# STATISTICAL ANALYSIS PLAN

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|---|---|
| **Protocol Title:** | An Open Label, Intra-Subject Dose Escalation Study of CCX140-B in Subjects with Primary Focal Segmental Glomerulosclerosis (FSGS) and Nephrotic Syndrome |
| **Protocol Number:** | CL012_140 |
| **Protocol Version/Date:** | Amendment 1.0/17 April 2018 |
| **Investigational Product:** | CCX140-B, a selective antagonist of human C-C chemokine receptor 2 (CCR2) |
| **Sponsor:** | ChemoCentryx, Inc.<br>Mountain View, California 94043, USA |
| **SAP Version/Date:** | V1.0, 29 July 2020 |

**CONFIDENTIAL**



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

# SIGNATURE PAGE

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

| Signature | Date |
|---|---|
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| ***Medical Monitor***<br>***Medpace, Inc.*** | |

# VERSION HISTORY

| Version | Version Date | Description |
|---|---|---|
| 1.0 | 29 July 2020 | Original signed version |

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# LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| ACTG-BPNST | AIDS Clinical Trials Group – Brief Peripheral Neuropathy Screening Tool |
| ADaM | Analysis Data Model |
| AE | Adverse event |
| ATC | Anatomical therapeutic chemical |
| AUC | Area under the curve |
| $AUC_{0-6}$ | Area under the curve, from time of dosing to 6 hours post-dose |
| $AUC_{0-12}$ | Area under the curve, from time of dosing to 12 hours post-dose |
| BID | Two doses per day, also represented as b.i.d. |
| BLQ | Below the Limit of Quantification |
| BMI | Body mass index |
| CDISC | Clinical Data Interchange Standards Consortium |
| CCR2 | CC Chemokine Receptor 2 |
| CCX140-B | Sodium salt of CCX140 |
| CKD-EPI | Chronic kidney disease epidemiology collaboration |
| Cmin | Minimum (minimal) plasma concentration |
| Cmax | Maximum (maximal) plasma concentration |
| CR | Complete Remission |
| CRF | Case report form |
| CSR | Clinical Study Report |
| DMC | Data Monitoring Committee |
| ECG | Electrocardiogram |
| eGFR | Estimated glomerular filtration rate |
| EQ-5D-5L | EuroQol-5 Dimensions-5 Levels |
| FSGS | Focal Segmental Glomerulosclerosis |
| GCP | Good Clinical Practice |
| INR | International Normalized Ratio |
| ITT | Intent to Treat |
| MCP-1 | Monocyte chemoattractant protein 1, also known as CCL2 |
| MDRD | Modification of Diet in Renal Disease |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NOAEL | No-observed-adverse-effect level |
| PK | Pharmacokinetic(s) |
| PR | Partial remission |
| PT | Preferred Term; also can refer to “Prothrombin Time” |
| PTT | Partial Thromboplastin Time |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SDTM | Study Data Tabulation Model |
| SF-36 | Short form (36) Health Survey |
| SOC | System Organ Class |
| $t_{1/2}$ | Half-life |
| TEAE | Treatment-emergent adverse event |
| TESAE | Treatment-emergent serious adverse event |

| Abbreviation | Definition |
|---|---|
| $T_{max}$ | Time of maximal concentration |
| UACR | Urinary albumin:creatinine ratio |
| UPCR | Urinary protein:creatinine ratio |
| WHO | World Health Organization |

# 1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with protocol number CL012_140. This document is based on protocol amendment 1.0 (17APR2018) and Case Report Form (CRF) version 8.0 (02APR2020). The statistical definitions and analytical methods described in this SAP supersede that in the protocol. The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

Following study CL011_140, 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), its results did not support the development of CCX140 in FSGS. Therefore a decision was made to not continue enrollment in study CL012_140, which also investigates CCX140 in patients with FSGS and nephrotic syndrome. In addition, the efficacy and safety summaries will be limited to specific parameters and an abbreviated CSR will be developed for this study. See further details in Section 6, Changes From Protocol-Specified Statistical Analyses.

# 2 STUDY OVERVIEW

## 2.1 Study Objectives

### *2.1.1 Primary Objective*

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

### *2.1.2 Secondary Objectives*

Secondary Efficacy endpoints of this study will be assessed through Study Week 12 and through End of Treatment and include:

- Achievement of partial or complete remission of urine protein to creatinine ratio (UPCR)
- Partial Remission (includes all of the following):
    - Reduction from baseline by $\geq$50% in UPCR
    - Reduction in UPCR to a level that is <3.5 g/g
    - Subject may not be a treatment Failure
- Complete Remission (includes the following):
    - Reduction in UPCR to <0.3 g/g
    - Serum albumin within normal range
    - For patients with abnormal serum creatinine levels at baseline, return to normal levels for that age group
    - For patients with normal serum creatinine levels at baseline, final value within 20% of baseline levels
    - Subject may not be a treatment failure
- Change from baseline in UPCR over time
- Time to and proportion with achievement of partial remission during the treatment period

- Time to and proportion with achievement of complete remission during the treatment period
- Time to rescue therapy, based on Investigator or physician initiation of glucocorticoids or new immunosuppressive agents or new major treatment modalities (e.g. plasmapheresis, dialysis)
- Changes over time in other laboratory and other parameters related to renal function, including:
    - Serum albumin
    - Creatinine
    - Cystatin C
    - eGFR, calculated by the Chronic kidney disease epidemiology collaboration (CKD-EPI) Cystatin C equation, CKD-EPI Creatinine equation, CKD-EPI Creatinine-Cystatin C equation and Modification of Diet in Renal Disease (MDRD) Creatinine equation
    - Urine albumin to creatinine ratio (UACR)
    - Total 24 hour urine protein excretion
- Quality of Life endpoints include:
    - Change in factors associated with quality of life from baseline over time as assessed using the SF-36 v2
    - Change in factors associated with quality of life from baseline over time as assessed using the EQ-5D-5L
- Safety will be evaluated via the following endpoints:
    - Adverse events
    - Vital signs
    - Electrocardiograms
    - AIDS Clinical Trials Group Brief Peripheral Neuropathy Screening Tool (ACTG BPNST)
    - Changes in laboratory parameters including:
        - Hematology, including complete blood count, reticulocyte count, smear evaluation
        - Serum haptoglobin, lactate dehydrogenase
        - Serum chemistry, expanded to include serum transaminases, CPK
        - Urinalysis
        - Coagulation factors
- Pharmacokinetics will be evaluated based on:
    - Exposure (AUC, $C_{max}$, $C_{min}$)

### *2.1.3 Exploratory Objectives*

Exploratory objectives include:

- Assessment of biomarkers associated with disease activity over time, including blood lipid profile, urinary MCP-1, and potentially other biomarkers of renal inflammation, fibrosis and injury;
- Assessment of biomarkers associated with risk of severity of disease, which may include allelic variations associated with the pathogenesis and/or prognosis of FSGS such as NPHS1, NPHS2, WT-1, LAMBD2, CD2AP, TRPC6, ACTN4, INF2, APOL1

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

## 2.2 Study Design

### *2.2.1 Overview*

This is a Phase 2, open-label clinical trial to test the efficacy, safety, pharmacokinetics, and tolerability of ascending doses of CCX140-B in subjects with primary FSGS and nephrotic syndrome. Six (6) male or female subjects will be enrolled at up to 10 sites in North America and Europe in the first stage of this study. An additional seven (7) subjects may be enrolled in the second stage of this study based on the observations in the first 6 subjects (see the sample size section for more information). The primary study period includes a screening period (up to 28 days), up to 12 weeks initial treatment (intra-subject dose escalation), followed by 4 weeks of follow-up after the last dose is administered. For subjects who meet pre-defined response criteria at 12 weeks, there is an extended treatment period for up to an additional 40 weeks. Subjects will visit the study center during Screening and on Day 1 (baseline), weekly throughout dose escalation, then every 2 weeks through Study Week 12.

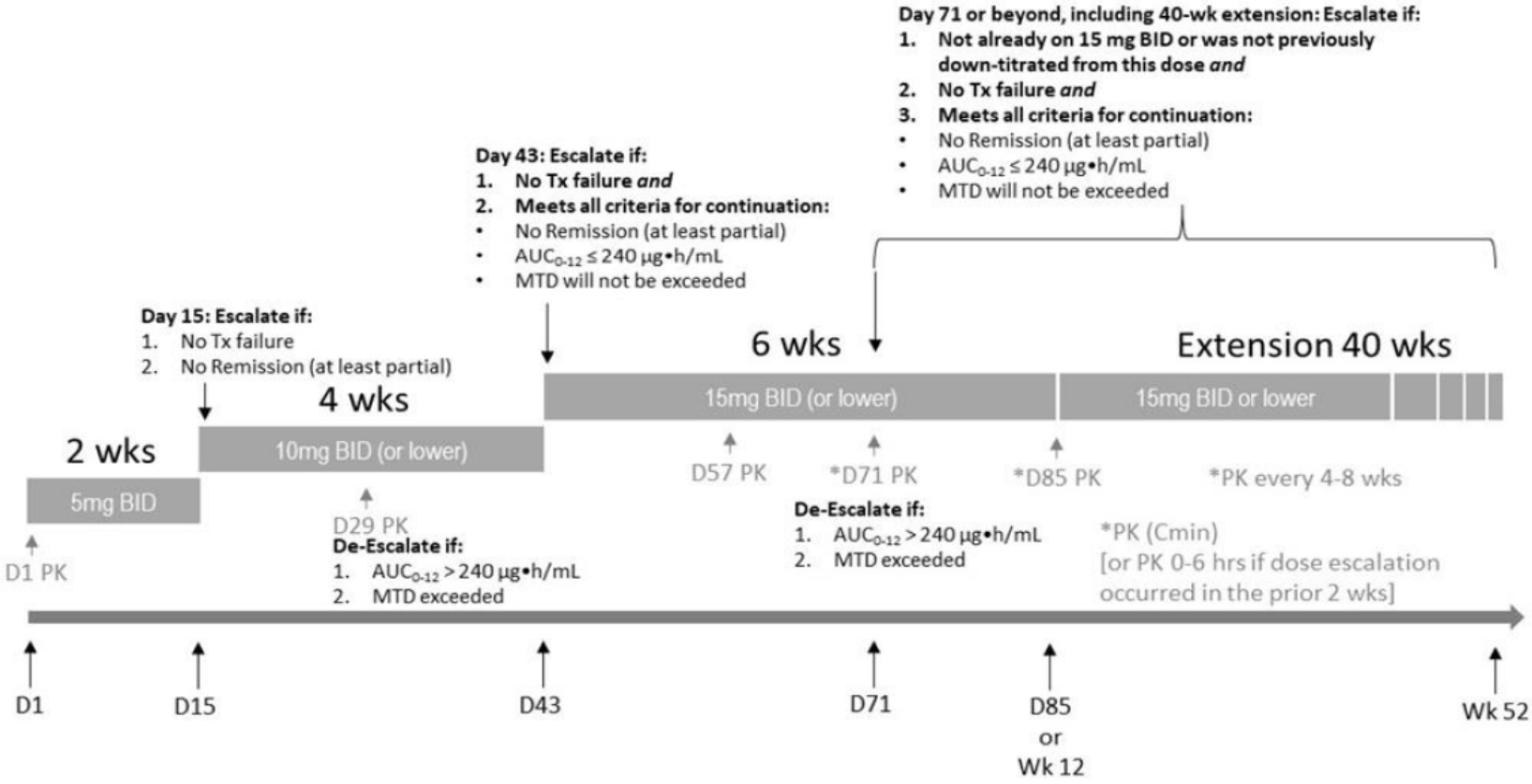
## Figure 1: Study Schematic

**Treatment failure = Tx failure:**

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

**Eligibility Criteria for Extended Treatment Period:**

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



## Table 1: Time and Events

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

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

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

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

### *2.2.2 Randomization and Blinding*

This is an open-label study, therefore randomization and blinding are not applicable for this study.

### *2.2.3 Study Drug*

Eligible subjects will begin the treatment with CCX140-B 5mg twice daily. CCX140-B will be taken orally without food at least one hour before a meal. The dose may be increased in a stepwise manner to 10 mg twice daily on Study Day 15, then to 15 mg twice daily on Study Day 43, while monitoring efficacy, PK, and safety. Dose escalations will occur according to the rules and schedule detailed in Figure 1 above, and Section 3 and Table 1 in Protocol (Amendment 1.0). Doses may be adjusted downward in the event of intolerance, laboratory evidence of toxicity, or a measured or steady state exposure that exceeds the pre-specified maximum safe exposure based on the No Observed Adverse Event Level (NOAEL) established in the non-clinical toxicology program.

In all subjects, treatment at the selected dose will be continued through 12 weeks or until the declaration of Treatment Failure.

Treatment Failure is defined as any of the following:

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

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

At any time during the study dose may be de-escalated for safety, or if projected exposure exceeds the maximum allowable exposure defined for the study. Because exposure may be impacted by changes in proteinuria, the protocol requires assessment of exposure if proteinuria declines significantly. See Section 7.5.1 of the protocol for further details on dose modification/stopping rules related to exceeding the maximum tolerated dose.

Subjects who completed 12 weeks of treatment are not considered treatment failures and who otherwise meet criteria for continuation may be extended for up to an additional 40 weeks to assess degree and duration of response. During the extension period the dose may be adjusted if indicated based on assessment of safety, PK, and efficacy. Starting with the extended treatment period (Study Day 85 and beyond), if the dose is adjusted upward or downward for any reason at Study Day 85, or during the extended treatment period, the subject will return approximately 2 weeks later for blood draws to assess PK ($AUC_{0-6}$).

### *2.2.4 Sample Size Determination*

Six (6) male or female adult subjects with biopsy-proven primary FSGS and nephrotic syndrome will be enrolled in the first stage of this study. The study will be paused to assess safety and efficacy after the initial 6 subjects have completed 12-weeks of treatment in the study. An additional seven (7) subjects may be enrolled in the second stage of this study based on observations in the first six subjects, resulting in a total of 13 subjects in the study. The relatively small sample size is selected based on the exploratory safety and efficacy nature of the study.

## 2.3 Study Endpoints

### *2.3.1 Primary Efficacy Endpoints*

The primary efficacy endpoint is the median reduction from baseline of urine protein to creatinine ratio (UPCR) of at least 20 % i.e. $\geq$20% by Week 12.

### *2.3.2 Secondary Efficacy Endpoints*

Secondary efficacy endpoints measured through Week 12 and End of Treatment include:

- Achievement of partial or complete remission of urine protein to creatinine ratio (UPCR)
    - Partial Remission (includes all of the following):
        - Reduction from baseline by $\geq$50% in UPCR
        - Reduction in UPCR to a level that is <3.5 g/g
        - Subject may not be a treatment Failure
    - Complete Remission (includes the following):
        - Reduction in UPCR to <0.3 g/g
        - Serum albumin within normal range
        - For patients with abnormal serum creatinine levels at baseline, return to normal levels for that age group
        - For patients with normal serum creatinine levels at baseline, final value within 20% of baseline levels
        - Subject may not be a treatment failure
- Change from baseline in UPCR over time
- Time to and proportion with achievement of partial remission during the treatment period
- Time to and proportion with achievement of complete remission during the treatment period

- Time to rescue therapy, based on Investigator or physician initiation of glucocorticoids or new immunosuppressive agents or new major treatment modalities (e.g. plasmapheresis, dialysis)

### *2.3.3 Exploratory Efficacy Endpoints*

Exploratory Efficacy Endpoints include:

- Assessment of biomarkers associated with disease activity over time, including blood lipid profile, urinary MCP-1, and potentially other biomarkers of renal inflammation, fibrosis and injury
- Assessment of biomarkers associated with risk of severity of disease, which may include allelic variations associated with the pathogenesis and/or prognosis of FSGS such as NPHS1, NPHS2, WT-1, LAMBD2, CD2AP, TRPC6, ACTN4, INF2, APOL1
- Assessment of blood and/or urinary biomarkers associated with CCR2 biology, which may include peripheral blood leukocyte subsets and selected cytokines and chemokines
- Assessment of mechanisms by which nephrotic syndrome may potentially impact pharmacokinetics of CCX140, including assessment of CCX140 in urine
- Assessment of edema as measured by physical examination, leg circumference and body weight
- Assessment of concentration of CCX140-B in urine

### *2.3.4 Pharmacokinetic Endpoints*

Concentrations of CCX140 will be determined in plasma from 4.0-mL blood samples collected in $K_2$EDTA tubes according to Table 1. The following parameters will be determined, where possible:

- $C_{max}$ Maximum plasma concentration
- $T_{max}$ Time of maximum plasma concentration
- $AUC_{0-6}$ Area under the plasma concentration-time curve from Time 0 to Hour 6 on Day 1, Day 29 (or Day 14 following 10 mg BID dosing), and Day 57 (or Day 14 following 15 mg BID dosing)
- $AUC_{0-12}$ Area under the plasma concentration-time curve from Time 0 to Hour 12 on Day 29 (or Day 14 following 10 mg BID dosing), and Day 57 (or Day 14 following 15 mg BID dosing) with the assumption of the concentration of Time 0 being equivalent to Hour 12.
- $C_{min}$ Trough level plasma concentrations at Day 57 visit or beyond

On Days 1, 29 and 57, 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 dose.

Total plasma concentrations of CCX140 will be determined using validated analytical methods.

### *2.3.5 Safety Endpoints*

Safety endpoints include:

- Adverse events
- Vital signs
- Physical Exam Abnormalities

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

# 3 STATISTICAL METHODOLOGY

## 3.1 General Considerations

### *3.1.1 Analysis Day*

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

### *3.1.2 Analysis Visits*

Scheduled visits will be assigned to analysis visits as recorded in the electronic data capture (EDC) system. If a scheduled visit is not available, unscheduled and early termination visits will be assigned to analysis visits using analysis visit windows based on the actual date the assessment took place. The start day of the analysis window will be calculated as the midpoint between the scheduled assessment and previously scheduled assessment for that parameter. The end of the analysis window will be calculated as the midpoint between the scheduled assessment and the next scheduled assessment for that parameter. Where multiple measurements for a particular parameter appear within an analysis window, the scheduled visit will be used. If no scheduled visit appears in the analysis window, the result closest to the target day will be used. If equidistant and both are unscheduled and/or early termination visits, the later result will be used for the summary measure.

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

| Analysis Visit | Target Analysis Day | Low Analysis Day | High Analysis Day |
|---|---|---|---|
| Day 15 | 15 | 2 | 22 |
| Day 29 | 29 | 23 | 43 |
| Day 57 | 57 | 44 | 71 |
| Week 12 | 85 | 72 | 99 |
| Week 16 | 113 | 100 | 127 |
| Week 20 | 141 | 128 | 155 |
| Week 24 | 169 | 156 | 183 |

| | | | |
|---|---|---|---|
| Week 28 | 197 | 184 | 211 |
| Week 32 | 225 | 212 | 239 |
| Week 36 | 252 | 240 | 266 |
| Week 40 | 281 | 267 | 295 |
| Week 44 | 309 | 296 | 323 |
| Week 48 | 337 | 324 | 351 |
| Week 52 | 365 | 352 | 379 |

#### *3.1.3 Definition of Baseline*

Baseline is defined as the last assessment prior to the first dose of study drug.

#### *3.1.4 Summary Statistics*

Categorical data will generally be summarized with counts and percentages of subjects. The denominator used for the percentage calculation will be clearly defined. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation, standard error of the mean, minimum, and maximum.

#### *3.1.5 Hypothesis Testing*

Since this is a small open-label study with one treatment group, formal hypothesis testing is not applicable.

#### *3.1.6 Evaluation of Site Effect*

Due to the small sample size, site effect will not be evaluated for this study.

#### *3.1.7 Adjustments for Potential Impact of COVID-19*

As no subjects' data was impacted by COVID-19, adjustments to analyses and summaries will not be required.

### 3.2 Analysis Populations

#### *3.2.1 Intent-to-Treat (ITT) Population*

The ITT Population is defined as all subjects who have received a dose of the study drug and have at least one post-baseline efficacy assessment.

#### *3.2.2 Safety Population*

The Safety Population is defined as all subjects who have received at least one dose of study drug.

#### *3.2.3 Pharmacokinetic Population*

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

## 3.3 Subject Data and Study Conduct

### *3.3.1 Subject Disposition*

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

### *3.3.2 Protocol Deviations*

Significant protocol deviations, i.e., those pertaining to Good Clinical Practice (GCP) violations and those that may affect the efficacy evaluation, will be captured in the Study Management System as CSR Reportable deviations. These significant deviations will be listed by category.

### *3.3.3 Analysis Populations*

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

### *3.3.4 Demographic and Baseline Characteristics*

The following demographic and baseline characteristics will be summarized:

- Age (years)
- Sex
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- Body mass index (BMI) ($kg/m^2$) and BMI categories ($<30\ kg/m^2$, $\geq 30\ kg/m^2$)
- FSGS duration (months)
- eGFR
- Proteinuria (UPCR)

### *3.3.5 Medical History*

Medical history including start date of FSGS diagnosis will be listed.

### *3.3.6 Concomitant Medications*

Concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term (PT) using the WHODrug Dictionary (September 2016E B2). Prior medications are defined as any medication taken prior to the first dose of study medication (within 12 weeks of screening). Concomitant medications are defined as any medication taken on or after the first dose of study medication. A medication can be classified as both prior and concomitant if it started before or during the screening period and continued into the treatment period.

If a medication has incomplete start or stop dates, dates will be imputed to determine whether a medication should be considered prior or concomitant. See Appendix A for further information.

Prior and concomitant medications will be listed by subject including ATC class and PT based on the Safety Population.

### *3.3.7 Concomitant Procedures*

Concomitant procedures performed during the study period will be listed.

### *3.3.8 Study Drug Exposure and Compliance*

Days of exposure to study drug will be calculated as date of last dose of study drug – date of first dose of study drug + 1. Note that the exposure calculation is intended to describe the length of time a subject was exposed to study drug and therefore does not take study drug interruptions into account. Study drug exposure will be listed by subject for each dispense/return record including dose level. Compliance to study drug as assessed at the study site will also be listed.

## 3.4 Efficacy Assessment

Efficacy data will be summarized by randomized treatment based on the ITT Population. The primary and secondary efficacy endpoints are different than what was specified in the protocol. Partial remission, complete remission and associated endpoints (proportion and time to achievement of) as well as time to rescue therapy will not be calculated. See Section 6, Changes From Protocol-Specified Analyses for further details.

### *3.4.1 Primary Efficacy Endpoints*

Primary Analysis

The primary efficacy endpoint analysis will include the following parameters: UPCR (Morning void), UPCR (24 hour Urine), and eGFR. This will be summarized by treatment group over time using descriptive statistics. Both change from baseline to Week 12, and percent change from baseline to Week 12 will be included in the summary.

Change and percent change from baseline in renal function will be based on eGFR (calculated using the CKD-EPI Cystatin C equation, the CKD-EPI Creatinine equation, the CKD-EPI Other Efficacy Endpoints

### *3.4.2 Other Efficacy Endpoints*

All other efficacy assessments will be listed. These include the following:

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

### *3.4.3 Subgroups*

Since analysis will be limited in scope and ITT population will consist of a maximum 13 subjects total, subgroups will not be included in analysis.

## 3.5 Pharmacokinetic Assessment

Dosing and pharmacokinetic sampling times for CCX140 for individual subjects will be summarized in terms of dose, subject, visit, date/time of reference dose, scheduled timepoint, date/time of specimen collection, actual hour relative to reference dose (hr) and deviation from scheduled time. Individual and mean plasma concentrations of CCX140 will be listed, plotted, and summarized descriptively and graphically for subjects receiving CCX140-B.

The following PK parameters of individual subjects and their summary statistics will be determined for CCX140 on Day 1, Day 29 (or 14 days following initial 10 mg BID dosing) and Day 57 (or 14 days following initial 15 mg BID dosing) 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 Hour 0 to Hour 6

$AUC_{0-12}$ on Day 29 and Day 57 will also be estimated assuming that steady state has been achieved, treating the pre-dose concentration also as the 12 hour concentration.

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

The sample time of the pre-dose samples on Day 1, Day 29 and Day 57 will be uniformly considered as time “0”.

For the trough concentration, all missing or below the limit of quantification (BLQ) concentrations will not be imputed and will be excluded from the descriptive summary.

For Day 1, Day 29 and Day 57 visits, individual PK plots or individual PK parameters, since there is no collection window specified for post-dose PK sampling, will be based on actual times recorded. For concentration versus time descriptive statistical summaries and mean plot preparation, nominal time points will be used. If the difference of post-dose sampling time is > 5 minutes from the nominal sampling times for time points <2 hours or >5% for time points ≥2 hours, the corresponding concentration data will be excluded from the concentration summary and mean plot preparation, but will still be used in the individual plots and the calculation of PK parameters.

For Day 57 and beyond, the allowable time window for PK trough sampling is ± 3 hours (i.e., 25% of dosing interval of 12 hours) for 15 mg BID dosing period including the open label extension phase (Day 85 and beyond). If the exact time (measured from dosing) is outside of the collection window, the corresponding concentration will be excluded from trough concentration versus time descriptive statistical summaries.

For the PK blood samples collected at 7 days and 14 days following the last dose of study drug, the actual sampling time should not exceed 5% of the nominal sampling time. If the exact time (measured from dosing) is outside of the collection window, the corresponding concentration will be listed but excluded from descriptive statistical summaries.

### *3.5.1 Pharmacokinetic Concentrations*

The individual plasma concentration of CCX140 will be listed.

For subjects with serial samples collected (pre-dose and at 0.5, 1, 2, 3, 4, and 6 hour post-dose after the CCX140-B dose on Day 1, Day 29 (or 14 days following initial 10 mg BID dosing) and Day 57 (or 14 days following initial 15 mg BID dosing):

- Concentration data will be summarized by dose at each nominal time point descriptively;
- Mean (±SD) plasma concentrations of CCX140 will be plotted on a linear scale against nominal time points by dose.

For subjects with sample collected for trough concentration (Day 57 visit and beyond):

- Trough concentration data, within allowable time windows, will be at each visit descriptively.
- Mean trough concentrations (Cmin) of CCX140 will be plotted overlaid with the scatter plot of individual trough concentrations on a linear scale against visits.
- The average steady state trough concentration of CCX140 for each individual subject will be calculated (each subject needs to have at least 3 time points in this steady state period for the calculation). The global average steady state trough concentration of CCX140 will be listed and summarized descriptively.

For subjects with sample collected at 7 days and 14 days following the last dose of study drug,

- Concentration data, within allowable time windows, will be listed and summarized descriptively.

### *3.5.2 Pharmacokinetic Parameters*

For subjects with serial samples collected (pre-dose and at 0.5, 1, 2, 3, 4, and 6 hour post-dose after the first CCX140-B dose on Day 1, Day 29 (or 14 days following initial 10 mg BID dosing) and Day 57 (or 14 days following initial15 mg BID dosing), $C_{max}$, $T_{max}$, and $AUC_{0-6}$ will be determined based on individual CCX140 plasma concentration data. $AUC_{0-12}$ will be determined for Day 29 and Day 57 assuming pre-dose level being the same as the concentration at the end of the dosing interval.

| Parameters | Description |
|---|---|
| $C_{max}$ | Maximum drug concentration after the first dose; observed directly from the data. If not unique, then the first maximum concentration is used |
| $T_{max}$ | Time to $C_{max}$ |
| $AUC_{0-6}$ | Area under the concentration-time curve (AUC) from time 0 to 6 hours post-dose. For 6 hours post-dose sample, the corresponding observed concentrations will be used for AUC calculation if the difference of the actual time point is <5% from the nominal time point; otherwise, the concentration at the nominal 6-hour time point will be predicted and then used for the AUC calculation. |
| $AUC_{0-12}$ | AUC from time 0 to 12 hours post-dose on Day 29 and Day 57. The concentration at 12-hour time point will be assumed to be the same as the pre-dose level. |

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

PK parameters will be listed and summarized descriptively.

## 3.6 Safety Assessment

Safety data will be summarized based on the Safety Population.

### *3.6.1 Adverse Events (AEs)*

AEs will be captured from the first dose of study drug and SAEs will be captured from the date of informed consent through study completion and summarized overall. All AEs will be coded to system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) version 20.1. Treatment-emergent adverse events (TEAEs) are defined as AEs that start after the first dose of study drug.

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

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

All adverse events will be listed by subject including TEAE status (Yes/No), MedDRA SOC, PT, verbatim term, AE start/stop day, severity, relationship to study drug, action taken with study treatment, outcome, and SAE categories (if applicable).

#### *3.6.2 Clinical Laboratory Tests*

Blood and urine samples for clinical laboratory tests will be collected at Screening, Day 1, Day 15, Day 29, Day 57, Day 85 (Week 12), Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 52, Early Termination (if applicable), and follow-up visit. Midstream spot urine void for UPCR during the site visits will be collected at every timepoint during the study. All chemistry, hematology, and urinalysis tests will be processed by a central laboratory. Local laboratory data will be listed.

#### *3.6.3 Vital Signs*

Vital signs will be measured at every study visit during the Treatment Period and Extension Period. Vital sign parameter values will be listed by subject at each visit.

#### *3.6.4 Electrocardiograms*

Triplicate 12-lead ECGs will be taken at Screening, Day 1, Day 29, Day 57, Day 85 (Week 12), Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 52/Early Termination, and follow-up. ECG parameter values will be listed by subject at each visit.

#### *3.6.5 Physical Examinations*

Physical examination abnormalities will be listed by subject.

#### *3.6.6 AIDS Clinical Trials Group – Brief Peripheral Neuropathy Screening Tool (ACTG BPNST)*

ACTG-BPNST results will be listed by subject at each visit.

# 4 DATA MONITORING COMMITTEE

Due to the unblinded nature of the study, a Data Monitoring Committee (DMC) was not utilized for this study. However, a Study Review Committee as described in the protocol was convened to review efficacy and safety data.

# 5 ANALYSIS TIMING

## 5.1 Interim Analysis

No interim analysis is planned.

## 5.2 Pre-Final Analysis

After the database is locked, the pre-final analysis will be generated. Pre-final TFLs will be provided approximately 2 weeks after database lock.

## 5.3 Final Analysis

After all comments on the pre-final analysis have been resolved and the study database is declared final, the final analysis will be generated. Final TFLs will be provided approximately 1 week after the study database is declared final. If there were no changes to the pre-final analysis or the study database, the pre-final TFLs may be considered final. In addition to TFLs, SDTM data and ADaM data along with associated files will be provided. Associated files may include: annotated case report forms (CRFs), SDTM specifications, SDTM programs, ADaM

specifications, ADaM programs, TFL programs, and CDISC Define packages for both SDTM and ADaM data.

# 6 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

There are several changes to the protocol-specified statistical analyses provided below:

- Due to the small sample size and abbreviated summary of data, no per-protocol analyses will be carried out.
- Primary endpoint analysis changed from assessing median reduction from Baseline to Week 12 of UPCR of at least 20%, to producing summary statistics for UPCR and eGFR.
- Secondary endpoint analyses have been removed. Instead this data will be listed, including:
    - Time-to-Event analysis for Partial Remission and/or Complete Remission
    - Proportion of subjects with Partial Remission or Complete Remission
    - Change from Baseline Serum Albumin over time
    - Change in UACR from Baseline over time
    - Time to investigator or physician initiation of rescue therapy including glucocorticoids, new immunosuppressive agents, or new major treatment modalities
    - Duration between achievement of remission and relapse or treatment failure
    - Changes over time in Health Quality Assessment (SF-36 v2 and EQ-5D-5L)

Rationale: Following study CL011_140, 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), its results did not support the development of CCX140 in FSGS. Therefore a decision was made to not continue enrollment in study CL012_140, which also investigates CCX140 in patients with FSGS and nephrotic syndrome. In addition, the efficacy and safety summaries will be limited to specific parameters and an abbreviated CSR will be developed for this study.

# 7 PROGRAMMING SPECIFICATIONS

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

# APPENDIX A: IMPUTATION FOR MISSING/PARTIALLY MISSING ADVERSE EVENT AND CONCOMITANT MEDICATION DATES

**Incomplete Adverse Event Start Date:**

Partially missing AE start/stop dates will be imputed in the ADaM dataset for AEs, according to the rules below. However, listings of AE data will present the date as is, with missing date components left blank.

If the AE end date is complete with no missing year, month, or day, and a partially missing start date imputed by the rules below is after the AE end date, then the start date will be imputed by the AE end date.

*Missing day and month*

- If the year is the **same** as the year of the first dosing date, then the day and month of the first dosing date will be assigned to the missing fields.
- If the year is **prior to** the year of first dosing date, then December 31 will be assigned to the missing fields.
- If the year is **after** the year of first dosing, then January 1 will be assigned to the missing fields.

*Missing day only*

- If the month and year are the **same** as the year and month of first dosing date, then the first dosing date will be assigned to the missing day.
- If either the year of the partial date is **before** the year of the first dosing date or the years of the partial date and the first dosing date are the same but the month of partial date is **before** the month of the first dosing date, then the last day of the month will be assigned to the missing day.
- If either the year of the partial date is **after** the year of the first dosing date or the years of the partial date and the first dose date are the same but the month of partial date is **after** the month of the first dosing date, then the first day of the month will be assigned to the missing day.

*Missing day, month, and year*

- No imputation is needed. The corresponding AE will be included as TEAE.

**Incomplete AE Stop Date:**

- If the imputed stop date is before the start date, then the imputed stop date will be equal to the start date.

*Missing day and month*

- If the year of the incomplete stop date is the **same** as the year of the last dosing date, then the day and month of the last dosing date will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date or prior to the year of the first dosing date, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date but is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing date.
- If the year of the incomplete stop date is **after** the year of the last dosing date, then January 1 will be assigned to the missing fields.

*Missing day only*

- If the month and year of the incomplete stop date are the **same** as the month and year of the last dosing date, then the day of the last dosing date will be assigned to the missing day
- If either the year of the partial date is **not equal to** the year of the last dosing date or the years of the partial date and the last dosing date are the same but the month of the partial date is not equal to the month of the last dosing date, then the last day of the month will be assigned to the missing day

**Incomplete Stop/Start Dates for Prior/Concomitant Medications/Procedures**

Partially missing start/stop dates for prior/concomitant medications and partially missing start dates for prior/concomitant procedures will be imputed in the ADaM dataset for prior/concomitant medications/procedures. However, listings of prior/concomitant medications/procedures data will present the date as is, with missing date components left blank.

For prior/concomitant medications, if the stop date is complete with no missing year, month, or day, and the partially missing start date imputed by the rule below is after the stop date, then the start date will be imputed by the stop date.

Partially missing prior/concomitant medication/procedure start dates will be imputed by the earliest possible date given the non-missing field(s) of the date, if the partial dates are either before or after the date of the first dose of the study drug. Otherwise, they will be imputed with the date of the first study drug dose.

Partially missing prior/concomitant medication stop dates will be imputed by the latest possible date given the non-missing field(s) of the date.