A Phase 2, Proof-of-Concept, Randomized, Double-Blinded, Placebo-Controlled Study of ACH-0144471 Treatment for 6 Months in Patients with C3 Glomerulopathy (C3G), with an Open-Label Extension

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STATISTICAL ANALYSIS PLAN

PROTOCOL NUMBER: **ACH471-204**

A PHASE 2, PROOF-OF-CONCEPT, RANDOMIZED, DOUBLE-BLINDED, PLACEBO-CONTROLLED STUDY OF ACH-0144471 TREATMENT FOR 6 MONTHS IN PATIENTS WITH C3 GLOMERULOPATHY (C3G), WITH AN OPEN-LABEL EXTENSION

Author: PPD

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List of Abbreviations

AE	Adverse event
AP	Alternative Pathway (Complement)
AUC_{tau}	Area under the plasma concentration-time curve from time of administration to the end of dosing interval
BLQ	Below the lower limit of quantification
C3G	C3 glomerulopathy
C3GN	C3 glomerulonephritis
CKD-EPI	Chronic kidney disease - Epidemiology collaboration
CL/F	Apparent oral drug clearance
C_{max}	Maximum plasma concentration
CV%	Coefficient of variation
DDD	Dense deposit disease
ECG	Electrocardiogram
EOT	End of treatment
EQ-5D-3L	Three-level version of EuroQol 5 Dimensions questionnaire
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue scale
FAS	Full Analysis Set
KDQOL-SF	Kidney Disease Quality of Life short form questionnaire
LFT	Liver function tests
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
PD	Pharmacodynamic
PK	Pharmacokinetic
QTcF	QT interval corrected using Fridericia's formula

SAP	Statistical Analysis Plan
SD	Standard deviation
TE	Treatment emergent
TEAE	Treatment-emergent adverse event
T_{max}	Time after administration of a drug when the maximum plasma concentration is reached
ULN	Upper limit normal
VAS	Visual analog scale

1 Overview

This statistical analysis plan (SAP) describes in detail the statistical procedures and presentations to be implemented for the data analysis of Study ACH471-204. This version of the SAP (V5.0) will be the final version.

It is noted that changes in protocol amendments 4 and 5 included study objectives (both primary and secondary), study design to increase sample size, and inclusion of adolescents (12 years and older) which had major regulatory impact. Protocol amendment 6 restores initial sample size projections and includes adult patients only, restoring the primary objectives to be the same as in Amendment 3 CCI [redacted] Protocol amendment 7 implements risk mitigations due to the COVID-19 global pandemic. Section 4.4 below briefly summarizes the changes in each protocol amendment.

As stated above, this study has completed enrollment of patients. Twelve (12) patients have been treated which is about two-thirds of the planned sample size of 20. Only descriptive statistical methodologies will be utilized. Inferential comparisons between ALXN2040 (formerly ACH-0144471) and placebo will be considered if deemed meaningful and appropriate from a clinical perspective.

Throughout this document, '6 months of treatment' is synonymous with 'at least 24 weeks of treatment'.

2 Objective

2.1 Primary Objectives

The primary objective of this study is to evaluate the efficacy, relative to placebo, of six months of oral ALXN2040 in patients with C3G based on:

- Improvement in renal biopsy results
- Improvement relative to baseline in proteinuria.

2.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the clinical effect relative to placebo, of six months of oral ALXN2040 in patients with C3G based on slope of estimated glomerular filtration rate (eGFR) relative to baseline over time
- To evaluate the clinical effect, relative to placebo, of six months of oral ALXN2040 in patients with C3G based on change in estimated glomerular filtration rate (eGFR) relative to baseline over time
- Where available, evaluate the change in measured (m) GFR relative to baseline at end of 6 months study drug treatment.
- To evaluate the safety and tolerability of six months of oral treatment with ALXN2040 in patients with C3G by assessing serious adverse events (SAEs).

2.3 Exploratory Objectives

Complement Biomarkers

- To evaluate the change in Complement proteins C3, Bb and Ba (split products) relative to baseline and compare these changes as they relate to clinical outcomes described in primary and secondary objectives.
- To evaluate the PK measures as they relate to complement biomarkers and alternative pathway (AP) inhibition assays (AP Wieslab and AP Hemolysis)
- To evaluate the effect of ALXN2040 therapy on complement biomarkers compared with placebo at 6 months relative to baseline

2.4 Quality of Life Objectives

The quality of life (QoL) objectives of the study are:

- To evaluate kidney disease and health-related quality of life instruments in patients with C3G, over the course of ALXN2040/placebo treatment

3 Endpoints

The following sections intend to provide a list of outcome measures from data collected on efficacy, including pharmacodynamics (PD), safety, and pharmacokinetics (PK) to address the study objectives. The result from qualitative patient interviews will not be included in the study clinical database, and therefore, is not listed below.

Note that the outcome measures to address exploratory objectives are data-dependent and are provided as guide for clinical interpretations.

3.1 Efficacy Outcome Measures

3.1.1 Brief Description of Renal Biopsy Scoring System

A new preliminary renal biopsy scoring system for C3G disease has been developed for use in this proof of concept (POC) study. A single biopsy composite index consisting of three components: activity index, glomerular C3c staining, and glomerular macrophage infiltration, will be used as one of the primary efficacy outcome measures in this study. The chronicity index for C3G disease will also be explored to assess the effectiveness of ALXN2040.

Individual biopsy features as described below are classified into four quantifiable categories. Severity scores of 0, 1, 2, and 3 are assigned to the corresponding four categories for each biopsy feature. Score of 0 indicates the normal state (0 or extremely low quantities) of a particular feature.

The activity index includes five features of the biopsy assessment, each with a possible score of 0 to 3, that are combined to give an overall activity index score ranging from 0 to 15. The corrected activity score was calculated by the central pathologist by assessing each of the following five features in viable glomeruli. A viable glomerulus is one that does not show global sclerosis.

- Endocapillary hypercellularity – defined as the presence of cells in capillary loops with loop occlusion. Each viable glomerulus is evaluated for the percentage of the tuft that has endocapillary hypercellularity and classified the percentages into four categories: 0, 1-25%, 26-50%, and >50%, corresponding to scores 0-3. The overall score is the median of scores of all viable glomeruli involved.
- Neutrophils in capillary lumens - score each viable glomerulus as 0, 1-3, 4-10, >10 corresponding to scores of 0-3. The overall score is the median of scores of all viable glomeruli involved.
- Mesangial hypercellularity – defined as more than 4 cells in a mesangial area away from the hilum (% glomeruli). Score as percentage of viable glomeruli involved: 0, 1-25%, 26-50%, >50% corresponding to scores of 0-3.
- Necrosis - defined as disruption of the glomerular basement membrane with fibrin exudation and karyorrhexis. At least two of these three lesions need to be present to meet the criteria for necrosis (% glomeruli). Score as percentage of viable glomeruli involved: 0, 1-10%, 11-25%, >25% corresponding to scores of 0-3.
- Cellular or fibrocellular crescents (% glomeruli) – Score as percentage of viable glomeruli involved: 0, 1-10%, 11-25%, >25% corresponding to scores of 0-3.

Glomerular C3c staining is scored 0-3 based on the standard semiquantitative score in which negative, 1+, 2+ and 3+ will correspond to scores of 0-3.

Glomerular macrophage infiltration – defined as macrophage counts per glomerulus in a CD68 immunostain. The counts of each glomerulus will be assigned to one of four categories, 0 cell, 1-3 cells, 4-10 cells, >10 cells, corresponding to scores of 0-3. The overall score is the median of scores of all glomeruli involved.

The scores from the above three elements (corrected activity index, glomerular C3c staining and glomerular macrophage infiltration) added to together provides a single **composite biopsy score**, ranging from 0 to 21, and serves as one of the primary efficacy measures.

Chronicity index includes assessment of four lesion types in the biopsy, each with a possible score of 0 to 3; therefore, the total possible scores range from 0 to 12.

- Glomerular sclerosis – defined as % of glomeruli with segmental or global sclerosis. Scores will be based on percentage glomeruli affected: <10%, 10-25%, 26-50%, >50% corresponding to scores of 0-3.
- Fibrous crescents -- defined as % of glomeruli with fibrous crescents. Scores will be based on percentage glomeruli affected: none, <25%, 26-50%, >50% corresponding to scores of 0-3.
- Tubular atrophy – Four categories will be given to assess tubular atrophy, <5%, 6-25%, 26-50%, and >50%, corresponding to scores of 0, 1, 2, and 3.

- Interstitial fibrosis -- Four categories will be given to assess interstitial fibrosis, <5%, 6-25%, 26-50%, and >50%, corresponding score of 0, 1, 2, and 3.

3.1.2 Proteinuria Definitions

Quantitative assessment of proteinuria will be based on two types of urine collection sources in this study, and using both total protein and albumin measurements in urine:

1. 24-hour urine collection samples which will be obtained at Screening, Month 6, Month 12, and Month 24 visits;
2. Spot urine samples which will be collected at protocol specified visit time points.

For 24-hour urine samples, proteinuria will be assessed as the measurements of total protein (mg/day) and albumin (umol/day).

For spot urine samples, proteinuria will be assessed as the ratio of total protein/creatinine and the ratio of albumin/creatinine.

For comparison and quality control of protein measurements for 24-hour urine samples, ratios of protein/creatinine and albumin/creatinine will also be calculated for the samples.

3.1.3 Primary Efficacy Outcome Measures

- Change from baseline in biopsy, based on a score incorporating changes in both the activity index and C3 staining, at the end of 6 months of treatment
- Number and percent of patients with reduction in proteinuria at the end of 6 months of treatment

Reduction is defined as ≥30% decrease in proteinuria (total protein/day) relative to baseline from 24-hour urine collections.

3.1.4 Secondary Efficacy Outcome Measures

- Change and percent change from baseline in proteinuria over 6 months of treatment
- Change and percent change from baseline in eGFR over 6 months of treatment
- Number and percent of patients with significant improvement relative to baseline in eGFR at the end of 6 months of treatment
- Descriptive analysis of slope of GFR from baseline to 6 months
- Descriptive analysis of slope of GFR after 12 months of ALXN2040 therapy

3.1.5 Other Efficacy / PK / PD / Quality of Life Outcome Measures

- Changes in kidney disease and health related quality of life measurements using KDQOL-SF v1.3 and FACIT-Fatigue scale (version 4.0) at 6 months and 12 months of treatment

- Determination of health state values using the 3-level version of the EuroQol 5 dimensions (EQ-5D-3L) questionnaire at 6 months and 12 months of treatment
- Changes in the following biomarkers over the 6 months of treatment: AP activity, CP activity, Factor D, C3, C4, Bb, sC5b-9and other biomarker measurements available from central laboratories.
- Plasma concentrations and pharmacokinetic (PK) parameters on data from C3G patients receiving ALXN2040
- Change and percent change from baseline in measured GFR, based on iohexol clearance, over the 6 months of treatment for patients for whom this data is available.

3.2 Safety Outcome Measures

- Frequency of SAE
- Frequency of AEs leading to discontinuation of the study drug
- Frequency of AEs (related and regardless of relationship to study drug)
- Frequency of laboratory abnormalities by toxicity grade
- Change from baseline on selected laboratory test results over treatment duration
- Change from baseline on parameters of vital signs and weight over treatment duration
- Treatment emergent abnormalities on selected ECG parameters
- Change from baseline on ECG parameters over treatment duration

3.3 Pharmacokinetic (PK) Parameters

- C_{max}, $AUC_{0\text{-}tau}$, and t_{max} for Day 10
- C_{trough} concentrations for other days

4 Study Description

4.1 Study Design

This is a randomized, placebo-controlled, double-blinded (sponsor-open) study with six months (24-28 weeks) of blinded treatment, followed by 6 months of open-label treatment period and up to an additional 21-month long term follow up. The study was planned to include approximately 20 patients with C3 glomerulopathy (C3G) who have not undergone renal transplant. Patients are randomized 1:1 to ALXN2040 or placebo, stratified by the disease diagnosis: dense deposit disease (DDD) and C3 glomerulonephritis (C3GN).

Patients must have biopsy-confirmed diagnosis of either DDD or C3GN and significant proteinuria, defined as ≥500 mg/day of protein in a 24-hour urine, that is attributable to C3G in the opinion of the principal investigator.

Study eligibility requires an adequate renal biopsy sample for evaluation by all three standard modalities: light microscopy, electron microscopy, and immunofluorescence. In addition, patients must have the diagnosis of DDD or C3GN for at least 3 months prior to dosing, unless otherwise approved by the sponsor.

All patients must be vaccinated against *Haemophilus influenzae* (*H. influenzae*), *Streptococcus pneumoniae* (*S. pneumoniae*), and *Neisseria meningitidis* (*N. meningitidis*) according to national and/or local guidelines to minimize the risk of serious infection with an encapsulated organism, unless precluded by local vaccination guidelines, licenses, or availability.

The starting dose of ALXN2040 is 100 mg TID, a total dose of 300 mg per day. After two weeks of treatment, dosing is escalated to 200 mg TID. Additional dosage regimens may be investigated if supported by emerging data from this and other clinical studies.

Safety, efficacy (including biopsy results, PD biomarkers, and three kidney disease and health related quality of life instruments), and PK assessments are carried out at pre-specified time points throughout treatment and post-treatment follow up period. Note that renal biopsy is performed pre-treatment, at the end of blinded dosing period (between Week 26 and Week 28), and optionally at Week 52 and Week 104.

In addition, qualitative exploratory interviews are conducted by independent outcomes researchers chosen by the Sponsor with patients prior to initiation of study treatment (during the screening period) and at the end of study treatment administration (Week 28) to collect patients' experience of their disease and treatment, its impact on everyday lives, and the disease trajectory over the course of ALXN2040/placebo treatment.

The primary analysis will occur after all patients complete the Week 28 visit or withdraw from the study early.

4.2 Treatment Assignment

Patients are randomized 1:1 to either active treatment (ALXN2040) or placebo, stratified by disease diagnosis, DDD and C3GN.

A web-based centralized randomization scheme, stratified by disease diagnosis, is used to provide treatment assignment of either ALXN2040 or placebo to each patient. Prior to randomization, each patient is assigned to one of the two disease diagnoses, DDD or C3GN, based on the biopsy results. The randomization block design is utilized within each stratum. In addition, the randomization schedule may also be provided to the bioanalytical laboratory responsible for analysis of PK samples.

4.3 Blinding and Unblinding

Randomized treatment assignment will be double-blind and placebo-controlled for ALXN2040. The study sites and the patients are blinded to treatment assignment during the blinded treatment period. Although all patients receive active drug during the open-label extended treatment period, the first portion of the study is not unblinded until all patients have completed the blinded treatment period. Designated staff of Achillion Pharmaceuticals, Inc. will be unblinded to the treatment assignments. In

addition, a member (or designate) of the Bioanalytical Science section will be unblinded to treatment assignments in order to minimize unnecessary analysis of samples from patients receiving placebo.

4.4 Protocol Amendments

Amendment No.	Amendment Date	Main Purposes of Amendment
1	25-OCT-2017	• Allow visits on Weeks 14, 18, 22, and 26 to be conducted by phone rather than in the clinic, at the discretion of the investigator, in order to reduce the burden on patients in the study.
2	12-DEC-2017	• Allow investigators who wish to do so to collect measured GFR in addition to the existing eGFR calculations. • The contraception requirements are being modified to align with updated Achillion standard wording, and SAE reporting contact information is being updated.
3	07-MAR-2018	• Change improvement in eGFR from a primary to a secondary objective and to align endpoints with this change. • Adjust inclusion/exclusion criteria related to complement components in order to facilitate enrollment of suitable patients. • Remove the planned collection PK profile samples on Day 3 in order to reduce the burden on patients. • The contraception requirements are being modified to align with updated Achillion standard wording. • Vaccination procedures are being updated to refer to national and/or local guidelines, minor wording changes are being made for clarity.
4	02-NOV-2018	• Allows the inclusion of adolescents • Expands enrollment to 45 patients enrolled after approval of Amendment 4, and changes the randomization to 2:1 ALXN2040 or placebo • Makes the collection of renal biopsy samples optional, and changes the improvement in biopsy score from a primary to an exploratory objective • Makes the study sponsor-blinded, in addition to the patients and investigators being blinded • Makes changes to the inclusion and exclusion criteria to better reflect the intended patient population and to facilitate enrollment • Reduces sample collection and adds flexibility to the collection schedule to reduce the burden on patients • Adds a 6-month open-label treatment period after the blinded treatment period

Amendment No.	Amendment Date	Main Purposes of Amendment
5	15-FEB-2019	• Makes changes to the inclusion and exclusion criteria to better reflect the intended patient population and to facilitate enrollment • Changes the dose escalation strategy, so that all patients will escalate after 2 weeks • Reduces sample collection and adds flexibility to the collection schedule to reduce the burden on patients (including making collection of renal biopsies an optional sub-study)
6	05-JUN-2019	• Makes changes to the inclusion and exclusion criteria to remove the allowance of adolescents in the study population • Reduces sample collection and adds flexibility to the collection schedule to reduce the burden on patients • Removes the biopsy sub-study option (all patients had biopsy-confirmed diagnosis) • Extends the study to Week 104 (addition of a 12-month long-term follow-up period) • Removes DSMB since the study is only blinded to the Investigator, site staff and patient (Sponsor not blinded) • Reduces the number of in-clinic study visits by having the ability to do visits as phone calls • Reduce the number of expected patients to 20
7	15-MAY-2020	• Increases duration of study treatment • Allows home and telephone visits, local laboratory testing, and study drug to be sent directly to patient's home when clinic visits are not possible due to COVID-19 global pandemic • Allows optional renal biopsy at Week 52 and Week 104 to be postponed due to COVID-19 global pandemic, and to be performed when possible • Updates contraceptive language to align with most recent Investigator Brochure

5 Sample Size

The planned sample size of 20 patients, 10 each of ALXN2040 and placebo, was determined based on very limited clinical cases of C3G patients to evaluate the effectiveness of ALXN2040.

6 Analysis Sets

6.1 Randomized Analysis Set

All patients who are randomized and are assigned to either ALXN2040 or placebo will be included in this analysis data set.

6.2 Full Analysis Set (FAS)

All randomized patients receiving at least one dose of study drug, ALXN2040 or placebo, will be included in the full analysis set. Data from patients in FAS will be used for efficacy, safety, and pharmacodynamic (PD) analyses. However, for pharmacokinetic (PK) analysis, only data from patients receiving ALXN2040 will be utilized.

7 Statistical Analyses

Statistical analyses and data presentations are performed using the using Statistical Analysis System® (SAS®) Version 9.4 or higher (SAS Institute Inc., Cary, NC, USA) or other validated statistical software.

7.1 General Methods

Data will be summarized separately for the 6-Month Blinded Treatment Period and Open-Label Extension and Long-Term Follow-up Periods.

Data listings by patient identification will be provided for all data, including efficacy, safety, PD, and PK parameters.

To summarize continuous data, descriptive statistics will include: number of patients, mean, standard deviation, median, minimum, and maximum. For the calculation of summary statistics and analysis, unrounded data will be used.

To summarize categorical data, frequency counts and percentages will be presented.

Only descriptive statistical procedures, including graphic presentations, will be performed on the efficacy, safety, and other outcome measures, unless otherwise specified. No statistical comparisons between ALXN2040 and placebo will be provided.

Missing data for QoL instruments will be handled as specified in the instructions for each instrument (see Appendix). All other data will be summarized for observed cases, with no imputation for missing data.

Although the study is randomized by stratification factor of disease diagnosis, statistical analysis procedures and presentations will not take into consideration the stratification factor. Due to small sample size of this study, the stratified randomization process is utilized to balance the treatment assignments across the two disease diagnoses.

Longitudinal summaries of efficacy and safety parameters use pre-defined visit Week / Day as described in Appendix 1, schedule of assessment, of the protocol. It should be noted that some patients enrolled using later versions of protocol amendments will have reduced scheduled visits. Longitudinal summary presentations may have different number of patients at various scheduled visits.

For longitudinal summaries of data, windows around planned measurement times are based on the midpoint between planned study visits unless specified otherwise. If there are multiple measurements within the same window, use the value in the visit window closest to the day of the planned visit for each time point (as determined by the absolute difference in days between the planned visit and the collection date, and the absolute difference in days between the planned visit and the assay date).

For laboratory test results, when both local and central laboratory values are collected on the same date, the central laboratory value will be used.

Baseline values for efficacy / PD and safety parameters are defined as the last measurement, including unscheduled visits, prior to first dose of study drug.

7.2 Study Population

7.2.1 Patient Discontinuation and Disposition

The patient disposition summary table(s) will include the following:

- Number of patients (randomized / treated)
- Number of patients who completed 28 weeks of dosing
- Reasons for not completing 28 weeks of dosing
- For patients entering open-label period of the study:
    - Number of patients who have reached Week 52
    - Reasons for not completing the open-label study period
- For patients entering dose tapering phase of the study:
    - Number of patients who completed dose tapering
    - Reasons for not completing dose tapering

In addition, a summary of study visits will be provided including the number of patients who complete each visit as planned and the number of patients who complete modified study visits. A patient listing will detail the reason for modified visit as well as the assessments that were modified and the modification.

7.2.2 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized by ALXN2040 and placebo:

- demographics: age, gender, race, country

- physical measurement at baseline: height, weight, BMI, BP
- disease characteristics at baseline: disease diagnosis, duration of the disease, biopsy results, proteinuria, eGFR
- selected PD markers and laboratory tests at baseline: 24-hour urine protein, 24-hour protein/creatinine, 24-hour albumin/creatinine, spot urine protein/creatinine, spot urine albumin/creatinine, serum albumin, and serum creatinine.
- prior medications: use of ACE inhibitors or ARB drugs or immunosuppression (IS) medications.

7.2.3 Medical History

Medical history will be coded with the most current version of Medical Dictionary for Regulatory Activities (MedDRA®) and will be summarized by preferred term and system organ class by treatment group of ALXN2040 and placebo.

7.3 Extent of Exposure

Treatment durations will be computed for each patient as (last date of dose – first date of dose + 1). The last date of dose will be the end date of 12-month treatment period.

If patients enter the 7-day dose taper schedule, duration of tapering dosing period may also be provided as a separate computation. The duration will be calculated similarly as (last date of taper dose – first date of taper dose +1).

Treatment duration will be summarized by ALXN2040 and placebo.

Compliance with study drug was collected as number of tablets dispensed and number of tablets returned beginning in July 2019, after patients had already been enrolled and completed study visits. The number of tablets taken during this time period will be derived from the number recorded as dispensed at the current visit minus the number recorded as returned at the next consecutive visit. A patient listing of number of tablets taken by visits during this time period will be provided by treatment group. A separate patient listing will be provided including study drug compliance during this time period as derived by:

Compliance = (# tablets taken / # tablets assigned) * 100.

In addition, a summary of missed doses due to COVID-19 will be provided by treatment group.

7.4 Concomitant Medications

Concomitant medications are summarized by ALXN2040 and placebo. These are medications taken any time on or after the first active dose of study therapy. Medications are presented alphabetically by anatomic class, therapeutic class and generic name using the most recent version of WHO dictionary.

Separate summary tables may be provided for allowable concomitant medications for C3G patients.

7.5 Efficacy and PD Markers Assessment

7.5.1 Analysis of Primary Efficacy Outcome Measures

The analysis methods described below utilize data from patients in FAS.

Composite Biopsy Score

Change and percent change from baseline for the composite biopsy score at the end of 6 months and 12 months of treatment will be computed for each patient.

Difference in mean changes from baseline between ALXN2040 and placebo group will be presented. Means from original scores at baseline and each visit will also be presented.

Proteinuria

Number and percent of patients with reduction in proteinuria relative to baseline as defined in section 3.1.3 will be summarized by ALXN2040 and placebo.

In addition to the primary analysis of the primary efficacy endpoints, a sensitivity analysis will be performed excluding patients who had modified assessments due to COVID-19 to assess the robustness of the results.

7.5.2 Analysis of Secondary Efficacy Outcome Measures

In addition, change and percent change from baseline for proteinuria from a 24-hour specimen at each visit will be computed for each patient based on 24 hour urine protein, 24 hour urine albumin, 24 hour urine protein/creatinine ratio, 24 hour urine albumin/creatinine ratio, spot urine protein/creatinine ratio, and spot urine albumin/creatinine ratio.

Difference in mean changes from baseline between ALXN2040 and placebo group will be presented. Means from original scores at baseline and each visit will also be presented.

Change and percent change from baseline for eGFR at each pre-defined time point will be computed for each patient.

Difference in mean changes from baseline between ALXN2040 and placebo group will also be presented.

Number and percent of patients with significant improvement relative to baseline (ie, ≥20% increase from baseline) in eGFR will be summarized by ALXN2040 and placebo for each visit.

As stated in Section 3.1.4, descriptive analysis on slope of eGFR over 6-month blinded treatment period will be performed. Graphic presentation on eGFR measurements over time will be provided to observe the trend and profile of the effect of ALXN2040 on change of eGFR. The time-measurement graph will be provided for each patient. Mean time-measurement graph by treatment, ACH0144471 and placebo, will also be available for visual examination and interpretation.

The descriptive measure of slope will be estimated using a simple linear regression for each patient with eGFR as the dependent variable and time as the independent variable. The mean slope (mL/min/1.73 m^2 per month) will be summarized descriptively by treatment group.

In addition, the number and percentage of patients who achieve the following response statuses will be summarized at the end of 6 months and at the end of 12 months by ALXN2040 and placebo:

- Complete response, defined as proteinuria <500 mg/d based on 24-hour urine samples plus stable eGFR (ie, less than 25% decrease from baseline)
- Partial response, defined as ≥30% decrease from baseline in proteinuria but not <500 mg/d based on 24-hour urine samples plus stable eGFR (ie, less than 25% decrease from baseline)
- Worsening, defined as >25% decrease from baseline in eGFR or >30% increase from baseline in proteinuria based on 24-hour urine samples

The number and percentage of patients who achieve partial response based on 24-hour urine protein/creatinine ratio and spot urine/protein creatinine ratio, defined as ≥30% decrease from baseline in proteinuria plus stable eGFR (ie, less than 25% decrease from baseline), will also be summarized at each visit by treatment group.

The number and percentage of patients who achieve worsening based on 24-hour urine protein/creatinine ratio and spot urine/protein creatinine ratio, defined as >25% decrease from baseline in eGFR or >30% increase from baseline in proteinuria, will also be summarized at each visit by treatment group.

7.5.3 Analysis of Other Efficacy Outcome Measure and PD Markers

Original values and changes from baseline at each pre-defined time point will be computed for each patient and will be summarized by ALXN2040 and placebo for the following outcome measures as listed in Section 3.1.5.

- AP activity
- CP activity
- Factor D
- C3
- C4
- Bb
- sC5b-9

For Wieslab test results (AP activity), only original values will be used for summary tables.

Graphic presentations for the longitudinal data may also be provided for the above outcome measures if clinically deemed meaningful.

The patient report outcomes (PRO) instruments listed in section 3.1.5 will be described in the next section.

Section 7.8 below describes in detail on PK data presentation and analysis methods.

7.6 Patient Report Outcomes (PRO)

Three PRO instruments are used to evaluate kidney disease and health related quality of life on patients with C3G. The following sections briefly describe the utility and interpretation of these instruments. Details of computing and summarizing the scores and/or scales can be found in the respective user manuals.

The PRO presentations utilize data from patients in FAS.

7.6.1 KDQOL-SF™ version 1.3

The kidney disease quality of life short form (KDQOL-SF™) is a widely used health-related quality of life (HRQOL) measure for patients with chronic kidney diseases. The questionnaire consists of the generic SF-36 as well as 11 multi-item scales focused on quality of life issues specific to patients with kidney disease. Two of the eleven (11) subscales of the kidney disease (KD) targeted areas are for patients requiring kidney dialysis and, therefore, are excluded from questionnaire for this study. The remaining 9 KD targeted areas are:

- symptoms/problems
- effects of kidney disease
- burden of kidney disease
- work status
- cognitive function
- quality of social interaction
- sexual function
- sleep
- social support

The generic 36-item health survey, SF-36, consists of two component summaries with their respective domains.

- Physical Component Summary (PCS)
    - Physical functioning
    - Role-physical
    - Pain
    - General health
- Mental Component Summary (MCS)

- Emotional well-being
- Role-emotional
- Social function
- Energy/fatigue

The questionnaire items included in each of SF-36 domains and KD targeted areas are listed in Appendix 2.

The scoring procedure for the KDQOL-SF™ first transforms the raw pre-coded numeric values of items to a 0-100 possible range, with higher transformed 'scale scores' always reflecting better quality of life. Each item is put on a 0 to 100 range so that the lowest and highest possible scores are set at 0 and 100, respectively. Details of transforming each item score to corresponding scale are provided in the KDQOL-SF user manual.

Original values and change from baseline values over time will be summarized by treatment group at protocol-specified time points. Patient listings on score scales will be provided for each of KD targeted areas and SF-36 domains.

7.6.2 FACIT Fatigue Scale (Version 4)

There are 13 items in the FACIT Fatigue scale questionnaire. Each item includes 5 possible responses, 0-4, with 0 being "Not at all" and 4 being "Very much". Total score from these 13 items will be provided for each patient at each protocol pre-defined time points.

Negatively stated items must be reversed before being added to obtain the scale total score. Therefore, the negatively stated items will be reversed by subtracting the response from "4". Note that all items, except for items #7 and #8, are negatively stated.

The FACIT Fatigue scale and the calculation of total score are presented in Appendix 3 of this document. Note that the total score range is 0 to 52, with higher total scored indicating better quality of life.

Original values and change from baseline values over time will be summarized by treatment group at protocol-specified time points. Patient listings for total score and change from baseline in total score will be provided for protocol-specified time points.

7.6.3 EQ-5D-3L

The self-reported questionnaire EQ-5D-3L has two parts. The first part is a descriptive system with 5 dimensions: mobility, self-care, usual activities, pain / discomfort, and anxiety / depression. Each dimension has three response levels, 1, 2, and 3, representing "no problems", "some problems", and "extreme problems", respectively. A scoring function can be used to convert the self-reported descriptive system to a single summary index (EQ-5D Index score) through a set of population-based preference weights.

The second part is a visual analog scale (VAS) which records patient's self-rated health status on a graduated (0–100) scale, with higher scores for higher heath related quality of life. The EQ-5D, therefore, produces three types of data for each patient:

- a profile indicating the extent of problems on each of the five dimensions;
- a population preference-weighted health index score based on the descriptive system;
- a self-reported assessment of health status based on the EQ-VAS

For this study, the U.S. population weights will be used to convert the descriptive system to an EQ-5D index score on a scale where 1.0 = perfect health and 0 = death.

Original values and change from baseline values over time will be summarized by treatment group at protocol-specified time points. Patient listings will be provided for the responses of 5-dimension descriptive system, EQ-5D-VAS, and U.S. population-based EQ-5D index.

7.7 Safety Assessment

Evaluation of safety includes assessment of the following clinical parameters and will be described in detail in the subsequent subsections. Safety data collected during blinded treatment period of the study (up to and include Week 28 visit) will be summarized separately from safety data collected during the open-label treatment period. Selected clinical laboratory parameters will be summarized. However, all laboratory test results will be included in the listings.

1. Treatment emergent adverse events (total as well as as related versus unrelated), including discontinuations due to adverse event
2. Clinical laboratory parameters
3. 12-lead ECG
4. Vital signs
5. Body weights
6. Physical findings

In addition, a listing of patients with known exposure to COVID-19 will be provided.

7.7.1 Treatment-Emergent Adverse Events (TEAE)

Adverse events (AEs) will be coded with the most current version of Medical Dictionary for Regulatory Activities (MedDRA®).

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges during treatment with ALXN2040 or placebo, having been absent pre-treatment, or worsens relative to the pre-treatment state.

If an AE that was reported during treatment increases in severity, then that AE is given a resolution date and time and a new record initiated with the new severity. If the severity of an AE remains the same or decreases, the AE will be kept open through to resolution, reflecting the maximum severity.

AEs will be listed by patient including preferred term, verbatim term, system organ class (SOC), days from first dosing date, onset and resolution dates/times, duration, frequency, severity, seriousness, outcome, action taken, and relationship to study drugs.

TEAEs will be summarized by preferred term and SOC by treatment group for the number of patients reporting the TEAE, the number of TEAEs reported, and the number of events by severity and relationship to study drugs. In addition, TEAEs will be summarized by decreasing order of frequency . Summaries of TEAEs include both non-serious and SAEs as defined in the protocol. Additionally, all SAEs, regardless of treatment emergent or not, will be listed in tabulated form. Summary of all SAEs, regardless of treatment emergent or not, will be provided if necessary, for ease of interpretation of the data. AEs with missing severity are included only in summaries of all severity grades (related or regardless of relationship to study drug). If a patient had an AE with different severities during treatment, then only the greatest severity is reported, unless otherwise specified.

It is not anticipated to encounter AE with missing start date in this study. Any AE with missing start date will be treated as TEAE.

All events captured in the database will be listed in by-patient data listings. However, only TEAEs will be summarized. Separate patient listings will be provided for TEAEs and pre-treatment AEs. If any patients report known exposure to COVID-19 during the study, a listing of all adverse events experienced by these patients will be provided separately.

Should any serious adverse events (SAEs) or discontinuation of study drug due to adverse events (TEAE or SAE) occur, patient listings for such adverse events will be displayed in a tabulated format and narratives will be included in the study report. If no such event occurs during the study, the tables should provide a statement clearly indicating as such, e.g. 'No SAE reported', 'No TEAE led to discontinuation of study drug'.

7.7.2 Clinical Laboratory Parameters

Descriptive statistics will be provided, at a minimum, for the following laboratory test results of hematology, serum chemistry, urinalysis, and coagulation tests as listed in Table 6 of the protocol. Descriptive statistics may be provided for additional laboratory parameters, if clinically warranted.

- hematocrit (Hct), hemoglobin (Hgb), mean corpuscular volume (MCV), platelet count, and WBC count
- all chemistry laboratory test results
- pH, specific gravity
- PT/PTT/INR

Levels and changes from baseline in the laboratory measurements will be summarized at baseline and at pre-defined visits by treatment group. Baseline is the last assessment before the first dose of study drug, including unscheduled assessments.

As noted in Section 7.1, when both local and central laboratory values are collected on the same date, the central laboratory value will be used. Laboratory parameters are summarized based on values and units from laboratory reports. Selected lab parameters may be converted to SI or US standard units, as clinically deemed appropriate. Laboratory abnormalities are determined from laboratory measurements analyzed at the central or local laboratories and are graded using Common Terminology Criteria for Adverse Events (CTCAE), as presented in Appendix 1 of this document.

For laboratory tests with CTCAE toxicity grades available, laboratory abnormalities are summarized by worst treatment-emergent grade [treatment emergent (TE) lab abnormalities]. For tests that have CTCAE toxicity grades in both high and low directions, e.g. serum glucose, etc., the summary table should specify separately for the TE abnormalities as being high or being low in toxicity grades. Note that the post-baseline laboratory value with the highest treatment-emergent toxicity grade is reported for each test.

Shift tables will be provided for liver function test (LFT) results and other selected laboratory test results based on CTCAE grades. In addition, shift tables based on multiple of upper limit normal (ULN) will also be produced for LFT measurements.

Laboratory abnormalities during treatment period will be further summarized by baseline toxicity grade and treatment therapy (shift tables).

Exploratory graphic presentations may be provided when data indicate that such analyses are appropriate and clinically meaningful.

7.7.3 12-lead ECG

Patient listing will be provided for ECG parameters: HR, RR, PR interval, QRS interval, QT interval, and QTcF. The abnormal and clinically significant findings will also be included in the listing.

Values and changes from baseline in ECG measurements are summarized at baseline and at each scheduled time points for the two treatment groups. Baseline ECG is the last assessment before first dose of study drug.

ECG results will also be classified as normal, abnormal (not clinically significant), and abnormal (clinically significant). Summary table will be provided for clinically significant abnormalities by treatment group. If no clinically significant abnormalities are found, the table should state 'No clinically significant ECG abnormality reported'.

The treatment-emergent (TE) ECG events indicate that the abnormality / prolongations were not present at baseline. TE abnormalities will be summarized for the following parameters. Note that TE QTcF interval abnormalities are based on modified CTCAE criteria.

- Treatment-emergent (TE) PR interval > 200 msec;

- TE QTcF interval:
    - Grade 1: 450 – 480 msec
    - Grade 2: 481 – 500 msec
    - Grade 3: ≥ 501 msec or > 60 msec change from baseline

The maximum interval (or increase from baseline) during blinded treatment period is reported for each ECG parameter.

7.7.4 Vital Signs and Body Weights

Patient listing will be provided for vital signs parameters: body temperature, systolic and diastolic blood pressures in triplicate, heart rate, and respiration rate. For systolic and diastolic blood pressures, average of triplicate readings will be computed for each time point.

Body weights are taken at the same time points as vital signs and will be included in the listing.

Summary of changes from baseline at individual time points will be provided for each parameter of vital signs and body weight. Blood pressures, both systolic and diastolic, are of particular interest for C3G patients. Additional analysis and presentations may be required if clinically deemed meaningful.

7.7.5 Physical Exam

Data collected from physical exams, both complete and brief, will be listed by patient and by time points, including unscheduled visit time points.

7.8 Pharmacokinetic (PK) Assessments

PK assessments will be performed on plasma concentrations from patients included in PK analysis set whose PK profiles can be determined.

7.8.1 PK Parameters

PK parameters from plasma concentrations for ALXN2040 will be calculated using a non-compartmental approach based on the concentration versus time data. The parameters listed in the table below will be obtained using Phoenix WinNonlin® Version 6.4 or higher, as data permit.

Patients for whom there is insufficient data to calculate the PK parameters will have available data included in the concentration tables with descriptive statistics only.

For the calculation of the PK parameters, concentrations that are below the lower limit of quantification (BLQ) prior to the Tmax will be set to 0 and those thereafter as missing. Concentrations that are missing or not reportable will be treated as missing values. For concentration summary statistics, concentrations that are BLQ will be set to 0. At least 3 time points with measurable concentration will be required for the calculation of AUC.

For Day 10, the following PK parameters will be estimated:

Parameter	Definition/Calculation
AUC_{tau}	Area under the plasma concentration-time curve from time of administration to the end of dosing interval, calculated by linear trapezoidal summation
C_{max}	Maximal plasma concentration
C_{trough}	Plasma trough (pre-dose) concentration over the dosing interval for the first daily dose
T_{max}	Time to reach the maximal plasma concentration
CL/F	Apparent oral drug clearance during a dosing interval, calculated as $Dose/AUC_{tau}$

AUC values will be estimated using the linear trapezoidal rule. Actual sampling times relative to dosing will be used in the computation.

Unless otherwise specified below, missing sampling or concentration values should not be imputed, but left missing in the calculation of derived PK parameters. If the actual sampling time is missing, but a valid concentration value has been measured, the scheduled protocol time will be used for the calculation of derived PK parameters.

On a case by case basis, it may be necessary to exclude individual PK concentration values for the calculation of derived PK parameters because they are erroneous, abnormal or appear implausible to the pharmacokineticist in charge of the analysis. Any excluded data will be flagged in the individual data listings. The reason for exclusion will also be documented. If the exclusion has a meaningful impact on the overall interpretation of the results, then it will be discussed.

Actual post-dose time will be used in calculation of PK parameters and in the generation of individual concentration-time profiles. Scheduled (nominal) sampling times will be used as a replacement for unknown or missing actual times and will be used for the pre-dose values. Nominal sampling times will be used in the generation of summary concentration-time profiles and the concentration-time listings.

In addition, the trough concentrations at protocol specified visits will be provided.

7.8.2 PK Analysis

Individual PK parameters will be listed. Descriptive statistics (number of non-missing observations (N), arithmetic mean, SD, median, coefficient of variation (CV%), minimum, maximum, geometric mean and geometric CV%) will be used to summarize the calculated PK parameters of ALXN2040.

Individual concentration profiles with actual post-dose time will be listed. Descriptive summary statistics (N, arithmetic mean, SD, median, CV%, minimum, maximum, geometric mean and geometric CV%) will be used to summarize the concentration profiles.

Individual time-concentration graphs will be provided for each patient in both linear and semi-log scales. Mean time-concentration graphs will also be provided.

7.8.3 Pre-Dose Concentrations (PK Troughs)

All individual pre-dose plasma concentrations (troughs) will be listed. Descriptive statistics (number of non-missing observations (N), arithmetic mean, SD, median, coefficient of variation (CV%), minimum, maximum, geometric mean and geometric CV%) will be used to summarize these concentrations of ALXN2040.

8 Changes from Protocol Specified Analysis

The protocol specifies using two-sample t-test for continuous outcome measures and Fisher's Exact test for categorical outcome measures to compare the difference between ALXN2040 and placebo. Ninety-five percent (95%) confidence intervals are also part of inferential statistical methodologies that protocol specifies. As described in Section 1 Overview and Section 7.1 General Methods, only about two-thirds of 20 patients are treated in this study, so descriptive statistics are sufficient and appropriate for interpreting the study results and obtaining a reasonable clinical understanding of C3G disease.

9 Document History

Version No.	Author(s)	Descriptions
1.0	Joanna Yang	Original version dated 18SEP2017
2.0	Joanna Yang	Incorporate the following changes (dated 20APR2018): • Update the first paragraph of Section 1 Overview; • Modify the second bullet of primary objectives in Section 2.1; • Have removed the first bullet of secondary objectives in Section 2.2; • Add last bullet of other objectives in Section 2.3; • Simplify the score for glomerular sclerosis of chronicity index in Section 3.1.1; • Modify and update the primary, secondary, and other efficacy outcome measures in Sections 3.1.3, 3.1.4, and 3.1.5 to be consistent with the objectives of the protocol amendment 3; • Modify and update the study design Section 4.1 to be consistent with the protocol amendment 3; • Change the placebo dose adjustment algorithm from Day 3 and Day 10 to Day 7 and Day 14, respectively, (as indicated in the Schedule of Assessment of the protocol) in Section 4.3; • Describe briefly the purposes for each protocol amendment in Section 4.4; • Remove proteinuria analysis set from Section 6; • Modify statements and wording in Section 7.5 to align with the efficacy outcome measures in Sections 3.1.3-5; • Modify the treatment emergent abnormality categories for ECG parameter QTcF, following the CTCAE severity grades, in Section 7.7.3; • Update PK analysis Section 7.8, removing references to Day 3.
3.0	Joanna Yang	Incorporate the following changes (dated 21NOV2019 and 09DEC2019): • Update Section 1 Overview, emphasize the SAP being applicable to data collected during 6 months of blinded treatment period; • Modify and update the format and bullet description of Sections 2.2, 2.3, and 2.3 to align with the format and bullet contents with protocol amendment 6; • Modify and update the secondary, and other efficacy outcome measures in Sections 3.1.3, 3.1.4, and 3.1.5 to be consistent with the objectives of the protocol amendment 6;

Version No.	Author(s)	Descriptions
		• Section 3.1.3, the improvement of proteinuria has been changed from 50% to 30%; • Add all biomarker measurements available from central laboratories in the Section 3.1.5, third bullet; • Modify and update study design section 4.1 in accordance with amendment 6; • Describe briefly the purposes for protocol amendments 4, 5, and 6 in Section 4.4; • Remove eGFR analysis set from Section 6; • Add Evaluable analysis set in Section 6; • Remove the statement of inferential statistical analysis procedures for selected efficacy outcomes from Section 7.1; • Add description on visit window definition in the third paragraph from the end of Section 7.1; • Add the list of baseline biomarker and lab tests to Section 7.2.2; • Add prior medications of interest to C3G clinical studies in Section 7.2.2; • Remove paragraphs stating statistical methods of comparing two treatment groups in Section 7.5; • Update the descriptive analysis of secondary and exploratory outcome measures in Sections 7.5.2 and 7.5.3; • Add Section 7.8.3 Pre-Dose Concentrations (PK Troughs).
4.0	Kara Rice	• Add clarity around timing of primary analysis • Update biopsy scoring details based on final scoring manual • Updated description of endpoints to match latest protocol version • Clarify duration of blinding for study sites and patients per protocol • Update definition of per-protocol set to specify excluded protocol deviations • Clarified approach to handling missing data • Removed summary of treatment compliance for interim analysis. • Updated calculation of eGFR slope to include all available data • Add summary of response statuses based on composite definitions including eGFR and proteinuria • Clarify planned analyses for PRO endpoints
5.0	Kara Rice	• Updated to include analyses for Open-Label Extension and Long-Term Follow-up Periods • Updated to align with Protocol Amendment 7 • Removed per protocol set given small sample size • Added summaries of modified study visits and missed doses due to COVID-19 pandemic • Added summary of treatment compliance • Added sensitivity analysis for primary efficacy and safety endpoints to assess impact of COVID-19 pandemic

Appendix 1. Grading the Severity of Laboratory Values

The Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (v4.03: June 14, 2010) does not provide a separate laboratory toxicity grading table. All the laboratory grades are part of the descriptions within various system organ classes (SOCs). The following table has been created as SAS programming specifications for producing tables and listings for clinical study report. The criteria for each grade are the same as in CTCAE descriptions.

Grading the Severity of Laboratory Values, Unmodified from CTCAE, Version 4.0 (v4.03: June 14, 2010)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 LIFE-THREATING
CHEMISTRIES				
Acidosis	pH < normal, but ≥7.3	-	pH <7.3	Life-threatening consequences
Albumin, Low	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated
Alkaline Phosphatase, High	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Alkalosis	pH > normal, but ≤7.5	-	pH >7.5	Life-threatening consequences
ALT, High	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Amylase, High	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN
AST	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Bilirubin, High	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
Calcium, High	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L
Calcium (Ionized), High	Ionized calcium >ULN - 1.5 mmol/L	Ionized calcium >1.5 - 1.6 mmol/L	Ionized calcium >1.6 - 1.8 mmol/L	Ionized calcium >1.8 mmol/L
Calcium, Low	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L
Calcium (Ionized), Low	Ionized calcium <LLN - 1.0 mmol/L	Ionized calcium <1.0 - 0.9 mmol/L	Ionized calcium <0.9 - 0.8 mmol/L	Ionized calcium <0.8 mmol/L
Creatine Kinase, High	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN
Creatinine, High	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 LIFE-THREATING
eGFR or CrCl	<LLN - 60 ml/min/1.73 m^2 or proteinuria 2+ present; urine protein/creatinine >0.5	59 - 30 ml/min/1.73 m^2	eGFR or CrCl 29 - 15 ml/min/1.73 m^2	eGFR or CrCl <15 ml/min/1.73 m^2
Glucose, *Fasting , High*	>ULN - 160 mg/dL; >ULN - 8.9 mmol/L	>160 - 250 mg/dL; >8.9 - 13.9 mmol/L	>250 - 500 mg/dL; >13.9 - 27.8 mmol/L;	>500 mg/dL; >27.8 mmol/L
Glucose, Low	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L
GGT, High	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Lipase, High	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN
Lipid Disorders, Cholesterol, High	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L
Triglycerides, High	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L
Magnesium, High	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L
Magnesium, Low	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L
Phosphate, Low	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L	<1.0 mg/dL; <0.3 mmol/L;
Potassium, High	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L
Potassium, Low	<LLN - 3.0 mmol/L	-	<3.0 - 2.5 mmol/L;	<2.5 mmol/L
SODIUM, High	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
SODIUM, Low	<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L
URICACID	>ULN - 10 mg/dL (0.59 mmol/L)	-	-	>10 mg/dL; >0.59 mmol/L
HEMATOLOGY				
CD4 Lymphocytes decreased	<LLN - 500/mm^3; <LLN - 0.5 x 10^9 /L	<500 - 200/mm^3; <0.5 - 0.2 x 10^9 /L	<200 - 50/mm^3; <0.2 - 0.05 x 10^9 /L	<50/mm^3; <0.05 x 10^9 /L

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 LIFE-THREATING
(Absolute) Lymphocyte Count, low	<LLN - 800/mm^3; <LLN - 0.8 x 10^9 /L	<800 - 500/mm^3; <0.8 - 0.5 x 10^9 /L	<500 - 200/mm^3; <0.5 - 0.2 x 10^9 /L	<200/mm^3; <0.2 x 10^9 /L
Absolute Neutrophil Count (ANC), low	<LLN - 1500/mm^3; <LLN - 1.5 x 10^9 /L	<1500 - 1000/mm^3; <1.5 – 1.0 x 10^9 /L	<1000 - 500/mm^3; <1.0 - 0.5 x 10^9 /L	<500/mm^3; <0.5 x 10^9 /L
Fibrinogen, Decreased	<1.0 – 0.75 x LLN or <25% decrease from baseline	<0.75 – 0.5 x LLN or 25 - <50% decrease from baseline	<0.5 – 0.25 x LLN or 50 - <75% decrease from baseline	<0.25 x LLN or 75% decrease from baseline or absolute value <50 mg/dL
Hemoglobin, Low	Hgb<LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated
INR, High (not on anticoagulation therapy)	>1 - 1.5 x ULN;	>1.5 - 2.5 x ULN;	>2.5 x ULN; >2.5	-
INR, High (on anticoagulation therapy)	>1 - 1.5 times above baseline	>1.5 - 2.5 times above baseline	>2.5 times above baseline	-
Platelets, Decreased	<LLN - 75,000/mm^3; <LLN -75.0 x 10^9 /L	<75,000 - 50,000/mm^3; <75.0 -50.0 x 10^9 /L	<50,000 - 25,000/mm^3; <50.0 -25.0 x 10^9 /L	<25,000/mm^3; <25.0 x 10^9 /L
WBC, Decreased	<LLN - 3000/mm^3; <LLN - 3.0 x 10^9 /L	<3000 - 2000/mm^3; <3.0 - 2.0 x 10^9 /L	<2000 - 1000/mm^3; <2.0 - 1.0 x 10^9 /L	<1000/mm^3; <1.0 x 10^9 /L
APTT or PTT	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN;	-
Proteinuria (Dipstick)	1+	2+	-	-
Proteinuria (24-hour urine)	<1.0 g/24 hrs	1.0 - 3.4 g/24 hrs	>=3.5g/24 hrs	-

Appendix 2. KDQOL-SF Scale Scoring Procedure

Scale	Number of Items	After Recoding, Average the Following Items
Kidney disease targeted areas		
Symptom/problem list	12	14a-k
Effects of kidney disease	8	15a-h
Burden of kidney disease	4	12a-d
Work status	2	20,21
Cognitive function	3	13b, d, f
Quality of social interaction	3	13a,c,e
Sexual function	2	16a, b
Sleep	4	17, 18a-c
Social support	2	19a, b
36-item health survey_ (SF-36)		
Physical functioning	10	3a-j
Role--physical	4	4a-d
Pain	2	7,8
General health	5	1, 1la-d
Emotional well-being	5	9b, c, d, f, h
Role--emotional	3	5a-c
Social function	2	6, 10
Energy/fatigue	4	9a, e, g, i

Note: The SF-36 change in health and the 0-10 overall health rating items are scored as single items.

Appendix 3. FACIT-Fatigue Scale and Calculation of Total Score

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

		Not At All	A Little Bit	Somewhat	Quite a Bit	Very Much
1	I feel fatigued	0	1	2	3	4
2	I feel weak all over	0	1	2	3	4
3	I feel listless ("washed out")	0	1	2	3	4
4	I feel tired	0	1	2	3	4
5	I have trouble starting things because I am tired	0	1	2	3	4
6	I have trouble finishing things because I am tired	0	1	2	3	4
7	I have energy	0	1	2	3	4
8	I am able to do my usual activities	0	1	2	3	4
9	I need to sleep during the day	0	1	2	3	4
10	I am too tired to eat	0	1	2	3	4
11	I need help doing my usual activities	0	1	2	3	4
12	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
13	I have to limit my social activity because I am tired	0	1	2	3	4

Scoring: Items are scored as follows: 4=Not At All; 3=A Little Bit; 2=Somewhat; 1=Quite A Bit; 0=Very Much, EXCEPT items #7 and #8 which are reversed scored. Total score range 0-52.

Item Number	Reverse Item?		Item Response	Item Score
1	4	-		=
2	4	-		=
3	4	-		=
4	4	-		=
5	4	-		=
6	4	-		=
7	0	+		=
8	0	+		=
9	4	-		=
10	4	-		=
11	4	-		=
12	4	-		=
13	4	-		=

Sum individual item scores: ____