An Open-Label Phase 2 Proof-of-Concept Study in Patients with C3 Glomerulopathy (C3G) or Immune-Complex Membranoproliferative Glomerulonephritis (IC-MPGN) Treated with ACH-0144471

Unique Protocol ID:	ACH471-205
NCT Number:	NCT03459443
EudraCT Number:	2017-002674-39
Date of SAP:	30 October 2020

STATISTICAL ANALYSIS PLAN

PROTOCOL NUMBER: **ACH471-205**

AN OPEN-LABEL, PHASE 2, PROOF-OF-CONCEPT STUDY IN PATIENTS WITH C3 GLOMERULOPATHY (C3G) OR IMMUNE-COMPLEX MEMBRANOPROLIFERATIVE GLUMERULONEPHRITIS (IC-MPGN) TREATED WITH ACH-0144471

Author: PPD

Date: 30 October 2020

Version: 2.0

1. APPROVAL SIGNATURES

PPD	Date dd Mmm yyyy
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List of Abbreviations

AE	Adverse event
AP	Alternative Pathway (Complement)
BLQ	Below the lower limit of quantification
C3G	C3 glomerulopathy
CKD-EPI	Chronic kidney disease - Epidemiology collaboration
CV%	Coefficient of variation
ECG	Electrocardiogram
EOT	End of treatment
EQ-5D-3L	Three-level version of EuroQol 5 Dimensions questionnaire
EQ-5D-Y	Youth version of EuroQol 5 Dimensions questionnaire
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue scale
FAS	Full Analysis Set
IC-MPGN	Immune complex mediated membranoproliferative glomerulonephritis
KDQOL-SF	Kidney Disease Quality of Life short form questionnaire
LFT	Liver function tests
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
Peds-FACIT-F	Pediatric Functional Assessment of Chronic Illness Therapy – Fatigue scale
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
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 ACH471-205.

2 Objective

2.1 Primary Objectives

The primary objective of this study is to evaluate the efficacy of 12 months of oral ALXN2040 (formerly ACH-0144471) in patients with C3G or IC-MPGN 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 of 12 months of oral ALXN2040 in patients with C3G or IC-MPGN based on significant improvement in slope of estimated glomerular filtration rate (eGFR) relative to baseline over time
- To evaluate for improvement in eGFR following treatment with ALXN2040
- Where available, evaluate the change in measured (m) GFR relative to baseline at end of 12 months of treatment with ALXN2040
- To evaluate the safety and tolerability of ALXN2040 in patients with C3G or IC-MPGN by assessing serious adverse events (SAEs).

2.3 Exploratory Objectives

The exploratory objectives of this study are:

- To evaluate whether changes in histopathology scoring correlate with observed clinical changes in those patients with biopsy results before and after treatment with ALXN2040
- To explore the effect of ALXN2040 on complement biomarkers including alternative pathway (AP) activity in patients with C3G or IC-MPGN over a 12-month treatment period
- To evaluate plasma concentrations of ALXN2040 in patients with C3G or IC-MPGN
- To evaluate kidney disease and health-related quality of life instruments in patients with C3G or IC-MPGN over the course of ALXN2040 treatment

- To explore patients' experience of their disease (C3G or IC-MPGN), its impact, and its management on their everyday lives, from first symptoms to definitive diagnosis and beyond
- To explore patients' expectations and perceptions of ALXN2040 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.

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

When possible, proteinuria will be evaluated in 24-hour urine collections, but if a 24-hour urine is not available, a calculated equivalent will be derived from albumin:creatinine and/or total protein: creatinine ratios, obtained from spot urine samples. The process for deriving this calculated equivalent will be described in detail in the laboratory manual.

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 12 months of treatment
- Number and percent of patients with reduction in proteinuria relative to baseline at the end of 12 months of treatment

3.1.4 Secondary Efficacy Outcome Measures

- Number and proportion of patients with significant (≥25%) increase in eGFR relative to baseline at the end of 12 months of treatment
- Change and percent change from baseline in proteinuria and eGFR over 12 months of treatment for all patients
- Change and percent change from baseline in eGFR over 12 months of treatment for patients meeting eGFR inclusion criteria at study entry
- Descriptive analysis of slope of eGFR over the treatment period of ALXN2040 therapy

The calculation of eGFR will be based on the following formulas:

  – For patients 19 years old and older the CKD-EPI creatinine equation (2009) will be used for inclusion/exclusion and primary endpoint analysis.

  – For patients <19 years old the creatinine-based "Bedside Schwartz" equation (2009) will be used for inclusion/exclusion and primary endpoint analysis.

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

- Changes in the following biomarkers over 12 months of treatment: AP activity, CP activity, Factor D, C3, C4, Bb, sC5b-9, and other biomarker measurements available from central laboratories.
- Changes in kidney disease and health related quality of life measurements using KDQOL-SF v1.3 and FACIT-Fatigue scale (version 4.0) for adults and Peds-FACIT-F for adolescents 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 (for adults) or EQ-5D-Y (for adolescents) at 6 months and 12 months of treatment

3.2 Safety Outcome Measures

- Number and incidence of SAEs
- Number and incidence of AEs leading to discontinuation of the study drug
- Number and incidence of Grade 3 or 4 AEs (related and regardless of relationship to study drug)
- Change from baseline on selected laboratory test results over treatment duration

- Number and incidence of Grade 3 or 4 laboratory abnormalities
- 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) Outcome Measures

- C_{trough} concentrations for C3G and IC-MPGN patients receiving ALXN2040

4 Study Description

4.1 Study Design

This is an open-label study in which all patients receive active treatment with ALXN2040 for approximately 40 months. The study is planned to enroll approximately 20 patients with biopsy-confirmed C3G or IC-MPGN, 12 years of age or older, who have not undergone renal transplant. Patients who completed ACH471-201 are eligible to participate, as long as they do not meet any exclusion criteria.

Patients must have biopsy-confirmed diagnosis of either C3G or IC-MPGN and significant proteinuria, defined as ≥500 mg/day of protein in a 24-hour urine, that is attributable to C3G or IC-MPGN in the opinion of the principal investigator. Patients who completed ACH471-201 may enroll in this study following a washout period of at least 30 days between the last dose of ALXN2040 in study ACH471-201 and the renal biopsy (if collected during screening) or the 24-hour urine collection during screening.

Once eligibility is confirmed, arrangements can be made for a renal biopsy, if necessary, to confirm the diagnosis of C3G or IC-MPGN, or to establish a baseline for patients who choose to participate in the renal biopsy sub-study and/or vaccinations. Biopsies are not obtained from patients less than 18 years of age (unless a biopsy is determined to be clinically indicated by the treating provider), or from patients for whom a biopsy is contraindicated. In addition, patients must have the diagnosis of C3G or IC-MPGN for at least 3 months prior to dosing, unless otherwise approved by the sponsor.

All patients should be vaccinated against *Haemophilus influenzae* (*H. influenzae*), *Streptococcus pneumoniae* (*S. pneumoniae*), and *Neisseria meningitidis* (*N. meningitidis*) as recommended by the Advisory Committee on Immunization Practices (ACIP) guidelines at least 2 weeks before the start of dosing with ALXN2040.

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 (or 150 mg TID for patients less than 60 kg). Additional dosage regimens may be investigated if supported by emerging data from this and other clinical studies. For each patient, the medical monitor must consult with the investigator before making the decision to dose escalate. Upon treatment discontinuation, regardless of the timing or reasons for discontinuation, a

6-day taper period is required unless the PI determines this taper period poses a risk to the patient. The taper period is in place to prevent the theoretical risk of marked increase or rebound in complement activity.

Safety, efficacy (including biopsy results, PD biomarkers, and 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.

An initial data snapshot will be performed when at least 20 patients complete the Week 28 visit or withdraw from the study early, and a preliminary analysis will be conducted that is descriptive in nature including the following data:

- Patient disposition
- Baseline demographics and disease characteristics
- Primary efficacy outcomes, including renal biopsy results and proteinuria
- Key secondary efficacy outcomes, including changes in eGFR
- Overall summary of treatment-emergent adverse events
- Treatment-emergent adverse events by preferred term
- PK/PD changes over time

The final analysis will occur will all patients complete the follow-up period or withdraw from the study early and will include analysis of all safety, efficacy, and PK data.

4.2 Treatment Assignment

All patients receive ALXN2040 and are assigned to the same treatment group. Patients entering following completion of ACH471-201 retain the same patient identification as in study ACH471-201. Newly enrolled patients are assigned a sequential patient identification number within each study site.

4.3 Blinding and Unblinding

This is an open-label study that does not require blinding or unblinding.

4.4 Protocol Amendments

Amendment No.	Amendment Date	Main Purposes of Amendment
1	01-DEC-2017	• Allow investigators who wish to do so to collect measured GFR in addition to the existing eGFR calculations.

Amendment No.	Amendment Date	Main Purposes of Amendment
		• The contraception requirements are being modified to align with updated Achillion standard wording, and SAE reporting contact information is being updated.
2	23-MAR-2018	• Revise to allow vaccinations to be administered according to local/national guidelines • Remove pharmacokinetic (PK) profile at Day 3 in order to reduce the burden to study patients • Simplify the complement-based inclusion/exclusion criteria • Updated contact information for reporting SAEs
3	02-NOV-2018	• Allows the inclusion of adolescents • Makes the collection of renal biopsy samples optional, and changes the improvement in biopsy score from a primary to an exploratory objective • Makes changes to the inclusion/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
4	30-JAN-2019	• Version 4 was not implemented
5	22-JUL-2019	• Addition of biopsy as a primary endpoint • Reduces sample collection and adds flexibility to the collection schedule to reduce the burden on patients • Removes the biopsy sub-study option at Week 52 • Extends the study to Week 104 (addition of a 12-month long-term follow-up period) • Reduces the number of in-clinic study visits by having the ability to do visits as phone calls
6	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 the COVID-19 global pandemic • Allows optional renal biopsy to be performed when possible due to COVID-19 global pandemic • Updates contraceptive language to align with most recent Investigator Brochure

5 Sample Size

The sample size of 20 patients was determined based on limited clinical cases of C3G and IC-MPGN. Note that the sample of 20 patients includes those who enrolled after completing study ACH471-201.

6 Analysis Sets

6.1 Full Analysis Set (FAS)

All patients receiving at least one dose of ALXN2040 will be included in the full analysis set. Data from patients in FAS will be used for efficacy, safety, pharmacokinetic (PK), and pharmacodynamic (PD) analyses.

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

Summary statistics will be provided for efficacy and safety parameters. Data will be summarized by disease type (C3G or IC-MPGN) as well as overall.

Data listing 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.

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.

Longitudinal summaries of efficacy and safety parameters use pre-defined visit Week / Day as described in Appendix 1, schedule of assessment, of the protocol. Analysis visit 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 (enrolled / treated)
- Number of patients who completed the study
- Reasons for not completing the study

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 disease type and overall:

- demographics: age, gender, race, country
- physical measurement at baseline: height, weight, BMI
- disease characteristics at baseline: disease diagnosis, duration of the disease, biopsy results
- 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 disease type and overall.

7.3 Extent of Exposure

Treatment durations will be computed for each patient as (last date of dose – first date of dose + 1).

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 disease type and overall.

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. 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.

7.4 Concomitant Medications

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

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 12 months of treatment will be computed for each patient and summarized by disease type and overall.

Proteinuria

Number and percent of patients with reduction in proteinuria relative to baseline at the end of 12 months of treatment, defined as ≥30% decrease in proteinuria (total protein/day) relative to baseline from 24-hour urine collections.

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

The secondary efficacy endpoints include:

- Number and proportion of patients with significant (≥25%) increase in eGFR relative to baseline at the end of 12 months of treatment
- Change and percent change from baseline in proteinuria and eGFR over 12 months of treatment for all patients
- Change and percent change from baseline in eGFR over 12 months of treatment for patients meeting eGFR inclusion criterion at study entry

- Descriptive analysis of slope of eGFR over the treatment period of ALXN2040

Change and percent change from baseline for proteinuria will be computed for each patient and summarized by disease type and overall at each visit 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.

When possible, proteinuria will be evaluated in 24-hour urine collections, but if a 24-hour urine is not available, a calculated equivalent will be derived from albumin:creatinine and/or total protein: creatinine ratios, obtained from spot urine samples. The process for deriving this calculated equivalent will be described in detail in the laboratory manual.

The number and proportion of patients with ≥20% and ≥25% increase in eGFR relative to baseline at the end of 12 months of treatment will be summarized descriptively by disease type and overall.

Change and percent change from baseline in eGFR will be summarized at each pre-defined time point by disease type and overall. Change and percent change from baseline in eGFR will also be summarized separately for patients meeting eGFR inclusion criterion at study entry.

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 disease type and overall.

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 as well as a mean time-measurement graph for visual examination and interpretation.

In addition, the number and percentage of patients who achieve the following response statuses will be summarized at each visit by disease type and overall:

- 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.

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.

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 disease type and overall for the following outcome measures:

- 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)

All adult patients enrolled in the trial will self-administer questionnaires for the FACIT-Fatigue (version 4), KDQOL version 1.3, and EQ-5D-3L scales, and all adolescent patients enrolled in the trial will self-administer questionnaires for the Peds-FACIT-F and EQ-5D-Y scales at the times specified in the protocol to assess their HRQOL, fatigue, and kidney-related fears and worries (e.g. kidney failure, dialysis, kidney transplant), and to determine health states value, over the course of treatment with ALXN2040. 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 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 for adult patients by disease type and overall for each scheduled visit. Patient listings for total score and change from baseline in total score will be provided for protocol pre-specified time points.

7.6.2 Peds-FACIT-F

There are 13 items in the Peds-FACIT-F questionnaire. Each item includes 5 possible responses, 0-4, with 0 being "None of the time" and 4 being "All of the time". 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 #2 and #3, are negatively stated.

The Peds-FACIT-F questionnaire 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 for adult patients by disease type and overall for each scheduled visit. Patient listings for total score and change from baseline in total score will be provided for protocol pre-specified time points.

7.6.3 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 for adult patients by disease type and overall for each scheduled visit. Patient listings on score scales will be provided for each of KD targeted areas and SF-36 domains.

7.6.4 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 for adult patients by disease type and overall at each scheduled visit. Patient listings will be provided for the responses of 5-dimension descriptive system, EQ-5D-VAS, and U.S. population-based EQ-5D index.

7.6.5 EQ-5D-Y

The EQ-5D-Y has two parts. The first part is a descriptive system with 5 dimensions: mobility, looking after myself, doing usual activities, having pain / discomfort, feeling worried, sad or unhappy. Each dimension has three response levels, 1, 2, and 3, representing “no problems”, “some problems”, and “a lot problems”, respectively.

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 number and percentage of patients reporting each level of problems will be summarized for each dimension for adolescent patients at each scheduled visit. Original values and change from baseline values over time in the VAS score will be summarized for adolescent patients by disease type and overall at each scheduled visit. Patient listings will be provided for the responses of 5-dimension descriptive system and EQ-5D-VAS.

7.7 Safety Assessment

Evaluation of safety includes assessment of the following clinical parameters and will be described in detail in the subsequent subsections.

1. Treatment emergent adverse events (total as well as related versus unrelated), including discontinuations due to adverse event
2. Clinical laboratory parameters
3. ECG
4. Vital signs
5. Physical exam

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, 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 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. 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 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 protocol-specified visits by disease type and overall. 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 (shift tables).

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

7.7.3 ECG

A protocol amendment during the study changed the frequency of ECG measurements to screening only and therefore not all patients have multiple measurements.

Patient listings 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.

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 by disease type and overall. 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.

7.8.2 Pre-dose Plasma Concentration

Single trough PK samples will be taken at the time points as listed in the protocol schedule of assessments.

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 by disease type and overall.

8 Changes from Protocol Specified Analysis

Not applicable

9 Document History

Version No.	Author(s)	Descriptions
1.0	PPD	Original version dated 30Apr2020
2.0		• Updated to align with Protocol Amendment 6 • 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: ____

Peds-FACIT-F 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.

		None of the time	A little bit of the time	Some of the time	Most of the time	All of the time
1	I feel tired	0	1	2	3	4
2	I have energy (or strength)	0	1	2	3	4
3	I could do my usual things at home	0	1	2	3	4
4	I had trouble starting things because I was too tired	0	1	2	3	4
5	I had trouble finishing things because I was too tired	0	1	2	3	4
6	I needed to sleep during the day	0	1	2	3	4
7	I got upset by being too tired to do things I wanted to do	0	1	2	3	4
8	Being tired made it hard for me to play or go out with my friends as much as I'd like	0	1	2	3	4
9	I needed help doing my usual things at home	0	1	2	3	4
10	I feel weak	0	1	2	3	4
11	I was too tired to eat	0	1	2	3	4
12	Being tired made me sad	0	1	2	3	4
13	Being tired made me mad (angry)	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 #2 and #3 which are reversed scored. Total score range 0-52.

Tiredness Scale (score range: 0-44)

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

Sum individual item scores: ____
Multiply by 11: _____
Divide by number of items answered: ___

Energy Scale (score range: 0-8)

Item Number	Reverse Item?		Item Response	Item Score
2	0	+		=
3	0	+		=

Sum individual item scores: ____
Multiply by 2: _
Divide by number of items answered: ___

Total Score (score range: 0-52)

Tiredness score + Enery score = Total score