM, Lewis EJ (1994) Primary focal segmental glomerulosclerosis: clinical course and response to therapy. Am J Kidney Dis 23(6):773-783.
23. Kriz W, LeHir M (2005) Pathways to nephron loss starting from glomerular diseases-insights from animal models. Kidney Int 67 (2):404-419.
24. Lee VW, Harris DC (2011) Adriamycin nephropathy: a model of focal segmental glomerulosclerosis. Nephrology (Carlton) 16(1):30-38.
25. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. (1999) A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med;130(6):461–470.
26. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. (2006) Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med;145(4):247–54.
27. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J, Ckd EPI (2009) A new equation to estimate glomerular filtration rate. Ann Intern Med 150(9):604-612 Lim BJ et al. (2016) Pathogenesis of Focal Segmental Glomerulosclerosis. J Pathol Transl Med 50 (6):405-410.
28. Miao,Z. et al(2017) CCR2 antagonism reduces proteinuria and glomerular injury in murine models of Focal Segmental Glomerulosclerosis (FSGS). Abstract submitted to 54th ERA-EDTA Congress, Madrid, Spain, June 3-6
29. PC0684_140 Effects of CCR2 antagonist in adriamycin-induced and 5/6 nephrectomy mouse models of focal segmental glomerulosclerosis.
30. Pokhariyal et al (2003) Duration of optimal therapy for idiopathic focal segmental glomerulosclerosis. J. Nephrol 2003 Sep-Oct;16(5):691-6.
31. Pokhariyal S et al. (2003) Duration of optimal therapy for idiopathic focal segmental glomerulosclerosis. J Nephrol 16 (5):691-696.
32. Reiser, J., & Altintas, M. M. (2016). Podocytes. *F1000Res, 5*.

33. Rydel J et al. (1995). Focal segmental glomerular sclerosis in adults: presentation, course, and response to treatment. *Am J Kidney Dis, 25*(4), 534-542.

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

35. Selistre L, et al. (2016) Comparison of the Schwartz and CKD-EPI Equations for Estimating Glomerular Filtration Rate in Children, Adolescents, and Adults: A Retrospective Cross-Sectional Study. PLoS Med;13: e1001979. doi:10.1371/journal.pmed.1001979

36. Sim, JJ et al. Distribution of Biopsy-Proven Presumed Primary Glomerulonephropathies in 2000-2011 Among a Racially and Ethnically Diverse US Population. Am J Kidney Dis. 2016 Oct, 68(4):533-544.

37. Stevens LA, Coresh J, Schmid CH, Feldman HI, Froissart M, Kusek J, Rossert J, Van Lente F, Bruce RD, 3rd, Zhang YL, Greene T, Levey AS (2008) Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. Am J Kidney Dis 51(3):395-406.

38. Troyanov S et al (2005) Toronto Glomerolnephritis Registry G Focal and Segmental Glomerulosclerosis: definition and relevance of a partial remission. J Am Soc Nephrol 16(4):1061-1068.

39. Wasilewska A et al. (2011) Urinary monocyte chemoattractant protein-1 excretion in children with glomerular proteinuria. Scand J Urol Nephrol 45 (1):52-59.

40. Yadav A et al. (2010) MCP-1: chemoattractant with a role beyond immunity: a review. Clin Chim Acta 411 (21-22):1570-1579.

APPENDIX A. Subject Instructions

Subject Instructions for Collection of 24 Hour Urine Samples

Subjects will be asked to fast (not eat anything) for at least 10 hours before the study visit. Subjects will collect the urine sample at home according to the instructions they were given. On some days they will be asked to collect their urine for a full day, starting with the second urine on the day before their visit and including the first urine on the day of their visit. The study staff will provide containers for collecting these urine samples.

Subject Instructions for Dosing of Study Medication on Visit Days

On the day of each study visit, the subject should not take their morning study medication until they get to the clinic. They will then take it in the presence of the study staff. On the days when they do not have a study visit, they will take their first dose of study medication in the morning at approximately the same time each day. Their second dose should be taken approximately 12 hours after the first dose.