PROTOCOL

Protocol Amendment 4.0

Study Title:	A Randomized, Double-Blind, Placebo-Controlled Dose-Ranging Study to Evaluate the Safety and Efficacy of CCX140-B in Subjects with Focal Segmental Glomerulosclerosis (FSGS)
Protocol Number:	CL011_140
Investigational Product:	Selective antagonist of human C-C chemokine receptor type 2 (CCR2)
Indication:	Focal Segmental Glomerulosclerosis (FSGS)
Sponsor:	ChemoCentryx, Inc.
Development Phase:	2
IND number	134007
EudraCT number	2017-003021-15
Sponsor's Responsible Medical Officer:	[redacted] ChemoCentryx, Inc. Mountain View, California 94043, USA
Sponsor Signatory:	[redacted] ChemoCentryx, Inc. Mountain View, California 94043, USA
Approval Date:	10 November 2017 **18 December 2017 Amendment 1.0** **18 January 2018 Amendment 2.0** **15 February 2018 Amendment 3.0** **29 October 2018 Amendment 4.0**

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: CL011_140

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

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: CL011_140

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

Medical Officer

[redacted]
ChemoCentryx, Inc.
Mountain View,
California 94043, USA
[redacted]

Clinical Operations Manager

[redacted]
Clinical Operations Consultant
ChemoCentryx, Inc.
Mountain View,
California 94043, USA
[redacted]

SPONSOR SIGNATURE FOR APPROVAL

Protocol Number: CL011_140

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

[redacted]

Vice President, Clinical Development &
Translational Medicine

29-Oct 2018

Date

PROTOCOL AMENDMENT 4.0: SUMMARY OF CHANGES

Section(s)	Original Text	Revised Text	Rationale for Change
TITLE PAGE	Protocol Amendment 3.0	**Protocol Amendment 4.0**	Updated protocol version number and date
	None	**19 October 2018**	
Global	Varied	Varied	Corrected typos and grammatical errors
Global	Varied	Varied	Defined acronyms at first occurrence to correct previous error or omission
SYNOPSIS, Objectives, bullet 2 & OBJECTIVES, Section 3.1, paragraph 2	• The primary efficacy objective ….change from baseline in the urine protein to creatinine ratio (UPCR).	• The primary efficacy objective ….change from baseline in the urine protein to creatinine ratio (UPCR) **at Week 12**.	To clarify the analysis of the primary endpoint
SYNOPSIS, Objectives, bullet 1	The secondary objectives…are: • To evaluate the effect of CCX140-B on…estimated glomerular filtration rate (eGFR);	The secondary objectives…are: • To evaluate the effect of CCX140-B on…estimated glomerular filtration rate (eGFR) **at Weeks 12 and 24**;	To harmonize Synopsis with OBJECTIVES, Section 3.2, bullet 1
SYNOPSIS, Objectives & OBJECTIVES, Section 3.2, bullet 2	None	**To evaluate the effect of CCX140-B treatment on fraction of subjects achieving complete and partial renal remission (by 2 different partial remission definitions)**	Added a new secondary objective
SYNOPSIS, Objectives & OBJECTIVES, Section 3.3, paragraph 3	• To explore the effect of CCX140-B on Health-related Quality of Life changes based on Short Form 36 version 2 (SF-36 v2 and EQ-5D-5L.)	• To explore the effect of CCX140-B on Health-related Quality of Life changes based on answers to the Short Form 36 version 2 (SF-36 v2) and **EuroQuality of Life-5 Domains-5 Levels** (EQ-5D-5L) **questionnaires**;	To clarify that the instruments used are questionnaires
SYNOPSIS, Methodology paragraph 9	For assessment of pharmacokinetics,…will include • Six blood samples collected over 6 hours	For assessment of pharmacokinetics,…will include • **Seven** blood samples collected over 6 hours	To harmonize Synopsis with Section 4 of the protocol; baseline (time 0) measurement omitted from Synopsis in error
SYNOPSIS & STUDY POPULATION, Section 5.2	10. Female subjects … if adequate contraception is used during, and for at least 5 half-lives after last dose…	10. Female subjects …if adequate contraception is used during, and for at least **1 month** after last dose	To standardize the required post-dosing duration of contraception for males and females

Section(s)	Original Text	Revised Text	Rationale for Change
SYNOPSIS & STUDY POPULATION, Section 5.3	4. Subjects that use of rituximab or other anti-CD20 monoclonal antibodies within 20 weeks prior to screening are excluded while subjects that used rituximab or other anti-CD20 monoclonal antibodies prior to 20 week of screening are allowed with confirmed recovery of CD20+ B cell population to within normal range	4. Subjects **who** used rituximab or other **B-cell depleting** monoclonal antibodies within 20 weeks prior to screening are excluded while subjects **who** used rituximab or other **B-cell depleting** monoclonal antibodies prior to 20 weeks before screening are allowed with confirmed recovery of the **B-cell population** to within normal range **at the time of screening**	Clarify class of restricted medications
	12. …associated with FSGS lesion (e.g. single kidney, surgical segmental and renal ablation…	12. …associated with FSGS lesion (**i.e. secondary FSGS, such as** single kidney, surgical segmental renal ablation… diabetic nephropathy, others)**, or histological collapsing variant subtypes of FSGS**	To clarify that the disorders associated with an FSGS lesion are considered secondary FSGS, and to exclude subjects with collapsing variants of FSGS as these patients do not respond to medical therapy
	13. …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.	13. …based on interferon γ release assay (IGRA) within 6 weeks prior to screening.	To clarify that only the IGRA can be used to exclude tuberculosis
	14. Evidence of hepatic disease…at baseline prior to dosing…	14. Evidence of hepatic disease…at **screening**…	To clarify timing of qualifying hepatic testing
	18. History of alcohol or illicit drug abuse or of lithium, pamidronate and interferon.	18. History of alcohol or illicit drug abuse.	Move reference to lithium, pamidronate and interferon to exclusion criterion #24
	20. Known hypersensitivity… (…magnesium stearate, or silicon dioxide).	20. Known hypersensitivity… (…magnesium stearate, silicon dioxide **or tartrazine**)	To add tartrazine, a component of the placebo, to the list of possible allergens in study drug
	24. Subjects taking lithium, or interferon;…	24. Subjects taking lithium, **pamidronate**, or interferon;…	Cite lithium, pamidronate and interferon in only one exclusion criterion

Section(s)	Original Text	Revised Text	Rationale for Change
SYNOPSIS, Efficacy Assessments & Bullet 2	• Proportion of subjects achieving complete renal remission (UPCR 0.3 g/g: eGFR normal or not less than 20% below baseline)… assessed at Weeks 12 and 24.	• Proportion of subjects achieving complete renal remission **at Weeks 12 and 24** **Complete Remission (includes all of the following):** **- reduction in UPCR to <0.3 g/g** **- Serum albumin within normal range** **- For subjects with abnormal serum creatinine levels at baseline, return to normal levels for that age group** **- For subjects with normal serum creatinine levels at baseline, final value within 20% of baseline levels**	Clarified the definition of complete renal remission
None	… or partial remission (UPCR decreased by 50% from baseline; UPCR <3.5g/g; and eGFR normal or not less than 20% below baseline), assessed at Weeks 12 and 24.	**• Proportion of subjects achieving partial remission at Weeks 12 and 24 by the following two different definitions:** **- UPCR reduction of ≥50% from baseline and UPCR <3.5 g/g** **- decrease in UPCR to less than 1.5 g/g and at least a 40% reduction in proteinuria from baseline assessed**	Clarified the definition of partial remission and added a second method for calculating partial remission
SYNOPSIS, Health Related Quality of Life Assessment	Change from baseline in domains assessed by Short Form 36 version 2 (SF-36 v2 and EQ-5D-5L) through Week 12 and Week 24	Change from baseline in domains assessed by **answers to the** SF-36 v2 and EQ-5D-5L **questionnaires** through Week 12 and Week 24	To clarify the instruments used
SYNOPSIS & Section 8.4 Exploratory Pharmacodynamic Assessments, bullet 5	• Change from baseline in… biomarkers…may include measurement of all or of a subset of the following:	• Change from baseline in… biomarkers…may include measurement of:	To harmonize the Synopsis with Section 8.4 (error)
TIME & EVENTS TABLE, Section 7 Study Schema	Column headings for Double Blind Treatment; Study Week: Day 1, Weeks 1, 2, 4, 8, 12, 13, 16, 20, 24, 28	Amended Column heading for Double Blind Treatment/Active Treatment; Study Week: Weeks 1, 2, 4, 8, 12	Clarify that Week 12 is the end of the Double-blind Treatment period

Section(s)	Original Text	Revised Text	Rationale for Change
	Column headings for Open-Label Treatment; Study Week: 16, 20, 24, 28	Amended Column heading for Open-Label Treatment; Study Week: 13, 16, 20, 24	Clarify that only subjects continuing in the study will attend these visits
	Column headings for Extension Phase; Study Week: 16, 20, 24, 28	Amended Column heading for Extension Phase; Study Week: 13, 16, 20, 24	Extension phase only for those subjects who are continuing in the study; Removed duplicate listing of Week 16,
	Column headings for Follow-up Phase; Study Week: 28	Amended Column heading for Follow-up Phase; Study Week: 16, 28	To consolidate listing of Follow-up visit for all subjects
	None	Added Column heading for Double Blind Treatment; Study Day: 1, **8, 15, 29, 57, 85**	Added a row to show both the Study Week and Study Day in the Time and Events Table
	None	Added Column heading for Open-Label Treatment /Follow-up; Study Day: **92, 113, 141, 170**	Added a row to show both the Study Week and Study Day in the Time and Events Table
	None	Added Column heading for Follow-up; Study Day: **113, 198**	Added a row to show both the Study Week and Study Day in the Time and Events Table
TIME & EVENTS TABLE, Section 7	None	24-hour urine collection; Study Day: **1, 85, 170**	Added 24-hour urine collection as a more accurate specimen for urinary measurements
TIME & EVENTS TABLE	Hematology, Serum chemistry including coagulation panel and lipids[9])	Hematology, Serum chemistry **(**coagulation panel and lipids **included at specified visits**[9])	To clarify the details of serum chemistry testing
TIME & EVENTS TABLE, Footnote 4	[4]Any one of the following may be done for TB screening: Interferon γ release assay (IGRA), tuberculin purified protein derivative (PPD) skin test, or chest radiography (done within 6 weeks prior to Screening or done during Screening).	[4]TB screening **by** Interferon γ release assay (IGRA) done within 6 weeks prior to Screening or done during Screening.	To clarify that only the IGRA can be used to provide evidence of exclusion of tuberculosis

Section(s)	Original Text	Revised Text	Rationale for Change
TIME & EVENTS TABLE, Footnote 5	[5]PK blood sample will be collected prior to the morning dose on Days 1 and 15, and at 0.5, 1, 2, 3, 4, and 6 hours following dosing. The remaining PK samples will be collected at time 0 only, just prior to administration of the first daily dose.	[5]PK blood sample will be collected **on Days 1 and 15** prior to the morning dose **(time 0)**, and at 0.5, 1, 2, 3, 4, and 6 hours following dosing. PK samples **at all other visits** will be collected at time 0 only, just prior to administration of the first daily dose.	To clarify the timing of PK sample collection
TIME & EVENTS TABLE, Footnote 9	[9] Serum chemistry to include coagulation panel (PT, PTT & INR) and lipids (HDL, LDL, Triglycerides and Total Cholesterol) at specified visits.	[9] Serum chemistry **at each visit to include liver panel (total, direct and indirect bilirubin, LDH, AST, ALT), alkaline phosphatase, etc. (see Section 8.2.2); at specified visits,** to include coagulation panel (PT, PTT & INR) and lipids (HDL, LDL, Triglycerides and Total Cholesterol) **as well**	To clarify the schedule and details of serum chemistry testing
TIME & EVENTS TABLE, Footnote 10	Concomitant medications will be recorded for all medications taken 12 weeks prior to screening. Glucocorticoids immunosuppressives and CD20+ antibodies will be recorded for up to 6 months prior to screening.	Concomitant medications will be recorded for all medications taken 12 weeks prior to screening. Glucocorticoids **and** immunosuppressives will be recorded for up to 6 months prior to screening. **If the subject has received prior rituximab treatment or other B-cell depleting antibodies, the rituximab use, as well as any available urinary protein values, should be recorded for up to 1 year prior to screening.**	To clarify the recording period for concomitant medications, and to capture 1 year of dosing with rituximab or other B-cell depleting antibodies, with any available urinary protein values
TIME & EVENTS TABLE, Footnote 11	[11] PK blood samples will be collected at 2 days, 7 days and 14 days following discontinuation of study drug to assess elimination.	[11] PK blood samples will be collected at 2 days, 7 days and 14 days following **the last dose** of study drug, **as well at the Follow-up Visit (Week 16 or Week 28)** to assess elimination PK.	To clarify the elimination PK sampling times
LIST OF ABBREVIATIONS AND ACRONYMS	None	**MDRD Modification of Diet in Renal Disease**	Omitted in error
INTRODUCTION, Section 2.4 paragraph 2	Anemia (red blood cell [RBC] parameter findings, with reticulocytosis),…	**…changes in** red blood cell [RBC] parameter findings, with reticulocytosis,…	To clarify the hematologic changes seen in the pre-clinical studies

Section(s)	Original Text	Revised Text	Rationale for Change
paragraph 3	…the highest dose of CCX140-B was…	…the highest dose **(50 mg/kg)** of CCX140-B was…	To identify the highest dose tested in the 39-week dog study
paragraph 4	Anemia findings are likely translatable to humans…	The **changes in RBC parameter findings**	To clarify the hematologic changes seen in the pre-clinical studies
	To ensure early detection of anemia…	To ensure early detection of **changes in RBC parameters**…	
paragraph 5	… higher safety margin than anemia…	…higher safety margin than **the changes in RBC parameters**…	
	….and will be evaluated for early symptoms…	….and will be **examined for vibration-sense deficits and** evaluated for early symptoms…	To update description of neurologic testing with all relevant procedures
paragraph 6	(based on reversible anemia)	(based on reversible **changes in RBC parameters**)	To clarify the hematologic changes seen in the pre-clinical studies
STUDY DESIGN, paragraph 1	Following the 12-week blinded treatment period, subjects will receive active treatment …	Following the 12-week blinded treatment period, **the study will evaluate up to 24 weeks of treatment with CCX140-B: all** subjects **who remain eligible** will receive active treatment…	To clarify the total duration of dosing
paragraph 2	Randomization will be stratified by FSGS classification (primary vs secondary) and…	Randomization will be stratified by **UPCR <3.5 g protein/g creatinine versus UPCR ≥3.5 g protein/g creatinine at baseline using the screening UPCR** and…	To harmonize the description of the stratification factors throughout the protocol

Section(s)	Original Text	Revised Text	Rationale for Change
paragraph 5	All subjects will take blinded study medication in the morning and evening, with or without food, for 84 consecutive days. Following the 84-day blinded dosing period, all subjects will take open label CCX140-B for an additional 84 days at the highest dose under evaluation, currently planned to be 15 mg twice daily. If the Sponsor, with the advice of the unblinded Data Monitoring Committee (DMC) determines that 15 mg twice daily exceeds the maximum tolerated dose, then the dose administered during the open label period will be adjusted downward from the planned dose to the highest dose that is still under evaluation. There will be a 28-day follow-up period after completion of treatment and all subjects are expected to return for assessment of elimination phase PK at 2, 7 and 14 days after taking the last dose of study medication.	All subjects will take blinded **oral** study medication **twice daily, 3 tablets** in the morning and **3 tablets in the** evening, with or without food, for **12 weeks (**84 consecutive days**)**. Following the 84-day blinded dosing period, all subjects **who remain eligible** will take open label CCX140-B for an additional **12 weeks (**84 **consecutive** days**)** at the highest **tolerated** dose under evaluation, currently planned to be 15 mg twice daily. **The decision on the dose for the open-label period will be made by** the Sponsor, with the advice of the unblinded Data Monitoring Committee (DMC). **After completion of treatment for whatever reason, including early termination,** all subjects are expected to return at 2, 7, and 14 days after taking the last dose of study medication **for assessment of elimination phase PK and at 28 days after taking the last dose of study medication for PK and safety monitoring**.	To clarify the sequence of events.

Section(s)	Original Text	Revised Text	Rationale for Change
paragraph 7	During the treatment period… collection of blood and urine. Subjects will discontinue study drug as of Study Day 169 (Week 24), and will return for a follow up visit on Week 28. When feasible, upon discontinuation… assessment of elimination 2, 7 and 14 days after the final dose of CCX140-B (or placebo).	During the treatment period… collection of blood and urine. **A 24 hour urine collection will be done the day before the Day 1 visit (baseline), the day before the Week 12 visit at the end of double-blind dosing, and the day before the Week 24 visit at the end of open-label dosing.** Subjects will return for a follow-up **safety** visit **4 weeks after the last dose of study drug (at Week 16 for those not entering the open-label phase, or at** Week 28 **for those who continue dosing into the open-label phase)**. When feasible, upon discontinuation…assessment of elimination **PK at** 2, 7 and 14 days after the final dose of **study drug (**CCX140-B or placebo**)**.	To add a 24-hour urine collection at Day 1, Week 12 and Week 24, since the UPCR from a 24-hour urine collection is considered most accurate; To clarify the sequence of events
paragraph 8, bullet 1	…LDH and total and bilirubin to assess early evidence of hemolysis;	…LDH**,** and bilirubin **(total and indirect)** to assess early evidence of hemolysis;	To clarify the reasons for bilirubin testing
paragraph 8, bullet 4	…AST and total and direct bilirubin; to assess…	**…**AST and bilirubin **(total and direct)**; to assess	
Figure 1	None	**24-hour urine collections**	To include the 24-hour urine collections
STUDY DESIGN, Section 4.2.1, Table 2	Timing, Line 3: Confirmed within 72 hours	**Retest** within 72 hours	To clarify retesting and stopping rules for liver enzyme elevations
Response, line 3:	Consider Discontinuation of Treatment	**If confirmed, discontinue treatment with CCX140-B**	
Event, line 4:	ALT or AST ≥ 5x ULN	ALT or AST ≥ 5x ULN **for more than 2 weeks**	
Timing, line 4:	Confirmed within 2 weeks…	**Retest** within **72 hours and then 2-3 times per week…**	
Response, line 4:	Consider Discontinuation of Treatment	**If confirmed, discontinue treatment with CCX140-B**	
Event, line 5:	ALT or AST ≥ 3x ULN and Total Bilirubin > 2 ULN or INR > 1.5	Event, Line 5: ALT or AST ≥ 3x ULN and **either** Total Bilirubin > 2 ULN or INR > 1.5	
Timing, line 5:	Confirmed within 72 hours…	**Retest** within 72 hours.	

Section(s)	Original Text	Revised Text	Rationale for Change
Response, line 5:	Consider Discontinuation of Treatment	**If confirmed, discontinue treatment with CCX140-B**	
Timing, line 6:	Confirmed within 72 hours (ALT, ASP, ALP, and Total Bilirubin should all be re-tested)	None	
Response, line 6:	Consider Discontinuation of Treatment	**Discontinue treatment with CCX140-B**	
Event, line 9:	Increase in reticulocyte count by ≥ 2 % (absolute) from baseline that is not otherwise explained	Increase **from baseline** in reticulocyte count by ≥ 2 **units (% of RBC)** that is not otherwise explained	To clarify the stopping rule for a change in reticulocyte measurement, since the percentage of red cells that are reticulocytes is reported, not the absolute reticulocyte count
STUDY POPULATION, Section 5.4 : Continuing Eligibility Criteria	None	**Subjects may enter the Open-Label Extension if the subject:** • **has not withdrawn consent for the study** • **has no new infections that, in the judgment of the investigator, would preclude addition of a new immunosuppressive or immunomodulatory treatment** • **has had no requirement for the addition of new immunosuppressive treatment during the prior 12 weeks and no anticipated requirement during the next 12 weeks.**	To clarify the Continuing Eligibility Requirements as stated in the Time and Events Table, Footnote #6

Section(s)	Original Text	Revised Text	Rationale for Change
STUDY MEDICATION/ TREATMENT, Section 6.8 Concomitant Medications and Restrictions, paragraph 1	None	**Medications taken prior to enrollment will be recorded:** • **rituximab or other B-cell depleting monoclonal antibodies for 1 year prior to screening;** **Subjects who have taken rituximab or other B-cell depleting monoclonal antibodies but stopped more than 20 weeks before screening will be allowed to participate if the recovery of the B cell population to within normal range is confirmed at the time of screening.** • **all FSGS medications (specifically glucocorticoids, immunosuppressives) for 6 months prior to screening;** • **all other medications, including plasma therapy regimens, for 12 weeks prior to screening.**	To specify the pre-study time period for recording potentially prohibited medication
STUDY MEDICATION/ TREATMENT, Section 6.8 Concomitant Medications and Restrictions, paragraph 5	Subjects taking lithium or interferon are also excluded. Note that subjects taking non-steroidal anti-inflammatory agents (NSAIDS) chronically (intermittent NSAIDS for pain or fever) are discouraged from study participation, but not excluded.	Subjects taking lithium, **pamidronate**, interferon, or **chronic NSAIDS** are also excluded. Note that subjects taking intermittent NSAIDS for pain or fever are discouraged from study participation, but **are** not excluded.	To align the Concomitant Medications section with Exclusion Criterion #24
STUDY MEDICATION/ TREATMENT, Section 6.8 Concomitant Medications and Restrictions, paragraph 6	All concomitant medications taken during…	All concomitant medications **including marijuana use (if applicable)** taken during	To clarify that marijuana use should be collected since it is a CYP3A4 inhibitor.
STUDY PROCEDURES, Section 7.1 Screening and Enrollment bullet 2	Recording… glucocorticoids, immunosuppressives and all CD20+ antibodies)	Recording…glucocorticoids, and immunosuppressives	To specify the pre-study time period for recording immunosuppressive medications

Section(s)	Original Text	Revised Text	Rationale for Change
STUDY PROCEDURES Section 7.1 Screening and Enrollment bullet 4	None	**If the subject has received prior rituximab treatment or other B-cell depleting antibodies, record the medication use, as well as any available urinary protein values, for 1 year prior to screening**	To specify the pre-study time period for recording use of rituximab or other B-cell depleting antibodies
STUDY PROCEDURES, Section 7.1 Screening and Enrollment bullet 5	In order to expedite the screening process, …the local laboratory for the following: Pregnancy test (in women of childbearing potential) Virology assessments (HIV, HCV, HBV) unless done within 6 weeks prior to screening	None	To remove the option for the use of local laboratories. All labs are to be processed through the Central Laboratory
STUDY PROCEDURES, Section 7.1 Screening and Enrollment bullet 5	- Test to exclude tuberculosis (interferon γ release assay [IGRA], tuberculin purified protein derivative [PPD] skin test, or chest radiography [X rays or CT scan]) if not done within 6 weeks prior to screening	• Test to exclude tuberculosis (interferon γ release assay [IGRA] within 6 weeks prior to screening	To clarify that only the IGRA can be used to provide evidence of exclusion of tuberculosis
STUDY PROCEDURES, Section 7.1 Screening and Enrollment,	None	**• The subject will be given instructions and supplies for the urine collections on the day before the next visit (kit for first morning void and jug for 24-hour urine collection)** **- Collect the first morning void the day before the first visit (Day 0) and put in the smaller container.** **- Collect all urine for 24 hours starting AFTER the first morning void, including first morning void on the day of the Study Day 1 visit, in the big jug.** **- Keep specimens refrigerated until they are brought to the site at the Study Day 1 visit.**	24-hour urine collection added before first study drug dose, and before Week 12 and Week 24 visits

Section(s)	Original Text	Revised Text	Rationale for Change
STUDY PROCEDURES, Section 7.6 & 7.10	None	• **Provide the subject with the kit for collection of the first morning void and jug for the 24-hour urine collection**	
	None	• **After all study procedures…** - **Collect the first morning void the day before the Week (12, 24) visit and put in the smaller container** - **Collect all urine for 24 hours starting AFTER the first morning void, including first morning void on the day of the Week (12, 24) visit, in the big jug.** - **Keep specimens refrigerated until they are brought to the site for the Week (12, 24) visit.**	
STUDY PROCEDURES, Section 7.2 through 7.12	First morning void urine sample…	**Process the first** morning void urine sample**…**	To clarify the procedure
STUDY PROCEDURES, Sections 7.2, 7.7, 7.11	None	• **Process the 24-hour urine sample collection for quantitative urinalysis, UPCR, UACR, Cystatin C, Urine MCP-1, MCP-1/creatinine ratio, urine PD assessment, and urine protein excretion/day**	To clarify the procedure
STUDY PROCEDURES, Section 7.2 & 7.4	PK blood samples will be collected at 0.5, 1,…	PK blood samples will be collected at **Time 0 (pre-dose),** 0.5, 1,…	To clarify that a predose sample must be taken.
STUDY PROCEDURES, Sections 7.2 through Section 7.11	None	• **Provide the subject with the kit for collection of the first morning void**	Instructions omitted in error
	None	• **After all study procedures…** - **On the morning of the next visit, collect the first morning void in the container provided and refrigerate until it is brought to the study center**	

Section(s)	Original Text	Revised Text	Rationale for Change
STUDY PROCEDURES, Section 7.7	None	• **Assessment of continuing eligibility requirements:** - **has not withdrawn consent for the study** - **has no new infections that in the judgment of the investigator would preclude addition of a new immunosuppressive or immunomodulatory treatment** - **has had no requirement for the addition of new immunosuppressive treatment during the prior 12 weeks and no anticipated requirement during the next 12 weeks**	Criteria for assessing continued eligibility
	• After all study procedures have been completed, the subject will be reminded to:	• After all study procedures have been completed, **discontinuing subjects** will be reminded to:	Specify procedures for those subjects continuing in the study and those who are discontinuing treatment.
	None	- **come to the study center at 2 days, 7 days and 14 days after the last dose for PK elimination and** - **come to the study center for the Week 16 follow-up visit**	
	None	• **Continuing subjects will be reminded to:**	
	- Come to the study center for the Week 13 study visit, before taking the dose of the visit day	• Come to the study center for the Week 13 study visit, before taking the dose of **study drug**	
STUDY PROCEDURES, Title of Sections 7.8 through 7.11	Study Week…	Study Week **… - Continuing Subjects Only**	To identify visits that only pertain to continuing subjects
STUDY PROCEDURES, Section 7	7.9 Study Week 16 (Day 114 +/- 3 days)- Safety Evaluation for Discontinuing Subjects Only	None	Removed separate instructions for subjects discontinuing at Week 16
STUDY PROCEDURES, Section 7 (now)	- First morning void urine sample collection for UPCR and UACR assessment	None	Removed redundant instruction

Section(s)	Original Text	Revised Text	Rationale for Change
STUDY PROCEDURES, Section 7.12 (now) Title	7.13 Study Week 28 (Day 197 +/- 3 days)- Follow Up visit (See Section 7.14 for PK elimination guidelines)	7.12 **Follow Up visit** - Study Week **16 (Day 114** +/- **3 days for discontinuing subjects) and Week 28 (**Day 197 +/- **3** days **for continuing subjects**) - (See Section 7.**13** for PK elimination guidelines)	Combined instructions for Follow-up visit at Week 16 for discontinuing subjects and Week 28 for Continuing subjects
STUDY PROCEDURES, Section 7.12 (now)	**The Study Week 28 visit should occur…**	**The follow-up** visit should occur…	Combined instructions for Follow-up visit at Week 16 for discontinuing subjects and Week 28 for Continuing subjects
	…samples will be collected before dose administration for serum	…samples will be collected for serum	Subjects are not on study drug at this visit, included in error.
STUDY PROCEDURES, Section 7.13 (now) paragraph 1	Upon discontinuation of treatment for any reason a sample…	Upon discontinuation of treatment for any reason, **including end of study**, a sample…	To clarify that discontinuation of treatment includes end of study
paragraph 2	… standard of care medical treatment will be provided to all subjects as needed	…standard of care medical treatment **should be implemented for** all subjects as needed	Clarify implementation of off-study treatment at study completion
STUDY PROCEDURES, Section 7.14 (now)	None	• **Whenever possible, the subject will be asked to collect all urine for the 24 hours after the last dose of study drug**	To include the 24-hour urine collection in the early termination procedures, whenever possible
	• First morning void urine sample…	• **If available, process the first** morning void urine sample**…**	To clarify instructions
	None	• **If available, process the 24-hour urine sample for quantitative urinalysis, UPCR, UACR, Cystatin C, Urine MCP-1, MCP-1/creatinine ratio urine PD assessment and urine protein excretion/day**	
STUDY ASSESSMENTS, Section 8.1.1 paragraph 2	Starting on Day 1, the urine samples will be sent…	**The** urine samples, **first morning void and 24-hour urine sample** will be sent…	All labs will be done through the central lab for uniformity of results

Section(s)	Original Text	Revised Text	Rationale for Change
	… (UPCR)… concentration assessed in a sample drawn from a first morning urine;	… (UPCR)… concentration;	Both first morning void and 24-hour urine samples will be used for efficacy assessments
	…(UACR)… concentration assessed in a sample drawn from first morning void;	…(UACR)… concentration;	
STUDY ASSESSMENTS, Section 8.2.2 bullet 1	…corpuscular volume and reticulocyte count;	…mean corpuscular volume**,** reticulocyte count **and schistocytes**;	Specify that the presence of schistocytes will be monitored to assess hemolysis
bullet 2	… liver panel (total and direct bilirubin,…	liver panel (total, direct **and indirect** bilirubin,	Specify that indirect bilirubin will be measured to assess hemolysis
bullet 4	Virology (measured only at screening and may be measured at the local laboratory):…	Virology (measured only at screening):…	All labs will be done through the central lab for uniformity of results
bullet 5	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.	TB screen: Only interferon γ release assay (IGRA) done within 6 weeks prior to screening is allowed for eligibility assessment.	To clarify that only the IGRA can be used to provide evidence of exclusion of tuberculosis
STUDY ASSESSMENTS, Section 8.4 Exploratory Pharmacodynamic Assessments paragraph 1	Blood samples (plasma and serum) for PD measurement…	Blood samples (plasma and serum) **and urine samples** for PD measurement…	Reference to the urine samples omitted in error

Section(s)	Original Text	Revised Text	Rationale for Change
STATISTICS, Section 9.2.2 bullet 1	• Change from baseline in eGFR calculated by the CKD EPI cystatin C equation as measured by eGFR at weeks 12 and 24.	• 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** at weeks 12 and 24.	To harmonize Section 9.2.2 of the protocol with Synopsis; methods for calculating eGFR omitted from Section 9.2.2 in error
bullet 2	• None	• **Proportion of subjects achieving complete renal remission at Weeks 12 and 24** **Complete Remission (includes all of the following)** **- reduction in UPCR to <0.3 g/g** **- Serum albumin within normal range** **- For subjects with abnormal serum creatinine levels at baseline, return to normal levels for that age group** **- For subjects with normal serum creatinine levels at baseline, final value within 20% of baseline levels**	To harmonize Section 9.2.2 of the protocol with Synopsis; secondary endpoints were different in error; Added endpoint and definition of complete renal remission
bullet 3	• Proportion of subjects achieving partial renal remission (UPCR 0.3 g/g: eGFR normal or not less than 20% below baseline) or partial remission (UPCR decreased by 50% from baseline; UPCR <3.5g/g; and eGFR normal or not less than 20% below baseline), assessed at Weeks 12 and 24.	• Proportion of subjects achieving partial remission **by the following two different definitions assessed at Weeks 12 and 24:** **- UPCR reduction of ≥50% from baseline and UPCR <3.5 g/g** **- decrease in UPCR to less than 1.5 g/g and at least a 40% reduction in proteinuria from baseline**	Clarified the definition of partial remission and added a second method for calculating partial remission
STATISTICS, Section 9.2.3 Secondary Efficacy Endpoints bullet 6	- Relationship among PK, serum albumin and UPCR;	- Relationship among PK, **eGFR**, serum albumin and UPCR;	Update exploratory endpoints
STATISTICS, Section 9.3.3	All CD20+ antibodies, glucocorticoids and…	All **B-cell depleting** antibodies, glucocorticoids and	Clarify the class of prior medications that may be summarized separately

Section(s)	Original Text	Revised Text	Rationale for Change
STATISTICS, Section 9.3.9 bullet 1	• Presence of nephrotic syndrome (yes vs. no). Nephrotic syndrome is defined as proteinuria of at least 3.5 grams/day in association with hypoalbuminemia (<3 g/dL) and peripheral edema	• **UPCR <3.5 g protein/g creatinine at baseline versus UPCR ≥3.5 g protein/g creatinine at baseline**	To harmonize the wording of the stratification factors
APPENDICES	Section 13.1 Statement of Obligations of Sponsor, Monitor, and Clinical Investigator, Section 13.2 Informed Consent Form	None	Section not needed in protocol

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. STUDY SYNOPSIS

Name of Sponsor	**Name of Active Ingredient**	**Study number**
ChemoCentryx, Inc.	CCX140-B	CL011_140

Title

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

Investigators

Several

Study centers

Multi-center; approximately 40 sites planned in North America, Europe, Australia

Study period

- Time from first subject first visit to last visit for assessment of primary endpoint at 12 weeks: approximately 68 weeks:
  - 4 weeks screening
  - 52 weeks recruitment
  - 12 weeks to last subject last visit
- Participation time for each subject approximately 32 weeks
  - 4 weeks screening
  - 12 weeks blinded treatment period
  - 12 week open label treatment period
  - 4 week follow-up

Phase of development

Phase 2

Aim

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

Objectives

- The primary safety objective of this study is to evaluate the safety and tolerability of CCX140-B in subjects with FSGS with proteinuria.
- The primary efficacy objective of this study is to evaluate the effect of CCX140-B treatment on urinary protein excretion in subjects with FSGS, as assessed by change from baseline in the urine

protein to creatinine ratio (UPCR) **at Week 12**.

The secondary objectives of this study are:

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

Exploratory objectives of this study are:

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

Rationale

Focal segmental glomerulosclerosis (FSGS) describes a group of disorders that share a common histologic lesion characterized by scarring that appears on light microscopy to occur in some but not all glomeruli (focal) and to affect only part of the involved glomeruli (segmental). FSGS is classified as primary when the etiology is not known, and as secondary when it occurs in the presence of nephron loss, diabetes, obesity, hypertension, drug exposure, high risk genetic variants, and other conditions recognized to increase risk.

Patients with FSGS lesions may present with nephrotic syndrome or with sub-clinical elevations of urinary protein or serum creatinine. Current guidelines (Kidney Disease: Improving Global Outcomes Practice Guideline for Glomerulonephritis, 2012) recommend a trial of glucocorticoids for patients with primary FSGS and features of nephrotic syndrome, followed by calcineurin inhibitors if needed for intolerance or inadequate response to glucocorticoids. Non-nephrotic or secondary FSGS is treated with optimal management of co-morbid conditions; blockade of the renin angiotensin aldosterone system (RAAS) is used to treat hypertension and reduce proteinuria when indicated. Despite best standard of care, progression of disease is common; in the US, the estimated incidence of newly-recognized FSGS, and the reported incidence of end stage renal disease (ESRD) due to FSGS, are both approximately 7/million/year. Thus current therapies may be delaying, but not preventing, renal failure.

The interaction between CCR2 and MCP-1 has emerged as a potential target for treatment of FSGS, based on association between levels of urine MCP-1 and disease activity in human, and on observations in murine models with features of FSGS.

CCX140-B, an orally administered selective antagonist of CCR2, has exhibited efficacy in murine models of renal damage as assessed by significant reductions in proteinuria, an important clinical endpoint for FSGS. CCX140-B was associated with a favorable safety profile when administered at 5 mg daily or 10 mg daily for up to 52 weeks in patients with diabetic nephropathy; a trend toward greater reduction in proteinuria compared to placebo was seen in both active treatment groups, and reached statistical significance in the group treated with 5 mg daily.

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.

Methodology

This study will evaluate the efficacy, safety, tolerability, and pharmacokinetics of up to 12 weeks of treatment with each of three dose regimens of CCX140-B or placebo, when used in combination with stable standard of care therapy in subjects with FSGS with significant proteinuria, assessed as UPCR ≥ 1g/g at Screening. Following the 12-week blinded treatment period, subjects will receive active treatment for an additional 12 weeks to assess safety and durability of effect.

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

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

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

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

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

Subjects will be screened within a period not to exceed 28 days prior to Study Day 1 (the first day of dosing).

All subjects will take blinded study medication in the morning and evening, with or without food, for 84 consecutive days. Following the 84-day blinded dosing period, all subjects will take open label CCX140-B for an additional 84 days at the highest dose under evaluation, currently planned to be 15 mg twice daily. If the Sponsor, with the advice of the unblinded Data Monitoring Committee (DMC), determines that 15 mg twice daily exceeds the maximum tolerated dose, then the dose administered during the open label period will be adjusted downward from the planned dose to the highest dose that is still under evaluation. There will be a 28-day follow-up period after completion of treatment.

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

For assessment of adverse events of special interest, study procedures will include

- Complete blood count with differential, morphology assessment, reticulocyte count, hemoglobin, LDH and total and direct bilirubin, to assess early evidence of hemolysis;
- The AIDS Clinical Trials Group Brief Peripheral Neuropathy Screening Tool (ACTG-BPNST), to assess early evidence of neuropathy;
- Monitoring for adverse events of infection;
- Alkaline phosphatase, ALT, AST and total and direct bilirubin; to assess for evidence of drug induced liver injury.

For assessment of pharmacokinetics, study procedures will include

- **Seven** blood samples collected over 6 hours on Study Day 1 and Study Day 15 to assess AUC_{0-6} following the first administration of study drug, and at steady state;
- Assessment of C_{min} at intervals to ensure that exposure is within the projected range, with adequate safety margin based on the NOAEL established in preclinical toxicology;
- Upon discontinuation of treatment for any reason, collection of blood at 2 days, 7, days and 14 days following discontinuation to assess elimination kinetics.

All study procedures are presented in the Time and Events table.

Subjects who are using an angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB) or other blocker of the renin angiotensin aldosterone system (RAAS), or who are using glucocorticoids, a calcineurin inhibitor or other immunomodulatory or immunosuppressive therapy, must be on a stable dose for at least 4 weeks prior to screening. The dose of these medications should be planned to be kept constant over the course of the study in order to prevent undue influence of changes in these medications on the efficacy and safety assessments, except when adjustment is required for patient safety. The investigator must also attempt to keep doses of other medications, and lipid-lowering medications fixed throughout the blinded study period in order to prevent undue influence of changes in these medications on the efficacy and safety assessments.

Subjects who experience deteriorating renal function based on an increase in serum creatinine of at least 50% (confirmed by a repeat measurement after 2 weeks) which is otherwise not explained (e.g., dehydration, new medication), or increase in UPCR of >3.0 g/g (confirmed by a repeat measurement after 2 weeks) during the 12-week treatment period, will exit the treatment phase of the study and be treated at the discretion of the treating physician. All subjects who discontinue treatment will remain in the study for follow up and outcome recording.

An independent Data Monitoring Committee (DMC) will be responsible for reviewing unblinded safety data throughout the course of the study.

Subjects will be discharged from the study at the completion of the Week 28 visit. To the extent possible, any adverse events that are deemed study drug-related and are ongoing at discharge will be followed-up to resolution or until a determination is made that the unresolved event is stable.

Number of Subjects

The target number of subjects is 40. Subjects who discontinue during the first 14 days of taking study drug for reasons other than adverse events related to study drug may be replaced to ensure that sufficient data are available for assessment of safety, PK, and efficacy.

Main Criteria for Inclusion

1. Male or female subjects aged 18-75 years inclusive
2. Urinary total protein:creatinine ratio (UPCR) ≥ 1 g protein/g creatinine at screening (or UPCR at 113 mg/mmol).
3. Diagnosis of FSGS based on at least one of the following:
    - Renal biopsy demonstrating the FSGS lesion and characteristic clinical presentation and course
    - High risk genetic variant and characteristic clinical presentation and course
4. Diagnosis of one of the following subtypes of FSGS:
    - Primary FSGS based on characteristic histopathology, medical history, and clinical course, or
    - FSGS secondary to a genetic variant associated with increased risk or severity, which may include NPHS1, NPHS2, WT-1, LAMB2, CD2AP, TRPC6, ACTN4 or INF2
5. Estimated glomerular filtration rate (eGFR) >30 mL/min/1.73m^2, with eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (using creatinine or cystatin C)
6. The typical blood pressure of the patient should be clinically stable prior to enrollment and not exceed 145/95 mmHg.
7. If using RAAS blockers, dose must be stable for a minimum of 4 weeks prior to Screening, and projected to remain stable through Study Week 12, unless adjustment is required for management of hypertension.
8. If using immunosuppressive or immunomodulatory therapy, dose must be stable for a minimum of 4 weeks prior to Screening, and projected to remain stable through Study Week 12
9. If using glucocorticoids, dose must be stable for a minimum of 4 weeks prior to Screening and projected to remain stable through Study Week 12
10. Female subjects of childbearing potential may participate if adequate contraception is used during, and for at least **1 month** 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.
11. Willing and able to give written Informed Consent and to comply with the requirements of the study protocol
12. 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's a reasonable possibility of getting an organ transplant within 6 months of screening
4. Subjects **who** used rituximab or other **B-cell depleting** monoclonal antibodies within 20 weeks prior to screening are excluded while subjects that used rituximab or other **B-cell depleting** monoclonal antibodies prior to 20 weeks of screening are allowed with confirmed recovery of **the** B-cell population to within normal range **at the time of screening**
5. Plasmapheresis within 12 weeks prior to screening
6. Body mass index (BMI) ≥40
7. 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 of investigational product
8. Currently on dialysis or likely to require dialysis during the projected blinded treatment period of 12 weeks
9. History or presence of any form of cancer within the 5 years prior to screening, with the exception of excised basal cell or squamous cell carcinoma of the skin, or 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
10. 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
11. Renal disease associated with disorders other than FSGS (e.g. lupus nephritis, C3 glomerulopathy, proliferative glomerulonephritis, IgA nephropathy, reflux nephropathy, surgical segmental renal ablation, sickle cell disease) that is active, or has significant risk of progressing during the course of the study
12. Disorders other than those listed in Inclusion Criterion 4 that are associated with FSGS lesion (i.e.. **secondary FSGS such as** single kidney, surgical segmental renal ablation, sickle cell disease, diabetic nephropathy, others**), or histological collapsing variant subtypes of FSGS**
13. Evidence of tuberculosis based on interferon γ release assay (IGRA) within 6 weeks prior to screening
14. Evidence of hepatic disease; AST, ALT, alkaline phosphatase >3x 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).

15. Clinically significant peripheral neuropathy.
16. Hematologic abnormalities as follows: Hb < 8 g/dL, platelets < 50,000, ANC < 1000 cells/µL) at baseline
17. Clinically significant abnormal ECG during screening, e.g., QTcF greater than 450 msec
18. History of alcohol or illicit drug abuse. Recreational use of cannabis is not excluded where legal.
19. History of gastrointestinal conditions that may interfere with study medication compliance, e.g., severe gastroparesis, with regurgitation of food or oral medication
20. Known hypersensitivity to CCX140-B or inactive ingredients of the CCX140-B tablets (including microcrystalline cellulose, starch, crospovidone, magnesium stearate, silicon dioxide**, or tartrazine**)
21. History or presence of systemic disorder other than FSGS that requires, or is expected to require, systemic glucocorticoids or immune modulators during the study; topical or inhaled glucocorticoids and immune modulators are not excluded
22. 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
23. 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
24. 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)

Test Product

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

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

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

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

Duration of Treatment and Observation

Subjects will be screened within a period not to exceed 28 days prior to Study Day 1 (the first day of dosing).

The placebo-controlled treatment period through the primary safety, PK and efficacy endpoints is 84 days (12 weeks). The total treatment period is 24 weeks. The safety follow up period is 4 weeks.

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

Safety and Other Assessments

Safety will be evaluated by periodic physical examinations and body system reviews, assessments of vital signs, routine clinical laboratory tests (including blood chemistry, hematology, and urinalysis), electrocardiographic (ECG) monitoring, and monitoring of adverse events and concomitant medications. The ACTG-BPNST will be used at each scheduled visit to assess early evidence of neuropathy.

Pharmacokinetic Assessments

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

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

Efficacy Assessments

Efficacy will be evaluated by assessment of urine protein:creatinine ratio (UPCR), urine albumin:creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR)

The primary efficacy endpoint is:

- Change from baseline in urine protein:creatinine ratio (UPCR)

Secondary endpoints include:

- 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 at Weeks 12 and 24
- Proportion of subjects achieving complete renal remission **at Weeks 12 and 24**

  Complete Remission (includes all of the following):
  - **Reduction in UPCR to < 0.3 g/g**
  - **Serum albumin within normal range**
  - **For subjects with abnormal serum creatinine levels at baseline, return to normal levels for that age group**

- **For subjects with normal serum creatinine levels at baseline, final value within 20% of baseline levels**

- **Proportion of subjects achieving partial remission at Weeks 12 and 24 by the following two different definitions:**
  - **UPCR reduction of ≥ 50% from baseline and UPCR <3.5 g/g**
  - **decrease in UPCR to less than 1.5 g/g and at least a 40% reduction in proteinuria from baseline**

Health Related Quality of Life Assessment

Change from baseline in domains assessed by **answers to the** SF-36 v2 and EQ-5D-5L **questionnaires** through Week 12 and Week 24

Exploratory Pharmacodynamic Assessments

Blood (plasma and serum) and urine samples will be collected according to the Time and Events Table for PD biomarker measurements.

Exploratory assessments may include:

- Profile of FSGS related gene mutations;
- Change from baseline in urinary MCP-1:creatinine ratio;
- Change from baseline in urinary albumin to creatinine ratio (UACR)
- Change from baseline in blood monocytes, T, B and NK cells
- Change from baseline in other urinary and blood exploratory biomarkers potentially associated with activity of FSGS or inhibition of the CCR2/MCP-1 pathways. These may include measurement of:

  -Transforming growth factor-beta (TGF-β), connective tissue growth factor (CTGF), N-acetylglucosamine (NAG), β2 microglobulin, adiponectin, C-reactive protein (CRP), cystatin C, synaptopodin, neutrophil gelatinase-associated lipocalin (NGAL), liver-fatty acid-binding protein (LFABP), kidney injury molecule-1 (KIM-1), intact PTH, leptin, resistin, chemerin, retinol binding protein 4 (RBP-4), MCP-1, IL-1β, IL-6, suPAR, suCD163, miR-193a, CLCF-1 and TNF-α.

Statistical Methods

A Statistical Analysis Plan (SAP) will be developed separately prior to the database lock and unblinding. This SAP will provide detail of the data summary and analysis specifications. When differences exist between the SAP and the protocol specified statistical methods, the SAP will supersede the protocol.

Demographics and Baseline Characteristics

All baseline subject characteristics, demographics, and prior/concomitant medications will be listed by subject and summarized by treatment group and overall.

Safety Analysis

All subjects who are randomized and received at least one dose of study medication will be included in the safety population.

Safety endpoints include:

- Subject incidence of treatment-emergent adverse events, adverse events leading to study withdrawal, and serious adverse events;
- Change from baseline and shifts from baseline in all safety laboratory parameters;
- Change from baseline in vital signs;
- Change from baseline in score on the ACTG- BPNST

- Clinically significant abnormal ECG findings
- Physical examinations

Treatment-emergent adverse events (TEAE) will be summarized for each treatment group by MedDRA System Organ Class (SOC) and preferred term (PT), by relatedness and maximum severity. Treatment-emergent serious adverse events (TESAE) and TEAE leading to study withdrawal will be separately listed and may be summarized if warranted by the subject incidences.

Vital signs and laboratory test results, and their changes from baseline will be summarized by treatment group and visit. Abnormal laboratory values will be flagged in the data listing. Shift tables will be generated by study visit.

Individual ECG findings and change from baseline in ECG findings will be listed by treatment group, subject, and study visit, and summarized by treatment group and visit.

Findings from physical examinations will be listed.

Pharmacokinetic Analysis

Individual plasma concentrations of CCX140 will be listed, plotted, and summarized descriptively and graphically for subjects receiving CCX140-B. The following parameters will be determined for CCX140:

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 Time 6

Summary statistics for steady state trough plasma concentrations will also be performed.

The relationship between PK parameters and renal function based on eGFR, UPCR and serum albumin will be evaluated. The data may also be used to evaluate the PK/PD relationship of CCX140-B treatment.

Efficacy Analysis

Summary statistics will be calculated for each of the efficacy parameters. For categorical endpoints, numbers and percentages will be calculated. For continuous variables, numbers, means, medians, ranges, and standard deviations will be calculated. Point estimates and corresponding 90% confidence intervals will be estimated for the difference between CCX140-B and placebo groups.

Because of the relatively small size of the study, inferential statistical analyses may not be appropriate. Where possible, change from baseline to Day 85 and from Day 85 to Day 169 in UPCR will be analyzed using the mixed-effects model for repeated measures (MMRM), with treatment group, visit, and treatment-by-visit as factors and baseline UPCR and age as covariates. The between group comparison will be computed using the simple contrast from the model. Analysis of covariance (ANCOVA) with last observation carried forward (LOCF) for missing data will also be used for sensitivity analysis. The MMRM and ANCOVA analyses will also be applied to the eGFR endpoint.

Proportion of subjects achieving partial response will be calculated for each treatment group. The between group comparison will be carried out using the Fisher's exact test.

The exploratory endpoints will be analyzed using MMRM model or ANCOVA as described for the primary efficacy endpoint analysis.

TIME AND EVENTS TABLE

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

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

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

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

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

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

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

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

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

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

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

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

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

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

LIST OF ABBREVIATIONS AND ACRONYMS

ACTG-BPNST	Aids Clinical Trial Group- Brief Peripheral Neuropathy Screening Tool
ACE	Angiotensin Converting Enzyme
ADME	Absorption, Distribution, Metabolism and Excretion
ANCOVA	Analysis of covariance
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.
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 plasma concentration
C_{max}	maximum (maximal) plasma concentration
CYP	cytochrome P450
DMC	Data Monitoring Committee
DN	Diabetic nephropathy
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
ESRD	End State Renal Disease
ESRF	End Stage Renal Failure
FDA	Food and Drug Administration
FSGS	Focal Segmental Glomerulosclerosis
GI	Gastrointestinal
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
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 Gamma Release Assay
IMP	Investigational medicinal product
IND	Investigational New Drug Application
INR	International Normalization Ratio
KDIGO	Kidney Disease Improving Global Outcomes
LOCF	Last observation carried forward
MCP-1	monocyte chemoattractant protein 1, also known as CCL2
MDRD	**Modification of Diet in Renal Disease**
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.”
PR	Partial remission
QD	one dose per day; also represented as “q.d.”
RAAS	Renin-angiotensin-aldosterone system
RBC	red blood cell(s)
SAE	Serious adverse event
$t_{1/2}$	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

2. INTRODUCTION

2.1. Background Information

CCX140-B is an orally administered, selective antagonist of C-C chemokine receptor type 2 (CCR2) that has demonstrated efficacy for reduction of proteinuria in a Phase 2 study in patients with diabetic nephropathy and is currently in development for treatment of patients with focal segmental glomerulosclerosis (FSGS).

2.2. Rationale for Study in FSGS: Unmet Medical Need

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 some but not all glomeruli (focal) and to affect only part of the involved glomeruli (segmental). FSGS is classified as primary when the etiology is not known, and as secondary when it occurs in the presence of nephron loss, diabetes, obesity, hypertension, drug exposure, high-risk genetic variants and other conditions recognized to increase risk. Several genetic variants have been identified that impact the structure or function of podocytes, and increase the risk or severity of FSGS (Chen et al, 2015). FSGS may present with nephrotic syndrome or with sub-clinical elevations of urinary protein or serum creatinine.

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 in 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, **the estimated glomerular filtration rate (**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 **end-stage renal disease (**ESRD**)** within 3 to 8 years (D'Agati, 2011). In the US, the estimated incidence of newly-recognized FSGS, and the reported incidence 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.

2.3. 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 **chronic kidney disease (**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), as summarized in Section 2.4.1. 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.

2.4. 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. The nonclinical toxicity studies with CCX140-B were supplemented with safety pharmacology studies including behavioral and autonomic neuronal function testing, pulmonary and cardiovascular function evaluations in conscious rats and dogs, and included an *in vitro* potassium channel hERG assay. There were no adverse findings attributable to CCX140-B in any of the organ systems studied. In addition studies of the effects of CCX140-B on the immune system (T cell dependent antibody production) were also conducted and did not identify any safety concerns. CCX140-B was not genotoxic *in vitro* or *in vivo*, and was not phototoxic *in vitro*.

In repeat-dose toxicity studies (up to 26 weeks in rats and 39 weeks in dogs) two adverse nonclinical findings of concern were revealed: **changes in r**ed blood cell [RBC] parameter findings, with reticulocytosis, which was observed across all species studied, and peripheral axon neuropathy which was observed only in dogs.

In these repeat dose nonclinical studies, there was clear evidence of rapid recovery of the RBC findings and reticulocytosis in the absence of drug. In the 39-week dog study, the highest dose **(50 mg/kg)** of CCX140-B was associated with slight to mild neuronal cell changes (based on thorough histological examinations), but these were not deemed to be of likely clinical relevance by the histopathologist and indeed there were no clinical correlates observed. Cessation of active damage (decreased immune cell infiltrates) was noted, however recovery was incomplete. Off-target binding assays, *in vivo* immune mechanism, and immunohistochemistry evaluations did not reveal a mechanism for the neuropathy findings in dogs, but may rule out direct CCR2 receptor inhibition. In *in vitro* assessments, there were no unique metabolites to dogs. However,

in dogs there is a higher percentage of free CCX140 in plasma which is unique among studied species, including humans. The neuronal findings appearing only in dogs suggests species specificity, however the mechanism is unknown, and a threshold effect of free drug concentration cannot be ruled out.

The changes in RBC parameter findings are likely translatable to humans, but are monitorable, reversible, and there was an acceptable safety margin across all species (see below). To ensure early detection of **changes in RBC parameters** 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.

Neuropathy findings in dogs are likely species-specific with a higher safety margin than **the changes in RBC parameters**, however reversibility was incomplete and the mechanism is unknown. Subjects in the Phase 2 study will be monitored for adverse events related to the nervous system, and will be **examined for vibration-sense deficits and** evaluated for early symptoms using a questionnaire validated for early detection of peripheral neuropathy in studies of patients with HIV infection.

The NOAEL in the 26-week rat studies of 15 mg/kg/day (based on reversible **changes in RBC parameters**) 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. Thus, for dose escalation in human subjects, exposures to CCX140 should not exceed total plasma $AUC_{0\text{-}24}$ exposures of 465 µg•hr/mL, or total C_{max} concentrations of 32 µg/mL.

Results from all the safety and toxicology studies support repeated dosing of CCX140-B to humans up to predicted exposure parity with the 26-week rat NOAEL levels. The NOAEL in the 26-week rat study was associated with systemic exposure to CCX140 which was approximately 3- to 4-fold the predicted human exposure with a 15 mg twice daily (b.i.d.) dose of CCX140-B.

2.4.1. CCR2 Inhibitor CCX140-B: Clinical Experience

CCX140-B is an orally administered, selective small molecule inhibitor of the chemokine receptor known as CCR2. To date it has not been administered in subjects with biopsy-proven FSGS.

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).

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.

3. OBJECTIVES

3.1. Primary Objective

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

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

3.2. Secondary Objectives

- To evaluate the effect of CCX140-B on renal function, as assessed by estimated glomerular filtration rate (eGFR) using the CKD-EPI Cystatin C equation, CKD-EPI **(chronic kidney disease epidemiology collaboration)** Creatinine equation, CKD-EPI Creatinine-Cystatin C equation and MDRD **(Modification of Diet in Renal Disease)** Creatinine equation assessed at Weeks 12 and 24
- **To evaluate the effect of CCX140-B treatment on fraction of subjects achieving complete and partial renal remission (by 2 different partial remission definitions)**
- To evaluate the pharmacokinetics (PK) profile of CCX140-B in subjects with FSGS

3.3. Exploratory Objectives

To evaluate the effect of CCX140-B on urinary monocyte chemoattractant protein-1 (MCP-1) and other serum and urinary markers of renal function and inflammation;

To explore the effect of CCX140-B on levels of blood monocytes, T, B and NK cells, and other blood and urinary markers potentially associated with CCR2 antagonism;

To explore the effect of CCX140-B on Health-related Quality of Life changes based on Short Form 36 version 2 (SF-36 v2) and **EuroQuality of Life-5 Domains-5 Levels** (EQ-5D-5L) **questionnaires**;

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

4. STUDY DESIGN

This study will evaluate the efficacy, safety, tolerability, and pharmacokinetics of up to 12 weeks of treatment with each of three dose regimens of CCX140-B or placebo, when used in combination with stable standard of care therapy in subjects with FSGS with significant proteinuria, assessed as UPCR $\geq$ 1g/g at Screening. Following the 12-week blinded treatment period, **the study will evaluate up to 24 weeks of treatment with CCX140-B: all** subjects **who remain eligible** will receive active treatment for an additional 12 weeks to assess safety and durability of effect.

The target is to enroll 40 male or female subjects in this randomized, double-blind, placebo-controlled, Phase 2 study. Randomization will be stratified by **UPCR <3.5 g protein/g creatinine versus UPCR ≥3.5 g protein/g creatinine at baseline using the screening UPCR**and by the use of glucocorticoids and/or immunosuppressive medications (yes, no).

Subjects will be randomized 1:1:1:1 to one of four treatment groups:

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

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

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

All subjects will take blinded **oral** study medication **twice daily, 3 tablets** in the morning and **3 tablets in the** evening, with or without food, for **12 weeks (**84 consecutive days**)**. Following the 84-day blinded dosing period, all subjects **who remain eligible** will take open label CCX140-B for an additional **12 weeks (**84 **consecutive** days**)** at the highest **tolerated** dose under evaluation, currently planned to be 15 mg twice daily. **The decision on the dose for the open-label period will be made by** the Sponsor, with the advice of the unblinded Data Monitoring Committee (DMC). **After completion of treatment for whatever reason, including early termination,** all subjects are expected to return at 2, 7 and 14 days after taking the last dose of study medication **for assessment of elimination phase PK and 28 days after taking the last dose of study medication for PK and safety monitoring.**

The screening period will be up to 28 days. All potential study subjects must sign written informed consent before any study screening procedures. Diagnosis of FSGS will be confirmed based on clinical judgment supported by a historical or current renal biopsy with characteristic features and/or presence of high-risk genetic variants. Other screening procedures include collection of demographic and medical history, physical examination and vital signs, 12-lead

ECG, serum chemistry including serum albumin and creatinine, hematology, urinalysis including assessment of urinary protein:creatinine ratio (UPCR) and urinary albumin:creatinine ratio (UACR) in a sample from a first morning void, viral and TB screening, pregnancy testing for all female subjects of childbearing potential, and recording of concomitant medication use. For subjects without prior biopsy to confirm diagnosis, needle biopsy may be completed during the screening period. For subjects without genetic screening for risk alleles associated with FSGS, genetic testing may be done during the screening period.

During the treatment period, eligible subjects will visit the study center on Study Days 1, 8, 15, 29 (Week 4), and Weeks 8, 12 (primary endpoint), 13, 16, 20, and 24 for study procedures including interval history, physical examination and vital signs, ECG, study questionnaires, and collection of blood and urine. **A 24 hour urine collection will be done the day before the Day 1 visit (baseline)**, **the day before the Week 12 visit at the end of double-blind dosing, and the day before the Week 24 visit at the end of open-label dosing**. Subjects will return for a follow-up **safety visit 4 weeks after the last dose of study drug (at Week 16 for those not entering the open-label phase,** or **at** Week 28 **for those who continue dosing into the open-label phase)**. When feasible, upon discontinuation of treatment for any reason, a sample of whole blood should be collected for assessment of elimination **PK at** 2, 7 and 14 days after the final dose of **study drug (**CCX140-B or placebo).

For assessment of adverse events of special interest, study procedures will include

- Complete blood count with differential, morphology assessment, reticulocytes count, hemoglobin, LDH, and bilirubin **(total and indirect)** to assess early evidence of hemolysis;
- The AIDS Clinical Trials Group Brief Peripheral Neuropathy Screening Tool Brief Peripheral Neuropathy Screening Tool (ACTG-BPNST) to assess early evidence of neuropathy;
- Monitoring for adverse events of infection;
- Alkaline phosphatase, ALT, AST and bilirubin (**total and direct**); to assess for evidence of drug induced liver injury.

For assessment of pharmacokinetics, study procedures will include

- Seven blood samples collected over 6 hours on Study Day 1 and at steady state (Study Day 15, or within 2 weeks thereafter) to assess $AUC_{0\text{-}6}$ following the first administration of study drug, and at steady state;
- Assessment of C_{min} at intervals to ensure that exposure is within the projected range, with adequate safety margin based on the NOAEL established in preclinical toxicology;
- Upon discontinuation of treatment for any reason, collection of blood at 2 days, 7 days and 14 days following discontinuation to assess elimination.

All study procedures are presented in the Time and Events table.

Subjects who are using an angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB) or other blocker of the renin angiotensin aldosterone system (RAAS), or who are using glucocorticoids, a calcineurin inhibitor or other immunomodulatory or immunosuppressive

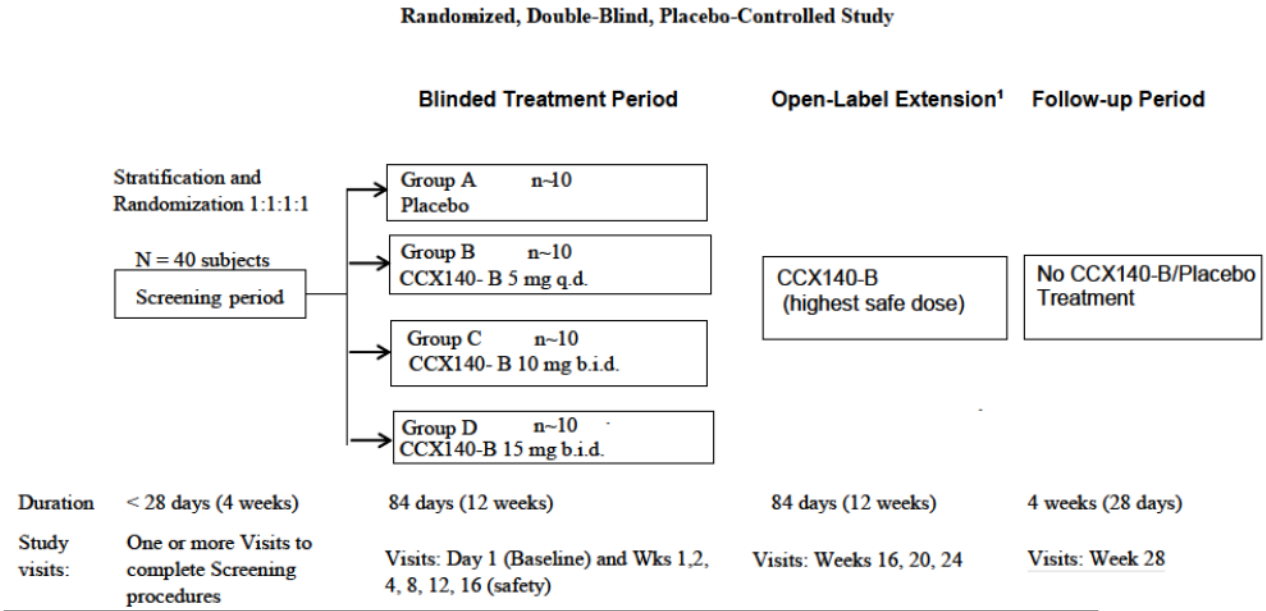
therapy, should be on a stable dose for at least 4 weeks prior to screening. The dose of these medications must be kept constant over the course of the study in order to prevent undue influence of changes in these medications on the efficacy and safety assessments except when adjustment is required for patient well-being. The investigator must also attempt to keep doses of other medications, and lipid-lowering medications fixed throughout the blinded study period in order to prevent undue influence of changes in these medications on the efficacy and safety assessments.

Subjects who experience deteriorating renal function based on an increase in serum creatinine of at least 50% (confirmed by a repeat measurement after 2 weeks) which is otherwise not explained (e.g., dehydration, new medication), or increase in UPCR of >3.0 g/g (confirmed by a repeat measurement after 2 weeks) during the 12-week treatment period, will exit the treatment phase of the study and be treated at the discretion of the treating physician. All subjects who discontinue treatment will remain in the study for follow up and outcome recording.

An independent Data Monitoring Committee (DMC) will be responsible for reviewing safety data throughout the course of the study.

Subjects will be discharged from the study at the completion of the Week 28 visit. 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.

Figure 1: Study Schema



4.1. Study Treatments

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

Table 1: CCX140-B for the Four Study Groups

	12 weeks			
Group	**5 mg CCX140-B QD**	**10 mg CCX140-B BID**	**15 mg CCX140-B BID**	**Placebo**
Morning dose	1 x 5 mg tablet + 2 placebo tablets orally	2 x 5 mg tablets+ 1 placebo tablet orally	3 x 5 mg tablets orally	3 placebo tablets orally
Evening dose	3 placebo tablets orally	2 x 5 mg tablets+ 1 placebo tablet orally	3 x 5 mg tablets orally	3 placebo tablets orally

4.2. Dose Modification Guidelines

The DMC will be responsible for reviewing safety data throughout the course of the study. In the event the DMC has a strong indication that there are significant dose-related adverse events the DMC can make the recommendation to discontinue enrollment to the affected arm and to step-down all subjects to the next lower dose arm. In addition to the planned data reviews, the DMC charter will include pre-specified rules that trigger an Ad Hoc review of data by un-blinded treatment group.

Subjects participating in the Open-Label Extension will be switched over to the highest safest dose of the CCX140-B.

4.2.1. Stopping Guidelines

An independent Data Monitoring Committee (DMC) will be responsible for reviewing safety data throughout the course of the study. Among other responsibilities, the DMC is tasked with implementing dose modification guidelines to assure the safety of all study participants. Guidelines will be defined for stopping the study, halting enrollment or halting treatment based on safety events occurring in more than 1 subject. General dose modification guidelines for individuals are provided below.

Table 2: Dose Modification Guidelines for Single Subjects

Assessment	**Event**	**Timing**	**Response**
Serum Creatinine	50% increase from baseline value	If confirmed by repeat measurement after 2 weeks	Discontinue treatment with CCX140-B
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	Discontinue treatment with CCX140-B

Assessment	**Event**	**Timing**	**Response**
ALT, AST	ALT or AST ≥ 8x ULN	**Retest** within 72 hours (ALT, ASP, ALP and Total Bilirubin should all be re-tested)	**If confirmed, discontinue treatment with CCX140-B**
ALT, AST	ALT or AST ≥ 5x ULN **for more than 2 weeks**	**Retest** within **72 hours and then** 2-**3 times per** week (ALT, ASP, ALP and Total Bilirubin should all be re-tested)	**If confirmed, discontinue treatment with CCX140-B**
ALT, AST, Total Bilirubin and INR	ALT or AST ≥ 3x ULN and **either** Total Bilirubin > 2 ULN or INR > 1.5	**Retest** within 72 hours (ALT, ASP, ALP, Total Bilirubin and INR should all be re-tested)	**If confirmed, discontinue treatment with CCX140-B**
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%)		**Discontinue treatment with CCX140-B**
LDH	LDH ≥ 2 times upper limit of normal, and confirmed to not be related to specimen handling	Halt treatment then reassess after 2 weeks	If within normal range, 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/**d**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 **from baseline** in reticulocyte count by ≥ 2 **units (% of RBC)** 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

Assessment	**Event**	**Timing**	**Response**
Peripheral Neuropathy	≥ moderate symptoms limiting (limiting instrumental activities of daily living) or asymptomatic (based on diagnostic evaluation only) and deemed clinically significant by the PI	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

5. STUDY POPULATION

5.1. Size of the Population

Approximately 40 male or female adult subjects with primary or genetic FSGS (see Section 5.2; for genetic variants) will be enrolled in this study. Subjects who discontinue during the first 14 days of taking study drug for reasons other than adverse events related to study drug may be replaced to ensure that sufficient data are available for assessment of safety, PK and efficacy.

5.2. Inclusion Criteria

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

1. Male or female subjects aged 18-75 years inclusive.
2. Urinary total protein:creatinine ratio (UPCR) ≥ 1 g protein/g creatinine at screening (or UPCR at 113 mg/mmol).
3. Diagnosis of FSGS based on at least one of the following:
   - Renal biopsy demonstrating the FSGS lesion and characteristic clinical presentation and course
   - High risk genetic variant and characteristic clinical presentation and course
4. Diagnosis of one of the following subtypes of FSGS:
   - Primary FSGS based on characteristic histopathology, medical history and clinical course, or
   - FSGS secondary to a genetic variant associated with increased risk or severity, which may include NPHS1, NPHS2, WT-1, LAMB2, CD2AP, TRPC6, ACTN4 or INF2
5. Estimated glomerular filtration rate (eGFR) >30 mL/min/1.73m^2, with eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD_EPI) equation (using creatinine or cystatin C)
6. The typical blood pressure of the patient should be clinically stable prior to enrollment and not exceed 145/95 mmHg.
7. If using RAAS blockers, dose must be stable for a minimum of 4 weeks prior to Screening, and projected to remain stable through Study Week 12, unless adjustment is required for management of hypertension.
8. If using immunosuppressive or immunomodulatory therapy, dose must be stable for a minimum of 4 weeks prior to Screening, and projected to remain stable through Study Week 12.
9. If using glucocorticoids, dose must be stable for a minimum of 4 weeks prior to Screening and projected to remain stable through Study Week 12.
10. Female subjects of childbearing potential may participate if adequate contraception is used during, and for at least **1 month** 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.

11. Willing and able to give written Informed Consent and to comply with the requirements of the study protocol.
12. 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.

5.3. 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. Subjects **who** used rituximab or other **B-cell depleting** monoclonal antibodies within 20 weeks prior to screening are excluded while subjects **who** used rituximab or other **B-cell depleting** monoclonal antibodies prior to 20 weeks **before** screening are allowed with confirmed recovery of **the B**-cell population to within normal range **at the time of screening**
5. Plasmapheresis within 12 weeks prior to screening.
6. Body Mass Index (BMI) ≥40
7. 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 of investigational product.
8. Currently on dialysis or likely to require dialysis during the projected blinded treatment period of 12 weeks.
9. History or presence of any form of cancer within the 5 years prior to screening, with the exception of excised basal cell or squamous cell carcinoma of the skin, or 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.
10. 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.

11. Renal disease associated with disorders other than FSGS (e.g. lupus nephritis, C3 glomerulopathy, proliferative glomerulonephritis, IgA nephropathy, reflux nephropathy, surgical segmental renal ablation, sickle cell disease) that is active, or has a significant risk of progressing during the course of the study
12. Disorders other than those listed in Inclusion Criteria 4 that are associated with FSGS lesion (**i.e. secondary FSGS, such as** single kidney, surgical segmental renal ablation, sickle cell disease, diabetic nephropathy, others)**, or histological collapsing variant subtypes of FSGS**
13. Evidence of tuberculosis based on interferon γ release assay (IGRA) within 6 weeks prior to screening.
14. Evidence of hepatic disease; AST, ALT, alkaline phosphatase >3x 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).
15. Clinically significant peripheral neuropathy.
16. Hematologic abnormalities as follows: Hb <8 g/dL, platelets <50,000, ANC <1000 cells/µL) at baseline.
17. Clinically significant abnormal ECG during screening, e.g., QTcF greater than 450 msec.
18. History of alcohol or illicit drug abuse. Recreational use of cannabis is not excluded where legal.
19. History of gastrointestinal conditions that may interfere with study medication compliance, e.g., severe gastroparesis, with regurgitation of food or oral medication.
20. Known hypersensitivity to CCX140-B or inactive ingredients of the CCX140-B tablets (including microcrystalline cellulose, starch, crospovidone, magnesium stearate, silicon dioxide **or tartrazine**).
21. History or presence of systemic disorder other than FSGS that requires, or is expected to require, systemic glucocorticoids or immune modulators during the study; topical or inhaled glucocorticoids and immune modulators are not excluded.
22. 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.
23. 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.
24. 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).

5.4. Continuing Eligibility Criteria

Subjects may enter the Open-Label Extension if the subject:

- **has not withdrawn consent for the study**
- **has no new infections that, in the judgment of the investigator, would preclude addition of a new immunosuppressive or immunomodulatory treatment**
- **has had no requirement for the addition of new immunosuppressive treatment during the prior 12 weeks and no anticipated requirement during the next 12 weeks.**

5.5. Removal of Subjects from Therapy of Assessment

Investigators must clearly distinguish between study drug treatment discontinuation and study withdrawal. Subjects who discontinue study drug treatment or who initiate medication changes (including those prohibited by the protocol) will not be automatically withdrawn from the study, but all efforts must be made to continue to follow the subjects for all regularly scheduled visits. The Medical Monitor should be contacted to determine how to address the specific situation.

Investigators must take appropriate measures to make sure that subjects are motivated to comply with all requirements of the protocol in order to minimize the amount of missing data. Subjects who discontinue study treatment early or initiate medication changes (including those prohibited by the protocol) should continue to be followed for all regularly scheduled visits for safety and efficacy assessments. Investigators and their staff must take measures to actively maintain contact with their subjects in the study, such as telephone calls, texts, or emails between visits, and offers for transportation support to visit the study site.

5.5.1. Subjects may be withdrawn from the study for the following reasons:

1. Subject withdrawal of consent to contribute additional outcome information;
2. Subject non-compliance with dosing or diary completion;
3. Loss to follow-up;
4. Sponsor's decision to terminate the study.

5.5.2. Subjects may discontinue study drug treatment for any of the following reasons:

1. Subject withdrawal of consent;
2. The Investigator may discontinue study drug treatment if, in his/her clinical judgment, it is in the best interest of the subject;
3. The Sponsor may request discontinuation of study drug treatment for safety reasons or non-compliance with treatment;
4. The Sponsor may request discontinuation of study drug treatment due to new or increased glucocorticoid/immunosuppressant treatment.

In the event of early withdrawal from the study, the tests and evaluations listed for the Early Termination visit in Section 7.14 will be performed, whenever possible. Data collected at this visit will be designated as an "Early Termination" visit in the EDC. The Sponsor should be notified of all study drug treatment and study withdrawals in a timely manner.

If the Investigator considers a change in background treatment for FSGS, this should be discussed with the Medical Monitor, and decision made regarding discontinuation of blinded

study drug. Independent of continuation or discontinuation of study drug, subjects should continue in the study for assessment of outcome.

6. STUDY MEDICATION/TREATMENT

6.1. Product Characteristics

The investigational medicinal products (IMP) are oral film coated tablets containing 5 mg of CCX140-B and matching placebos. The tablets are manufactured under current good manufacturing practice. The clinical trial material is packaged in high density polyethylene (HDPE) bottles containing 30 tablets of either placebo or active. These bottles will be packaged in kits to administer to subjects in a blinded fashion; placebo, 5 mg once daily, 10 mg twice daily, and 15 mg twice daily.

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

During the open label phase of the study CCX140-B will be administered as up to 3 tablets (5 mg each) twice daily, depending on determination of the highest safest dose. During study weeks 13 through 24, distinction between morning and evening doses and bottles are not required since each bottle will contain active study medication at the same dose. Therefore the bottles dispensed for this phase of the study will neither include yellow or blue markings or distinct numbers.

6.2. Randomization and Method of Treatment Assignment

Eligible subjects will be enrolled and stratified based on two stratification factors: UPCR <3.5 g protein/g creatinine at baseline versus UPCR ≥3.5 g protein/g creatinine at baseline, and on glucocorticoid/immunosuppressives or no glucocorticoid/ immunosuppressives, and randomized to one of the four treatment groups in a ratio of 1:1:1:1; placebo: 5 mg CCX140-B QD:10 mg CCX140-B BID: 15 mg CCX140-B BID. Randomization will be performed centrally via an interactive response technology (IRT) system and minimization algorithm, using the stratification factors. In order to protect the blinding, the randomization schedule will not be accessible to study personnel who have contact with study centers or who are involved in data management and analysis.

6.3. Doses and Regimens

Treatments for each group are shown in Table 1. Subjects will receive one of the following dose regimens: 5 mg CCX140-B once daily, 10 mg CCX140-B twice daily, 15 mg CCX140-B twice daily, or matching placebo.

6.3.1. Initial 12 Week Treatment Period

Study drug and placebo will be taken as follows by study subjects:

5 mg CCX140-B (QD):

- One 5 mg CCX140-B and two matching placebo tablets in the morning dose, and three matching placebo tablets in the evening dose; doses should be approximately 10-12 hours apart and taken daily for 12 weeks (84 days).

10 mg CCX140-B (BID):

- Two 5 mg CCX140-B and one matching placebo tablets in the morning dose, and two 5 mg CCX140-B and one matching placebo tablets in the evening dose, doses should be approximately 10-12 hours apart and taken daily for 12 weeks (84 days).

15 mg CCX140-B (BID):

- Three 5 mg CCX140-B tablets in the morning dose, and three 5 mg CCX140-B tablets in the evening dose, doses should be approximately 10-12 hours apart and taken daily for 12 weeks (84 days).

Placebo:

- Three matching placebo tablets in the morning and three matching placebo tablets in the evening, approximately 10-12 hours after the morning dose, daily for 12 weeks (84 days). (The placebo tablets will be identical in appearance to the CCX140-B tablets).

6.3.2. Open-Label Treatment 12 Week Treatment Period

(Only applicable to subjects who are eligible and willing to participate in the Open-Label Extension, after Week 12).

Study drug will be taken as follows by study subjects:

Open Label Dose:

The dose for the open label phase of this study is planned to be 15 mg twice daily. If, during the course of the study, the Sponsor, together with the independent Data Monitoring Committee determines that 15 mg twice daily is exceeds the maximally tolerated dose, the open label dose will be adjusted downward.

6.4. Rationale for Dose Selection

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

Five (5) mg daily is selected as the lowest dose that was tested and found to be both safe and to be associated with a clinically-meaningful therapeutic effect in subjects with diabetic nephropathy (DN) in Study CL005_140. A total of 332 subjects were enrolled in a randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy, safety and tolerability of 5 mg CCX140-B 5 and 10 mg CCX140-B compared to placebo, when administered for up to 52 weeks in subjects with DN. The Phase 2 trial met its primary endpoint by demonstrating that treatment with 5 mg of CCX140-B given orally once daily added to a standard of care (SOC) regimen of RAAS blockade treatment resulted in a statistically significant (p=0.01) improvement in UPCR, beyond that achieved with SOC alone. The maximum treatment effect (24% reduction) was reached at 12 weeks, and sustained reduction in albuminuria relative to placebo was observed over the full year (UACR at each one of the ten time points over the 52-week treatment period in the subjects who received 5 mg CCX140-B continuously for 52 weeks, were below

those of the SOC alone group). Both active treatment regimens were well-tolerated; no dose-related safety signals were reported.

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). 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 DN. Administration of 15 mg twice daily in humans without proteinuria is projected to achieve a peak concentration of ~6500 ng/mL (~13 μM) and a trough concentration of ~5500 ng/mL (~11 μM) 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.

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 special attention to assessment of early indication of hemolysis (e.g. increased reticulocytes, increase from baseline in bilirubin or LDH) and 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 an independent Data Monitoring Committee throughout the study.

6.5. Drug Supply

6.5.1. Packaging and Labeling

The investigational medicinal products (IMP) are oral film coated tablets containing 5 mg of CCX140-B and matching placebos. The tablets are manufactured under current good manufacturing practice. The clinical trial material is packaged in high density polyethylene (HDPE) bottles containing 30 tablets of either placebo or active. Theses bottles will be packaged in kits to administer to the subjects, in a blinded fashion; placebo, 5 mg once daily, 10 mg twice daily and 15 mg twice daily.

6.5.2. 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.

6.5.3. Blinding

This study is double-blind. Blinding of the study will be achieved by the following measures:

The study drug bottles and tablet appearance for CCX140-B and its matching placebo will be identical.

Limited access to the randomization code; Sponsor personnel directly involved in the conduct and monitoring of the study, study site personnel, study subjects, personnel responsible for study monitoring, and biostatisticians and data managers involved in data analysis of the study will remain blinded to treatment assignment for the duration of the study.

While laboratory personnel conducting the PK assays will not be blinded to treatment assignment, unblinded CCX140-B plasma concentration results will not be shared with the study site personnel or study staff who have direct contact with study sites during the study.

Efficacy data that could potentially be unblinding, (i.e. UPCR , serum albumin and CBC) data within the normal range will not be made available to study site personnel, study subjects, personnel responsible for study monitoring, and biostatisticians and data managers during the study unless for safety monitoring. Investigators, however, will be provided with safety laboratory data reports, flagging abnormally high and low values to make informed decisions regarding subject care.

Treatment assignments for individual subjects will remain blinded to the study team, investigators, and subjects until after the study database has been cleaned and locked. Designated study staff will be provided with instructions regarding how to unblind an individual subject treatment assignment. An individual subject treatment assignment may be unblinded only in the case of an adverse event that requires knowledge of the study medication received by the subject

in order to provide appropriate treatment or management of the adverse event. The study monitor and Sponsor should be notified as soon as possible in the event that unblinding of an individual subject's treatment assignment occurs prior to study completion.

An external data monitoring committee (DMC) will be constituted prior to start of the study. The DMC members will review data periodically over the course of the study in an unblinded manner. The DMC will provide recommendations to the Sponsor regarding further conduct of the study. The DMC will operate according to a charter developed prior to study initiation.

6.6. 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 (bottle, study medication and diary reconciliation) data.

6.7. Treatment Compliance

The CCX140-B and matching placebo 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 along with completed diaries. The study drug dispensed will be checked, and a tablet count will be done from Week 4 through the end of active study treatment of any remaining CCX140-B or placebo tablets. This information will be recorded and entered into the electronic data capture (EDC) system. Subjects who take less than 85% of their prescribed dose of study medication may be withdrawn from study due to treatment non-compliance.

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 and could result in withdrawal of the relevant subject.

6.8. Concomitant Medications and Restrictions

Medications taken prior to enrollment will be recorded:

- **rituximab or other B-cell depleting monoclonal antibodies for 1 year prior to screening;**

  Subjects who have taken rituximab or other B-cell depleting monoclonal antibodies but stopped more than 20 weeks before screening will be allowed to participate if the recovery of the B cell population to within normal range is confirmed at the time of screening.

- **all FSGS medications (specifically glucocorticoids, immunosuppressives) for 6 months prior to screening;**

- **all other medications, including plasma therapy regimens, for 12 weeks prior to screening.**

In order not to disrupt subject care, the protocol will allow continuation of treatment (background medications) with glucocorticoids, immunosuppresants, calcineurin inhibitors, or renin-angiotensin-aldosterone system (RAAS) blockers. The doses for these background medications must remain stable for a minimum of 4 weeks prior to screening and through the treatment period (24 weeks) following randomization, with the following exceptions. Adjustment of RAAS blockers is permitted for management of hypertension. During the open label period (after Week 12), glucocorticoids, immunosuppresants, and calcineurin inhibitor will be allowed only if essential for patient safety.

Experimental drugs, rituximab, and plasmapheresis are not allowed at any point during the course of the study. If the Investigator deems that any of these treatments are necessary for the best interest of a subject, this subject would discontinue study drug, but remain in the study to monitor outcomes.

CCX140-B is primarily cleared through CYP3A4 metabolism. 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) will be excluded from this clinical trial since these drugs may substantially increase the CCX140-B plasma levels.

Subjects taking lithium, **pamidronate**, interferon, **or chronic NSAIDS** are also excluded. Note that subjects taking intermittent NSAIDS for pain or fever are discouraged from study participation, but **are** not excluded.

All concomitant medications **including marijuana use (if applicable)** taken during the course of the study must be recorded meticulously on the concomitant medication pages of the CRF. Any investigational products taken up to 12 weeks prior to screening or within 5 half-lives after taking the last dose must be recorded on the concomitant medication page.

7. STUDY PROCEDURES

7.1. Screening and Enrollment

Informed Consent must be obtained prior to performance of any study-specific tests or evaluations. It is important to complete the screening procedures in the shortest time possible to allow subjects to start treatment. Within a period not to exceed 28 days prior to enrollment, subjects will undergo the following evaluations to determine their eligibility for study participation:

- Recording of demographic data and medical history
- Recording of all prior medications for FSGS (specifically glucocorticoids **and** immunosuppressives) for the 6 month period prior to screening
- Recording of all other prior medications, including plasma therapy regimen, for the 12 week period prior to screening,

- **If the subject has received prior rituximab treatment or other B-cell depleting antibodies, record the medication use, as well as any available urinary protein values, for 1 year prior to screening**
- Test to exclude tuberculosis (interferon γ release assay [IGRA] within 6 weeks prior to screening
- Serum chemistry, hematology, coagulation, lipids, lymphocyte subsets and urinalysis tests (results from tests done within 72 hours prior to screening may be used for eligibility assessment)
- Recording of renal biopsy results for FSGS confirmation
- The ACTG Brief Peripheral Neuropathy Screening Tool will be administered
- Results from tests that have been performed prior to screening may be used to determine study eligibility if these tests were performed as part of the practice of medicine and were done whether or not study entry was contemplated, such as for diagnosis or treatment of the subject's condition. Results from the prior tests must be recorded in the EDC
- A first morning void for assessment of urine protein and creatinine assays (UPCR / UACR and Cystatin C assessment)
- A complete physical examination will be performed
- Vital signs (weight, height, temperature, blood pressure, heart rate) will be measured after at least 3 minutes of rest
- A 12-lead ECG, after at least 3 minutes of rest, will be recorded and assessed for any clinically significant abnormality
- After all screening procedures have been completed, and the subject satisfies all eligibility criteria, the study schedule will be discussed with the subject and the schedule will be provided to the subject to ensure compliance with the study visits
- **The subject will be given instructions and supplies for the urine collections on the day before the next visit (kit for first morning void and jug for 24-hour urine collection)**
  - **Collect the first morning void the day before the first visit (Day 0) and put in the smaller container.**
  - **Collect all urine for 24 hours starting AFTER the first morning void, including first morning void on the day of the Study Day 1 visit, in the big jug.**
  - **Keep specimens refrigerated until they are brought to the site at the Study Day 1 visit.**

7.2. Study Day 1

If eligible for the study, the subject will visit the study center on Day 1. The following procedures will be performed before taking the first dose of CCX140-B:

- A complete physical examination
- Vital signs (weight, temperature, blood pressure, heart rate after at least 3 minutes of rest)

- A 12-lead ECG, after at least 3 minutes of rest, will be recorded and assessed for any clinically significant abnormality
- Blood samples will be collected for serum chemistry (including coagulation panel and lipids), pregnancy test (in women of childbearing potential), hematology, DNA, plasma MCP-1, PK, PD (including lymphocyte subsets) and baseline measurements
- **Process the first** morning void urine sample collection for quantitative urinalysis, UPCR, UACR, Cystatin C, Urine MCP-1, MCP-1/creatinine ratio and urine PD assessment
- **Process the 24-hour urine sample collection for quantitative urinalysis, UPCR, UACR, Cystatin C, Urine MCP-1, MCP-1/creatinine ratio urine PD assessment and urine protein excretion/day**
- Any pre-treatment adverse events (from time of the screening visit) will be recorded
- Subjects will be asked to complete the SF-36 v2 and EQ-5D-5L
- Subjects will be asked to complete their diary each day immediately after each dose
- The ACTG Brief Peripheral Neuropathy Screening Tool will be administered

Once deemed eligible, the following procedures will be performed:

- Study medication (in kits, containing 4-week supply bottles of CCX140-B/Placebo), will be provided to the subject with dosing instructions
- The subject will be asked to take the first dose of CCX140-B while at the study center and should remain at the study center for observation at the PI's discretion
- The time of the dosing of CCX140-B will be recorded
- PK blood samples will be collected at **Time 0 (pre-dose)**, 0.5, 1, 2, 3, 4, and 6 hours following CCX140-B or placebo dosing for plasma CCX140 concentration measurements; the actual time of each blood sample collection will be recorded
- A blood sample will be collected for pharmacodynamic marker measurements
- Any changes in concomitant medication use will be recorded
- Any post-dosing adverse events will be recorded
- **Provide the subject with the kit for collection of the first morning void**
- After all study procedures have been completed, the subject will be reminded to:
  - Come to the study center for the Week 1 study visit
  - Store the study medications in a cool and dry place according to label instructions for the duration of the study
  - **On the morning of the next visit, collect the first morning void in the container provided and refrigerate until it is brought to the study center**

7.3. Study Week 1 (Day 8 +/- 1 day)

The Study Week 1 visit should occur within ± 1 day of the scheduled date. During this visit, the following study procedures will be performed:

- An abbreviated, symptom-directed physical examination
- Vital signs (temperature, blood pressure and heart rate after at least 3 minutes of rest, weight)
- The date and time of the last dose of CCX140-B or placebo prior to collection of the PK sample will be recorded
- Blood samples will be collected before dose administration for serum chemistry (including coagulation panel and lipids), hematology, plasma MCP-1, PK, and PD (including lymphocyte subsets) measurements; record the time of blood collection.
- **Process the first** morning void urine sample collection for quantitative urinalysis, UPCR, UACR Cystatin C, Urine MCP-1 and MCP-1/creatinine ratio and urine PD assessment
- The ACTG Brief Peripheral Neuropathy Screening Tool will be administered
- If the subject has not yet taken the morning dose of CCX140-B for this day, the subject will be asked to take the dose
- Any changes in concomitant medication use will be recorded
- Any adverse events will be recorded
- Drug accountability and reconciliation with subject completed diaries
- **Provide the subject with the kit for collection of the first morning void**
- After all study procedures have been completed, the subject will be reminded to:
  - Complete their diary each day immediately after each dose
  - Come to the study center for the Week 2 study visit, before taking the dose of the visit day
  - Store the study medications in a cool and dry place according to label instructions for the duration of the study
  - **On the morning of the next visit, collect the first morning void in the container provided and refrigerate until it is brought to the study center**

7.4. Study Week 2 (Day 15 +/- 1 day)

The Study Week 2 visit should occur within ± 1 day of the scheduled date. During this visit, the following study procedures will be performed:

- An abbreviated, symptom-directed physical examination
- Vital signs (weight, temperature, blood pressure, heart rate) after at least 3 minutes of rest
- Blood samples will be collected for serum chemistry, hematology, plasma MCP-1, and PD (including lymphocyte subset) measurements

- PK blood samples will be collected at **Time** 0 (pre-dose), 0.5, 1, 2, 3, 4, and 6 hours following CCX140-B or placebo dosing for plasma CCX140 concentration measurements; the actual time of each blood sample collection will be recorded
- **Process the first** morning void urine sample collection for quantitative urinalysis , UPCR, UACR Cystatin C, Urine MCP-1, MCP-1/creatinine ratio and urine PD assessment
- The ACTG Brief Peripheral Screening Tool will be administered
- If the subject has not yet taken the morning dose of CCX140-B for this day, the subject will be asked to take the dose
- Any changes in concomitant medication use will be recorded
- Any adverse events will be recorded
- Drug accountability and reconciliation with subject completed diaries
- **Provide the subject with the kit for collection of the first morning void**
- After all study procedures have been completed, the subject will be reminded to:
  - Complete their diary each day immediately after each dose
  - Come to the study center for the Week 4 study visit, before taking the dose of the visit day
  - Store the study medications in a cool and dry place according to label instructions for the duration of the study
  - **On the morning of the next visit, collect the first morning void in the container provided and refrigerate until it is brought to the study center**

7.5. Study Week 4 (Day 29+/- 3 days)

The Study Week 4 visit should occur within ± 3 days of the scheduled date. During this visit, the following study procedures will be performed:

- An abbreviated, symptom-directed physical examination
- Vital signs (weight, temperature, blood pressure, heart rate) after at least 3 minutes of rest
- The date and time of the last dose of CCX140-B or placebo prior to collection of the PK sample will be recorded
- Blood samples will be collected before dose administration for serum chemistry (including coagulation panel and lipids), hematology, serum pregnancy test (in women of childbearing potential), PK (time 0 only), plasma MCP-1, and PD (including lymphocyte subset) measurement; record the time of blood collection
- **Process the first** morning void urine sample collection for quantitative urinalysis , UPCR, UACR, Cystatin C, Urine MCP-1, MCP-1/creatinine ratio and urine PD assessment
- Subjects will be asked to complete the SF-36 v2 and EQ-5D-5L.
- The ACTG Brief Peripheral Screening Tool will be administered

- If the subject has not yet taken the morning dose of CCX140-B for this day, the subject will be asked to take the dose
- Drug accountability and reconciliation with subject completed diaries
- A new kit, containing 4-week supply bottles of CCX140-B/Placebo will be dispensed
- Any changes in concomitant medication use will be recorded
- Any adverse events will be recorded
- **Provide the subject with the kit for collection of the first morning void**
- After all study procedures have been completed, the subject will be reminded to:
  - Complete their diary each day immediately after each dose
  - Come to the study center for the Week 8 study visit, before taking the dose of the visit day
  - Store the study medications in a cool and dry place according to label instructions for the duration of the study
  - **On the morning of the next visit, collect the first morning void in the container provided and refrigerate until it is brought to the study center**

7.6. Study Week 8 (Day 57 +/- 3 days)

The Study Week 8 visit should occur within ± 3 days of the scheduled date. During this visit, the following study procedures will be performed:

- An abbreviated, symptom-directed physical examination
- Vital signs (weight, temperature, blood pressure, heart rate after at least 3 minutes of rest)
- The date and time of the last dose of CCX140-B or placebo prior to collection of the PK sample will be recorded
- Blood samples will be collected before dose administration for serum chemistry, hematology and PK (at time 0 only); record the time of blood collection.
- **Process the first** morning void urine sample collection for quantitative urinalysis, UPCR,UACR and cystatin C assessment
- The ACTG Brief Peripheral Screening Tool will be administered
- If the subject has not yet taken the morning dose of CCX140-B for this day, the subject will be asked to take the dose
- Drug accountability and reconciliation with subject completed diaries
- A new kit, containing 4-week supply bottles of CCX140-B/Placebo will be dispensed
- Any changes in concomitant medication use will be recorded

- Any adverse events will be recorded **Provide the subject with the kit for collection of the first morning void and jug for the 24-hour urine collection.** After all study procedures have been completed, the subject will be reminded to:
  - Complete their diary each day immediately after each dose
  - Come to the study center for the Week 12 study visit and bring completed diaries and ALL used and unused containers of study medication to the next visit
  - **Collect the first morning void the day before the Week 12 visit and put in the smaller container**
  - **Collect all urine for 24 hours starting AFTER the first morning void, including first morning void on the day of the Week 12 visit, in the big jug**
  - **Keep specimens refrigerated until they are brought to the site for the Week 12 visit.**

7.7. Study Week 12 (Day 85 +/- 3 days) (See Section 7.13 for PK elimination guidelines)

The Study Week 12 visit should occur within ± 3 days of the scheduled date. During this visit, the following study procedures will be performed:

- An abbreviated, symptom-directed physical examination
- Vital signs (weight, temperature, blood pressure, heart rate) after at least 3 minutes of rest
- A 12-lead ECG, after at least 3 minutes of rest, will be recorded and assessed for any clinically significant abnormality
- The date and time of the last dose of CCX140-B or placebo prior to collection of the PK sample will be recorded
- Blood samples will be collected before dose administration for serum chemistry (including coagulation panel and lipids), hematology, serum pregnancy test (in women of childbearing potential), PK (time 0 only), plasma MCP-1, and PD (including lymphocyte subset) measurements; record the time of blood collection
- **Process the first** morning void urine sample collection for quantitative urinalysis, UPCR, UACR, Cystatin C, Urine MCP-1, MCP-1/creatinine ratio and urine PD assessments
- **Process the 24-hour urine sample collection for quantitative urinalysis, UPCR, UACR, Cystatin C, Urine MCP-1, MCP-1/creatinine ratio, urine PD assessment, and urine protein excretion/day**
- Subjects will be asked to complete the SF-36 v2 and EQ-5D-5L.
- The ACTG Brief Peripheral Screening Tool will be administered
- If the subject has not yet taken the morning dose of CCX140-B/placebo for this day, the subject will be asked to take the dose
- Drug accountability and reconciliation with subject completed diaries

- All study drug medication containers must be returned and drug usage must be reconciled against the completed diaries since continuing subjects will be given new drug supply of active study medication for open label dosing.
- Any changes in concomitant medication use will be recorded
- Any adverse events will be recorded
- **Assessment of continuing eligibility requirements:**
  - **has not withdrawn consent for the study**
  - **has no new infections that in the judgment of the investigator would preclude addition of a new immunosuppressive or immunomodulatory treatment**
  - **has had no requirement for the addition of new immunosuppressive treatment during the prior 12 weeks and no anticipated requirement during the next 12 weeks**
- **Provide the subject with the kit for collection of the first morning void**
- After all study procedures have been completed, **discontinuing subjects** will be reminded to:
  - **come to the study center at 2 days, 7 days and 14 days after the last dose for PK elimination and**
  - **come to the study center for the Week 16 follow-up visit**
- **Continuing subjects will be reminded to:**
  - Complete their diary each day immediately after each dose
  - Come to the study center for the Week 13 study visit, before taking the dose of **study drug**
  - **on the morning of the next visit, collect the first morning void in the container provided and refrigerate until it is brought to the study center**

7.8. Study Week 13 (Day 92 +/- 3 days) - Continuing Subjects Only

The Study Week 13 visit should occur within ± 3 days of the scheduled date. During this visit, the following study procedures will be performed:

- An abbreviated, symptom-directed physical examination
- Vital signs (weight, temperature, blood pressure, heart rate) after at least 3 minutes of rest
- A 12-lead ECG, after at least 3 minutes of rest, will be recorded and assessed for any clinically significant abnormality
- The date and time of the last dose of CCX140-B prior to collection of the PK sample will be recorded
- Blood samples will be collected before dose administration for serum chemistry (including coagulation panel and lipids), hematology, PK measurements (time 0 only), plasma MCP-1, and PD measurements; record the time of blood collection

- **Process the first** morning void urine sample collection for quantitative urinalysis , UPCR, UACR, Cystatin C, Urine MCP-1, MCP-1/creatinine ratio and urine PD assessment
- The ACTG Brief Peripheral Screening Tool will be administered
- If the subject has not yet taken the morning dose of CCX140-B for this day, the subject will be asked to take the dose
- Drug accountability and reconciliation with subject completed diaries
- Any changes in concomitant medication use will be recorded
- Any adverse events will be recorded
- **Provide the subject with the kit for collection of the first morning void**
- After all study procedures have been completed, the subject will be reminded to:
  - Complete their diary each day immediately after each dose
  - Come to the study center for the Week 16 study visit, before taking the dose of the visit day
  - **On the morning of the next visit, collect the first morning void in the container provided and refrigerate until it is brought to the study center**

7.9. Study Week 16 (Day 114 +/- 3 days - Continuing Subjects Only

The Study Week 16 visit should occur within ± 3 days of the scheduled date. During this visit, the following study procedures will be performed:

- An abbreviated, symptom-directed physical examination
- Vital signs (weight, temperature, blood pressure, heart rate) after at least 3 minutes of rest
- Subjects will be asked to complete the SF-36 v2 and EQ-5D-5L.
- The ACTG Brief Peripheral Screening Tool will be administered
- The date and time of the last dose of CCX140-B prior to collection of the PK sample will be recorded
- Blood samples will be collected before dose administration for serum chemistry (including coagulation panel and lipids), hematology, serum pregnancy test (in women of childbearing potential), PK (time 0 only) , plasma MCP-1, and PD (including lymphocyte subset) measurements; record the time of blood collection
- **Process the first** morning void urine sample collection for quantitative urinalysis, UPCR, UACR, Cystatin C, Urine MCP-1, MCP-1/creatinine ratio and urine PD assessment
- If the subject has not yet taken the morning dose of CCX140-B for this day, the subject will be asked to take the dose
- Drug accountability and reconciliation with subject completed diaries
- A new 4-week supply of bottles of CCX140-B will be dispensed

- Any changes in concomitant medication use will be recorded
- Any adverse events will be recorded
- **Provide the subject with the kit for collection of the first morning void**
- After all study procedures have been completed, the subject will be reminded to:
  - Complete their diary each day immediately after each dose
  - Come to the study center for the Week 20 study visit
  - Store the study medications in a cool and dry place according to label instructions for the duration of the study
  - **On the morning of the next visit, collect the first morning void and refrigerate until it is brought to the study center**

7.10. Study Week 20 (Day 141+/- 3 days) - Continuing subjects only

The Study Week 20 visit should occur within ± 3 days of the scheduled date. During this visit, the following study procedures will be performed:

- An abbreviated, symptom-directed physical examination
- Vital signs (weight, temperature, blood pressure, heart rate) after at least 3 minutes of rest
- The ACTG Brief Peripheral Screening Tool will be administered
- Blood samples will be before dose administration collected for serum chemistry, hematology, serum pregnancy test (for women of childbearing potential), PK (time 0 only); record the time of blood collection
- **Process the first** morning void urine sample collection for quantitative urinalysis, UPCR, UACR and cystatin C assessment
- If the subject has not yet taken the morning dose of CCX140-B for this day, the subject will be asked to take the dose
- Drug accountability and reconciliation with subject completed diaries
- A new 4-week supply of bottles of CCX140-B will be dispensed
- Any changes in concomitant medication use will be recorded
- Any adverse events will be recorded
- **Provide subject with container for collection of first morning void on the morning of the next visit and jug for the 24-hour urine collection**
- After all study procedures have been completed, the subject will be reminded to:
  - Complete their diary each day immediately after each dose
  - Come to the study center for the Week 24 study visit
  - Store the study medications in a cool and dry place according to label instructions for the duration of the study

- **Collect the first morning void the day before the Week 24 visit and put in the smaller container**
- **Collect all urine for 24 hours starting AFTER the first morning void, including first morning void on the day of the Week 24 visit, in the big jug**.
- **Keep specimens refrigerated until they are brought to the site for the Week 24 visit.**

7.11. Study Week 24 (Day 169 +/- 3 days) - Continuing Subjects Only

The Study Week 24 visit should occur within ± 3 days of the scheduled date. During this visit, the following study procedures will be performed:

- An abbreviated, symptom-directed physical examination
- Vital signs (weight, temperature, blood pressure, heart rate) after at least 3 minutes of rest
- 12 Lead ECG after at least 3 minutes of rest, will be recorded and assessed for any clinically significant abnormality
- The date and time of the last dose of CCX140-B prior to collection of the PK sample will be recorded
- Blood samples will be collected before dose administration for serum chemistry (including coagulation panel and lipids), hematology, serum pregnancy test (in women of childbearing potential), PK (time 0 only), plasma MCP-1, and PD (including lymphocyte subset) measurements; record the time of blood collection
- **Process the first** morning void urine sample collection for quantitative urinalysis, UPCR, UACR, Cystatin C, Urine MCP-1, MCP-1/creatinine ratio and urine PD assessment
- **Process the 24-hour urine sample collection for quantitative urinalysis, UPCR, UACR, Cystatin C, Urine MCP-1, MCP-1/creatinine ratio urine PD assessment and urine protein excretion/day**
- Subjects will be asked to complete the SF-36 v2 and EQ-5D-5L.The ACTG Brief Peripheral Screening Tool will be administered
- If the subject has not yet taken the morning dose of CCX140-B for this day, the subject will be asked to take the dose
- Drug accountability and reconciliation with subject completed diaries
- Any changes in concomitant medication use will be recorded
- Any adverse events will be recorded
- **Provide subject with container for collection of first morning void on the morning of the next visit**
- After all study procedures have been completed, the subject will be reminded to:
  - Come to the study center for the Week 28 follow-up visit
  - Return all used and unused containers of study medication along with completed diaries for final drug accountability

- **On the morning of the next visit, collect the first morning void and refrigerate until it is brought to the study center**

7.12. Follow Up visit - Study Week 16 (Day 114 +/- 3 days for discontinuing subjects) and Week 28 (Day 197 +/- 3 days for continuing subjects) - (See Section 7.13 for PK elimination guidelines)

The follow-up visit should occur within ± 3 days of the scheduled date. During this visit, the following study procedures will be performed:

- An abbreviated, symptom-directed physical examination
- Vital signs (weight, temperature, blood pressure, heart rate) after at least 3 minutes of rest
- 12 Lead ECG after at least 3 minutes of rest, will be recorded and assessed for any clinically significant abnormality
- Blood samples will be collected for serum chemistry (including coagulation panel and lipids), hematology, serum pregnancy test (in women of childbearing potential), PK (time 0 only), plasma MCP-1, and PD (including lymphocyte subset) measurements; record the time of blood collection
- **Process the first** morning void urine sample collection for quantitative urinalysis, UPCR, UACR, Cystatin C, Urine MCP-1, MCP-1/creatinine ratio and urine PD assessment
- Subjects will be asked to complete the SF-36 v2 and EQ-5D-5L.
- The ACTG Brief Peripheral Screening Tool will be administered
- Any changes in concomitant medication use will be recorded
- Any adverse events will be recorded

7.13. PK Elimination Visits

Upon discontinuation of treatment for any reason**, including end of study,** a sample of whole blood should be collected for assessment of elimination at 2, 7 and 14 days after discontinuation. Record the time of blood collection.

After all study procedures have been completed, the subject will be discharged from the study. The subject's condition will be evaluated by the Investigator at the end of the clinical trial (Week 28) and appropriate standard of care medical treatment **should be implemented for** all subjects as needed.

7.14. Early Termination Visit (See Section 7.14 for PK elimination guidelines)

If a subject will be withdrawn early from the study, the following termination procedures should be completed whenever possible:

- **Whenever possible, the subject will be asked to collect all urine for the 24 hours after the last dose of study drug**.

- An abbreviated, symptom-directed physical examination
- Vital signs (weight, temperature, blood pressure, heart rate) after at least 3 minutes of rest
- Blood samples and urine will be collected for shipment to the central laboratory for serum chemistry, hematology, serum pregnancy test (in women of childbearing potential) and quantitative urinalysis
- Need for dialysis will be recorded
- **If available, process the first** morning void urine sample collection for UPCR and UACR assessment
- **If available, process the 24-hour urine sample for quantitative urinalysis, UPCR, UACR, Cystatin C, Urine MCP-1, MCP-1/creatinine ratio urine PD assessment and urine protein excretion/day**
- 12 Lead ECG after at least 3 minutes of rest, will be recorded and assessed for any clinically significant abnormality
- Drug accountability and reconciliation with subject completed diaries
- Any changes in concomitant medication use, including plasma therapy regimen, will be recorded
- Any adverse events will be recorded. 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
- A final safety follow-up visit will be scheduled for 4 weeks after subject discontinues study drug

8. STUDY ASSESSMENTS

8.1. Efficacy Assessments

8.1.1. Urinary Measurements

Efficacy will be evaluated by assessment of urine protein:creatinine ratio (UPCR), urine albumin:creatinine ratio (UACR), and estimated glomerular filtration rate (eGFR) using the CKD-EPI Cystatin C equation, CKD-EPI Creatinine equation, CKD-EPI Creatinine-Cystatin C equation and MDRD Creatinine equation assessed at Weeks 12 and 24.

The urine samples, **first morning void and 24-hour urine sample** will be sent to the central laboratory for analysis. The following analyses will be performed according to the Time and Events Table:

- Urine protein to creatinine ratio (UPCR): the urine protein creatinine ratio is the ratio of the urine protein concentration to the urine creatinine concentration
- Urine albumin to creatinine ratio (UACR): the urine albumin creatinine ratio is the ratio of the urine albumin concentration to the urine creatinine concentration Urinalysis including

blood, protein, and nitrites; if positive for blood, protein, or nitrites, a microscopic assessment for RBC casts and RBC count will be performed;

Microscopic review is triggered if a urinary dipstick test is positive for blood, nitrite, or protein. When microscopy is performed, hematuria will be categorized as follows: None, Occasional (Occ), 1 - 2, 3 - 5, 6 - 9, 10 - 15, 16 - 29, 30 - 49, 50 - 75, and >75 RBCs per high power field.

8.1.2. Estimated Glomerular Filtration Rate

The estimated glomerular filtration rate (eGFR) will be calculated at all applicable study visits using the CKD-EPI Creatinine-equation (Schwartz GJ, et al. 2016, Selistre L et al 2016), the CKD-EPI Cystatin C (Dharnidharka VR, et al, 2002) equation the CKD-EPI Creatinine- Cystatin C equation (Stevens et al., 2008) and the MDRD Creatinine equation (Levey et al. 1999, Levey et al. 2006).

8.1.3. Serum Albumin

The serum albumin level provides an index of the degree of protein loss. Hypoalbuminemia may be seen in subjects with severe proteinuria and the nephrotic syndrome.

8.1.4. Health-Related Quality of Life and ACTG BPNST Assessments

The SF-36 v2 and EQ-5D-5L and ACTG BPNST will be completed by study subjects at visits specified in the Time and Events Table to measure changes from baseline in health-related quality of life and the ACTG BPNST will be completed by the study subject and the study doctor to assess changes in neuropathy. Proven translations will be used for non-English speaking subjects, whenever possible. An administrator will facilitate completion of the SF-36 and EQ-5D-5L questionnaires by the subjects, but will not complete the forms for the subjects. The administrator will establish a rapport with the subject, emphasize the importance of completing the form, and serve to answer questions and address concerns. The questionnaires should be completed by subjects before seeing the Investigator at the visit.

8.2. Safety Assessments

8.2.1. 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 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.

A baseline 12-lead ECG, after resting for at least 3 minutes, will be performed at screening and assessed for any clinically significant abnormalities. All abnormalities will be recorded in the

EDC system. Assuming the ECG abnormality does not preclude study entry, an ECG may be repeated as clinically indicated.

8.2.2. Clinical Safety Laboratory Assessments

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

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

8.2.3. 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 intercurrent illnesses or injuries, and exacerbation of pre-existing conditions.

An unexpected adverse event is an adverse event that is not identified in nature, severity, or frequency in the current 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 randomized to treatment 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/placebo, 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.

8.2.3.1. 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)

8.2.3.2. Causality Assessment

The relationship of study drug (CCX140-B/placebo) to an adverse event will be determined by the Investigator and Sponsor based on the following definitions:

- Probably Not Related: the adverse event was more likely explained by causes other than study drug (CCX140-B/placebo).
- Possibly Related: there is evidence for a reasonable possibility that study drug (CCX140-B/placebo) administration caused the adverse event.

8.2.3.3. 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.

8.2.3.4. 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/placebo) 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/placebo) 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.

8.2.3.5. Laboratory Abnormalities

Safety laboratory tests are performed frequently over the course of the study. Laboratory reports with abnormal findings will be reviewed by the Investigator and the Medical Monitor. The Investigator will be advised to follow subjects with notably high liver panel tests closely and to take appropriate steps, such as potentially discontinuing study medication, in case the abnormalities persist.

8.2.3.6. Pregnancies

Any pregnancies that occur in female subjects or partners of male study subjects must be reported to Medpace Clinical Safety within 24 hours of awareness to the contacts details outlined in Section 8.2.5. 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 Medpace Clinical Safety. Should the outcome of the pregnancy meet criteria for an SAE, this should be reported as indicated in Section 8.2.5.

8.2.4. 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 judgement 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 Medpace 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.

8.2.5. 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:

Medpace Clinical Safety

[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 Medpace 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 28 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.

8.3. Pharmacokinetic Assessments

Concentrations of CCX140 will be determined in plasma from 4.0 ml blood samples collected in K_2EDTA tubes according to the schedule in 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 on Day 1 and Day 15
C_{min}	Trough level plasma concentrations at PK visits other than on Days 1 & 15

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

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

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

8.4. Exploratory Pharmacodynamic Assessments

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

Exploratory assessments may include:

- Profile of FSGS related gene mutations;
- Change from baseline in urinary MCP-1; creatinine ratio;
- Change from baseline in urinary albumin to creatinine ratio (UACR)
- Change from baseline in blood monocytes, T, B and NK cells;
- Change from baseline in other urinary and blood exploratory markers potentially associated with activity of FSGS or inhibition of the CCR2/MCP-1 pathways. These may include measurement of:

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

8.5. Study Completion and Withdrawal

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 28). 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, when possible (see Section 7.14).

The clinical trial will be terminated early if there is a safety concern that cannot be addressed by a modification of the protocol.

9. STATISTICS

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.

Summary statistics will be calculated for each of the endpoints. For continuous variables, number (of subjects), mean, standard deviation, median, and range will be provided. For category variables, number and percent of subjects will be provided for each category. For variables requiring logarithmic transformation, e.g., UPCR, geometric means will be calculated.

Analysis will commence when all subjects have completed or discontinued prior to the Day 85 visit, and again when all subjects have completed or discontinued prior to the Day 169 visit.

9.1. Subject Populations

9.1.1. Modified Intent-to-Treat Population

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

9.1.2. Per Protocol Population

The Per Protocol (PP) population will consist of all mITT subjects who have ≥80% compliance with the study drug administration, 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 and unblinding.

9.1.3. Safety Population

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

9.2. Analysis Endpoints

9.2.1. Primary Efficacy Endpoints

Change from baseline in urine protein:creatinine ratio (UPCR) at week 12

9.2.2. Secondary Efficacy Endpoints

- Change from baseline in eGFR calculated by the CKDEPI cystatin C equation, **CKD-EPI Creatinine equation, CKD-EPI Creatinine-Cystatin C equation and MDRD Creatinine equation** at Weeks 12 and 24
- **Proportion of subjects achieving complete renal remission at Weeks 12 and 24**

  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**
- Proportion of subjects achieving partial remission **by the following two different definitions assessed at Weeks 12 and 24:**
  - **UPCR reduction of ≥ 50% from baseline and UPCR <3.5 g/g**
  - **decrease in UPCR to less than 1.5 g/g and at least a 40% reduction in proteinuria from baseline**

9.2.3. Exploratory Efficacy Endpoints

- Change from baseline of proteinuria in subjects treated with CCX140-B versus placebo over time
- Change from baseline in urinary MCP-1:creatinine ratio;
- Change from baseline in blood monocytes, T, B and NK cells;

- Change from baseline in Health-related Quality of Life changes based on Short Form 36 version 2 (SF-36 v2 and EQ-5D-5L.);
- Change from baseline in serum albumin;
- Relationship among PK, **eGFR**, serum albumin and UPCR;
- Change from baseline in UACR.

9.2.4. Safety Endpoints include

- Subject incidence of treatment-emergent adverse events, adverse events leading to study withdrawal, and serious adverse events;
- Change from baseline and shifts from baseline in all safety laboratory parameters;
- Change from baseline in vital signs;
- Change form baseline in score on the ACTG BPNST
- Clinically significant abnormal ECG findings
- Physical examinations

Treatment-emergent adverse events (TEAE) will be summarized for each treatment group by MedDRA System Organ Class (SOC) and preferred term (PT), by relatedness and maximum severity. Treatment-emergent serious adverse events (TESAE) and TEAE leading to study withdrawal will be separately listed and may be summarized if warranted by the subject incidences.

Vital signs and laboratory test results, and their changes from baseline will be summarized by treatment group and visit. Abnormal laboratory values will be flagged in the data listing. Shift tables will be generated by study visit.

Individual ECG findings and change from baseline in ECG findings will be listed by treatment group, subject, and study visit, and summarized by treatment group and visit.

Findings from physical examinations will be listed.

9.2.5. Pharmacokinetic Endpoints

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

9.2.6. Pharmacodynamic Endpoints

The following PD endpoints may be assessed:

- Change and percent change from baseline in plasma biomarkers.
- Change and percent change from baseline in urine biomarkers.

9.3. Statistical Analysis Methodology

This study will evaluate the efficacy, safety, tolerability and pharmacokinetics of up to 12 weeks of treatment with each of three dose regimens of CCX140-B or placebo, when used in

combination with stable standard of care therapy in subjects with primary FSGS or FSGS associated with high risk gene variants. Following the 12-week blinded treatment period, subjects will receive active treatment for an additional 12 weeks to assess safety and durability of effect.

The efficacy analyses will be performed using the mITT and PP populations, with the mITT analysis being the primary analysis. Safety analysis will be performed using the safety population.

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

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

9.3.1. Subject Disposition

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

9.3.2. 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), diagnosis of nephrotic syndrome, 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.

9.3.3. Prior and Concomitant Medications

All prior (within 12 weeks of screening,) and concomitant medications will be listed and summarized by Anatomic Therapeutic Chemistry (ATC) classification. All **B-cell depleting** antibodies, glucocorticoids and immunosuppresants taken within 6 months prior to screening may be summarized separately.

9.3.4. Study Drug Exposure and Compliance

Subject drug exposure will be calculated based on the study drug dispensing and return records, as well as CCX140 plasma concentrations over the course of the study. The CCX140-B/placebo compliance will be calculated comparing the study drug dispensed and the study drug returned. The study drug exposure (duration, total dose, and average daily dose) and compliance will be listed and summarized.

9.3.5. Efficacy Analyses

Summary statistics will be calculated for each of the efficacy parameters. For categorical endpoints, number and percentages will be calculated. For continuous variables, numbers, means, medians, ranges and standard deviations will be calculated. Point estimates and

corresponding 90% confidence intervals will be estimated for the difference between CCX140-B and placebo groups.

Data that are not normally distributed, e.g., UPCR, will be log-transformed before analysis.

Point estimates and corresponding 90% confidence intervals will be estimated for the difference between CCX140-B and placebo groups.

Because of the relatively small size of the study, inferential statistical analyses may not be appropriate. Where possible, change from baseline to Day 85 and from Day 85 to Day 169 in UPCR will be analyzed using the mixed-effects model for repeated measures (MMRM), with treatment group, visit, and treatment-by-visit as factors and baseline UPCR and age as covariates. The between group comparison will be computed using the simple contrast from the model. Analysis of covariance (ANCOVA) with last observation carried forward (LOCF) for missing data will also be used for sensitivity analysis. The MMRM and ANCOVA analyses will also be applied to the eGFR endpoint.

Proportion of subjects achieving partial response will be calculated for each treatment group. The between group comparison will be carried out using the Fisher's exact test.

The exploratory endpoints will be analyzed using MMRM model or ANCOVA as described for the primary efficacy endpoint analysis.

9.3.6. Safety Analyses

All clinical safety and tolerability data will be listed by treatment group and by subject, and will be summarized by treatment group and visit.

Treatment-emergent adverse events (TEAE) will be summarized for each treatment group by MedDRA System Organ Class (SOC) and preferred term (PT), by relatedness and maximum severity. Treatment-emergent serious adverse events (TESAE) and TEAE leading to study withdrawal will be separately listed and may be summarized if warranted by the subject incidences.

Vital signs and laboratory test results, and their changes from baseline will be summarized by treatment group and visit. Abnormal laboratory values will be flagged in the data listing. Shift tables will be generated by study visit.

Individual ECG findings and change from baseline in ECG findings will be listed by treatment group, subject, and study visit, and summarized by treatment group and visit.

Findings from physical examinations will be listed.

9.3.7. Pharmacokinetic and Pharmacodynamic Marker Analysis

Individual plasma concentrations of CCX140 will be listed, plotted, and summarized descriptively and graphically for subjects receiving CCX140-B. The following parameters will be determined for CCX140:

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 Time 6

Summary statistics for steady state trough plasma concentrations will also be performed.

The relationship between PK parameters and renal function based on eGFR, UPCR and serum albumin 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 first morning UPCR, eGFR, and other biomarkers may be used as PD markers. Pharmacodynamics biomarker data may be analyzed the same way as the efficacy data.

9.3.8. Handling of Missing Data

For the MMRM analysis, data will be analyzed as is without missing data imputation. For ANCOVA analysis and analysis of responses, missing data will be imputed using the last observation carried forward (LOCF) method. This method may impute Week 12 missing data with the baseline value if there are no scheduled or unscheduled data prior to the missing time point. Other imputation method will be detailed in the SAP.

9.3.9. Stratified Analysis

The analysis of the efficacy endpoints may be adjusted by the following variables in the form of stratified analysis:

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

9.4. Sample Size Justification

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

Assuming SD =8.5 for change from baseline in eGFR, with 10 subjects per group, the 90% CI for the between group difference will have a ½ width of 6.6. If the difference between treatment and placebo is observed to be 10 mL/min/1.73m^2, the 90% CI will be (3.4, 16.6).

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

9.5. Protocol Deviations

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

The Sponsor will assess each protocol deviation and decide whether they should be reported to Competent Authorities as a serious breach of GCP and the protocol. Examples of major deviations may include but are not limited to:

1. Failure to properly obtain informed consent
2. Enrollment of ineligible subjects
3. Performance of procedures not in the protocol or omission of protocol-required procedures
4. Study medication dosing and dispensing errors
5. Failure to properly report Serious Adverse Events
6. Any deviations from the protocol that jeopardize either subject safety or the integrity of the study

10. STUDY COMPLETION AND TERMINATION

10.1. Study Completion

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

10.2. Study Termination

The end of study is defined as the last study visit of the last clinical trial subject. Note that all study subjects are expected to return to the clinic for blood draws 2, 7 and 14 days after discontinuation from treatment for any reason.

11. REGULATORY AND ADMINISTRATIVE REQUIREMENTS

11.1. 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, a Medical License (from relevant countries) and 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.

11.2. 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.

11.3. 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.

11.4. 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.

11.5. 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.

11.6. 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.

11.7. 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 the Sponsor 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.

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

11.9. Monitoring

At intervals during the study, as well as after the completion of subject enrollment at the study center, 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, all regulatory documentation and drug accountability records. The study will be conducted

according to the principles of GCP as accepted in the United States and according to CPMP/ICH/135/95.

11.10. On-site Visits and Audits

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

In certain circumstances, a secondary audit may be conducted by members of a Quality Assurance group designated by the Sponsor. The Investigator will be informed if this is to take place and advised as to the nature of the audit. Representatives of the Food and Drug Administration (FDA) and/or representatives of other regulatory authorities may also conduct an audit of the study. If informed of such an audit, the Investigator should notify the Sponsor immediately.

11.11. 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.

12. 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. Clin Nephrol 36(2) 53-9.
2. Besbas N et al. (2015) MCP1 2518 A/G polymorphism affects progression of childhood focal segmental glomerulosclerosis. Ren Fail 37 (9):1435-1439.
3. 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.
4. Cattran and Appel, in Treatment of Primary Focal Sclerosis Glomerulosclerosis, Up To Date, 2016
5. Cattran DC, Reich HN, Beanlands HJ, Miller JA, Scholey JW, Troyanov S, Genes G, Glomerulonephritis G (2008) The impact of sex in primary glomerulonephritis. *Nephrol Dial Transplant* 23(7):2247-2253.
6. Cattran, DC and Rao, P (1998) Long-term outcome in children and adults with classic focal segmental glomerulosclerosis. Am J Kidney Dis. Jul;32(1) 72-9.
7. Chen, Y-C et al. (2015) 13-year nationwide cohort study of chronic kidney disease risk among treatment-naïve patients with chronic hepatitis B in Taiwan. BMC Nephrology 16:110.
8. 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.
9. 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.
10. D'Agati VD, Kaskel FJ, Falk RJ (2011) Focal segmental glomerulosclerosis. N Engl J Med 365(25):2398-2411.
11. D'Agati, V. D., Fogo, A. B., Bruijn, J. A., & Jennette, J. C. (2004). Pathologic classification of focal segmental glomerulosclerosis: a working proposal. *Am J Kidney Dis, 43*(2), 368-382.
12. 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.
13. 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.
14. 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.
15. Gipson DS, Troost JP, Lafayette RA, et al. (2016) Complete Remission in the Nephrotic Syndrome Study Network. Clin J Am Soc Nephrol 11(1):81-89.

16. Inker LA et al, (2012) Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med.; 367(1):20-29.
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. 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.
23. 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.
24. PC0684_140 Effects of CCR2 antagonist in adriamycin-induced and 5/6 nephrectomy mouse models of focal segmental glomerulosclerosis.
25. Rydel,JJ et al. (1995) Focal segmental glomerular sclerosis in adults: presentation, course, and response to treatment. Am J Kidney Dis Apr;25(4):534-42.
26. Schwartz GJ, et al. (2009) New equations to estimate GFR in children with CKD. J Am Soc Nephrol; 20:629–637.
27. 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
28. Sim, JJ et al. (2016) Distribution of Biopsy-Proven Presumed Primary Glomerulonephropathies in 2000-2011 Among a Racially and Ethnically Diverse **US** Population. Am J Kidney Dis. Oct;68(4):533-544.
29. Stevens, LA, et al. (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 KD, 51(3): 395-406.
30. Sullivan TJ et al. (2013) Experimental evidence for the use of CCR2 antagonists in the treatment of type 2 diabetes. Metabolism 62 (11):1623-1632.

31. Troyanov S, Wall CA, Miller JA, Scholey JW, Cattran DC, Toronto Glomerulonephritis Registry G (2005) Focal and segmental glomerulosclerosis: definition and relevance of a partial remission. J Am Soc Nephrol 16(4):1061-1068.

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

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