STATISTICAL ANALYSIS PLAN

A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study
to Evaluate the Safety and Efficacy of Avacopan (CCX168) in
Patients with C3 Glomerulopathy

Investigational Product: Complement 5a Receptor Antagonist CCX168 (INN/USAN avacopan)

Protocol Number: CL011_168

Sponsor:

ChemoCentryx, Inc.
Mountain View, CA 94043

Version Number: 1.0

Date: 05 Nov 2020

Original Protocol: 29 June 2017
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Amendment 3.0: 10 September 2018
Amendment 4.0: 20 March 2019

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SIGNATURE PAGE

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We, the undersigned, have reviewed and approve this Statistical Analysis Plan.

Signature	Date
[redacted]	13-Nov-2020
[redacted] Project Statistician [redacted]	
[redacted] Senior Vice President, Clinical Development ChemoCentryx, Inc.	13-Nov-2020
[redacted] Executive Director of Biostatistics ChemoCentryx, Inc.	13-Nov-2020
[redacted] Medical Monitor [redacted]	

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VERSION HISTORY

Version	Date	Description
1.0	05 Nov 2020	Original Version

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ACE	Angiotensin-converting enzyme
ARB	Angiotensin receptor blockers
AE	adverse event
ALT	alanine aminotransferase
ANCA	anti-neutrophil cytoplasmic antibody
ANCOVA	Analysis of Covariance
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Chemistry
BP	blood pressure
BMI	body mass index
C3G	C3 glomerulopathy
C3GN	C3 glomerulonephritis
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CPK	creatine phosphokinase
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DDD	Dense Deposit Disease
DMC	Data Monitoring Committee
EDC	Electronic Data Capture system
ECG	electrocardiogram
EQ-5D-5L	EuroQOL-5D-5L
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EOS	End of Study
GCP	Good Clinical Practice
HEENT	head, eyes, ears, nose, throat
INR	International normalized ratio

IRT	interactive response technology
ITT	Intent-to-Treat
LDH	lactate dehydrogenase
LOCF	last observation carried forward
MAR	missing at random
mg	milligram
MCP-1	monocyte chemoattractant protein-1
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed effects model for repeated measures
MNAR	missing not at random
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PP	Per Protocol
PT	Prothrombin time
RAAS	Renin-Angiotensin-Aldosterone System
SAP	statistical analysis plan
SAE	serious adverse event
SD	standard deviation
SEM	standard error of the mean
SF-36 v2	Short Form-36 version 2
TEAE	treatment emergent adverse event
TESAE	treatment emergent serious adverse events
UACR	urinary albumin:creatinine ratio
WHO	World Health Organization

1 INTRODUCTION

The purpose of this document is to provide a description of the statistical methods and procedures to be implemented for the analysis of data from ChemoCentryx, Inc. Protocol CL011_168. This document is based on protocol amendment 4.0 (20MAR2019) and CRF version 11.2 (07MAY2020). If circumstances arise during the study such that more appropriate analytic procedures become available, the statistical analysis plan (SAP) may be revised. The statistical definitions and analytical methods described in this SAP supersede that in the protocol. Any revisions to the primary endpoint analyses and significant revisions to the secondary endpoint analyses will be made prior to the database lock/snapshot. Reasons for such revisions will be described in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective is to evaluate the efficacy of avacopan compared to placebo based on histologic changes in kidney biopsies taken before and during treatment.

2.1.2 Secondary Objectives

The secondary objectives of this study include evaluation of:

1. Changes in laboratory parameters of renal disease including estimated glomerular filtration rate (eGFR), proteinuria, urine protein creatinine ratio and urinary excretion of monocyte chemoattractant protein-1 (MCP-1) with avacopan compared to placebo
2. The safety of avacopan compared to placebo based on the incidence of adverse events, changes in clinical laboratory measurements, and vital signs;
3. Health-related quality-of-life changes based on Short Form-36 version 2 (SF-36 v2) and EuroQOL-5D-5L (EQ-5D-5L) with avacopan compared to placebo;
4. The pharmacokinetic profile of avacopan in patients with C3G.

2.1.3 Exploratory Objectives

Changes from baseline in markers of the alternative complement pathway involvement and other markers of inflammation may be assessed in plasma/serum or urine over the course of the treatment period.

2.2 Study Design

2.2.1 Overview

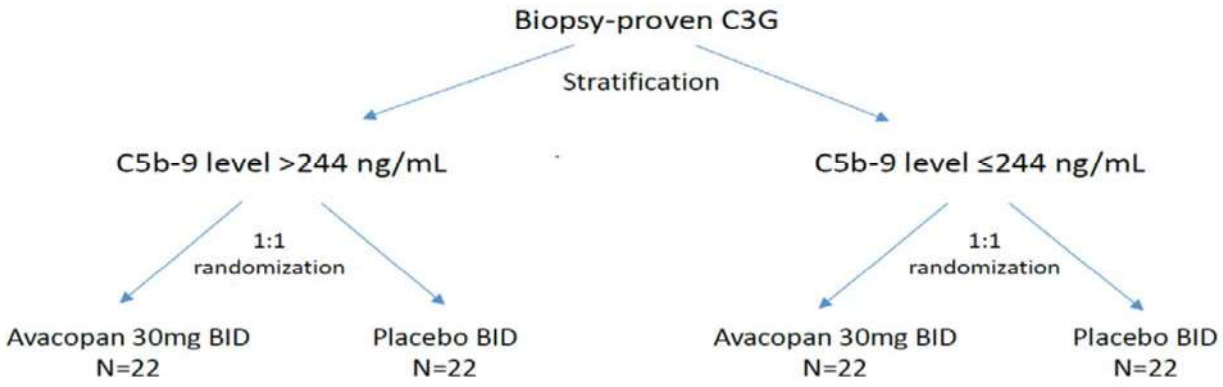
This is a Phase 2, randomized, double-blind, placebo-controlled, multicenter international clinical trial. The aim of this study is to evaluate the effect of avacopan treatment on renal disease activity in patients with complement component 3 glomerulopathy (C3G). Up to 88

subjects with C3G who fulfill all the eligibility criteria will be enrolled into the study from sites in North America, Canada and Europe.

All subjects have scheduled visits during the screening period, on Day 1 and at Weeks 1, 2, 4, 8, 12, 16, 20, 23, 26, 28, 32, 35, 38, 41, 44, 48, 52, 54, 57, and 60 (follow up). The study schema is provided below. For additional details regarding the study design, please refer to the protocol.

2.2.2 Stratification

Subjects will be stratified by elevated or non-elevated levels of C5b-9, and then randomized using a minimization algorithm to receive 30 mg avacopan twice daily or avacopan-matching placebo twice daily for 26 weeks in a double-blind manner:



Both strata, (i.e., C5b-9 levels >244 ng/ml and ≤244 ng/mL) will include approximately 44 subjects; each level will have approximately 22 subjects randomized (1:1) to the avacopan or avacopan-matching placebo arm, respectively. However, enrollment for the stratum with C5b-9 levels ≤244 ng/ml could terminate early if subject enrollment in the other stratum (C5b-9 level >244 ng/mL) reaches target enrollment first.

To obtain balance across treatment groups, eligible subjects within each of the C5B-9 level strata will be further stratified based on two factors:

1. C3 glomerulonephritis (C3GN) or Dense Deposit Disease (DDD), and
2. Whether the subject has received a kidney transplant or not.

2.2.3 Randomization and Blinding

There are two treatment period during this study. The first treatment period is the 26-week double-blind, placebo-controlled treatment period from Study Day 1 – week 26 called Treatment Period A. During the second 26-week treatment period, called Treatment Period B, the avacopan group will continue receiving avacopan for another 26 weeks, and the avacopan-matching placebo group subjects will be switched over in a blinded manner to receive 30 mg avacopan

twice daily treatment, instead of avacopan-matching placebo, for another 26 weeks. Subjects in Period A will be randomized using the stratification factors in a 1:1 ratio to one of the following two study treatments:

Group A: avacopan-matching placebo twice daily

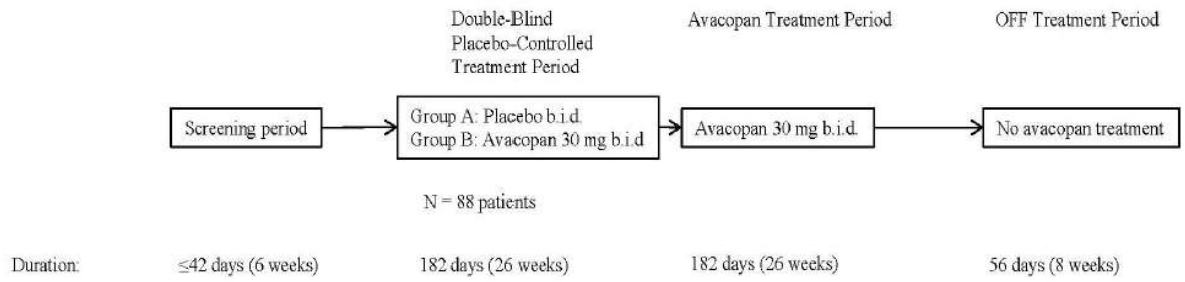
Group B: avacopan 30 mg twice daily

All adults will receive 30 mg twice daily or avacopan-matching placebo twice daily in the initial 26-week, double-blind, placebo-controlled treatment period. After entering the open-label 26-week treatment period, all subjects will receive avacopan 30 mg twice daily, regardless of prior treatment in the double-blind period.

For adolescent subjects, the dose of avacopan or placebo on Day 1 of the placebo-controlled period will be calculated based on the body weight at screening. Dose could be adjusted based on avacopan plasma exposure (AUC0-6hr). See the protocol for further details.

The treatment period is 52 weeks, followed by an 8-week follow-up.

STUDY SCHEMA



2.2.4 Screening Period (Up to 6 Weeks)

Screening evaluations will be performed to determine subject eligibility for the study including written informed consent/assent, demographics, medical history, medication history, physical exam and vital signs, 12-lead ECGs, serum pregnancy test for women of child bearing potential, serum chemistry, hematology, urinalysis, urinary albumin:creatinine ratio (UACR) and protein: creatinine ratio (UPCR), viral and TB screening. If a subject did not have a renal biopsy in the preceding 12 weeks, a renal biopsy was performed prior to dosing.

After all screening procedures have been completed, and the subject satisfies all eligibility criteria, the study schedule will be discussed with the subject and the schedule will be provided to the subject to ensure compliance with the study visits.

2.2.5 26-Week Double-blind Placebo-Controlled Treatment Period A

During the 26-week placebo-controlled double-blind period (Treatment Period A), eligible subjects will take avacopan 30 mg or matching placebo orally twice daily. For adolescent subjects (12 to 17 years old), the dose of avacopan or placebo dose will be calculated based on their body weight and avacopan plasma exposure (AUC0-6hr) or avacopan trough concentrations.

Eligible subjects will visit the study center on Day 1 for physical examination and vital signs, blood samples for serum chemistry, hematology, lymphocyte subset analysis, and PK and PD baseline measurements, serum pregnancy test (in women of childbearing potential), SF-36 v2 and EQ-5D-5L assessment, and stratification and randomization. Blinded study medication will be dispensed and the subject will be asked to take the first dose at the study center. At post-Day 1 study visits, blood and urine samples will be collected for safety, efficacy, and pharmacokinetic and biomarker measurements. Physical examinations, vital sign assessments, and ECG measurements will be performed throughout the study.

Health-related quality of life using the EQ-5D-5L and SF-36 v2 surveys will be assessed at Day 1 and Weeks 1, 4, 12, 20 and 26. Blinded study drug will be dispensed and drug accountability will be performed. Concomitant medication and adverse event assessments will be made at every study visit.

Within 2 weeks prior to the Week 26 visit, a follow-up renal biopsy will be performed and should be completed before avacopan is started.

2.2.6 26-Week Avacopan Treatment Period B

During the 26-week avacopan treatment period, regardless of prior treatment assignments, all adult subjects will receive avacopan orally 30 mg twice daily. Adolescent subjects will also take avacopan twice daily. Refer to the protocol and Section 6.2 below for details on dose selection in adolescents.

During the avacopan treatment period, physical examinations and vital signs assessments will be performed at Weeks 28, 32, 38, 44 and 52. 12-lead ECGs will be performed at Weeks 28, 32, and 52. Blood samples for serum chemistry and hematology will be collected at all study visits. Urine samples for urinalysis, urine albumin, protein and creatinine will be collected at weeks 28, 32, 38, 44, and 52.

Renal biopsy was to be completed after the Week 52 treatment period or if a subject is withdrawn early from the study. In adolescents, the Week 52 biopsy is optional.

2.2.7 8-Week Off Treatment Follow-up Period

After completion of the 52-week treatment period, subjects will be followed up for an additional 8 weeks during which the blinding will be maintained. Subjects will be discharged from the study when all the Study Week 60 visit procedures have been completed. Each subject's condition will be evaluated by the Investigator at the end of the clinical trial (Week 60) and appropriate standard of care medical treatment will be provided to all subjects as needed.

See the Time and Events Table in the Protocol for the schedule of urine and blood samples for pharmacodynamic (PD) and pharmacokinetic (PK) assessments throughout the entire study.

2.3 Study Endpoints

2.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the percent change from baseline to Week 26 in the C3G Histologic Index for disease activity.

2.3.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

1. The percent change from baseline in UPCR over the placebo-controlled 26-week treatment period;
2. The change and percent change from baseline in eGFR over the double-blind, placebo-controlled 26-week Treatment Period A;
3. The change from baseline in the C3G Histologic Index for disease chronicity over the placebo-controlled 26-week treatment period;
4. The proportion of subjects who have a histologic response, defined as a decrease (improvement) in the C3G Histologic Index for disease activity of at least 35% from baseline to Week 26 (see section 2.3.4).

2.3.3 Other Efficacy Endpoints

1. Other efficacy endpoints include: The percent change from baseline in urinary MCP-1:creatinine ratio over the placebo-controlled 26-week treatment period;
2. Change from baseline in EQ-5D-5L (visual analogue scale and index) and SF-36 v2 (domains and component scores) over the placebo-controlled 26-week treatment period.

2.3.4 Efficacy Assessments

Renal biopsy assessment based on light microscopy, immunohistochemistry, and electron microscopy; light microscopy and immunohistochemistry will be used to determine the C3G Histologic Index for disease activity and chronicity. Renal biopsies will be evaluated by a central reader, an expert in C3G renal pathology, who will be blinded to treatment assignment from either slides or digitized high-resolution images.

C3G Histologic Index for Disease Activity

The C3G Histologic Index for disease activity will consider 7 lesions:

1. Mesangial hypercellularity, defined as >3 mesangial cells per mesangial area;
2. Endocapillary hypercellularity/proliferation, defined as an increased number of cells within glomerular capillary lumina, causing luminal narrowing;
3. Membranoproliferative morphology;
4. Leukocyte infiltration;
5. Crescent formation, defined as extracapillary cell proliferation of more than two cell layers with >50% of the lesion occupied by cells;
6. Fibrinoid necrosis;
7. Interstitial inflammation.

Definitions are based on the Mayo Clinic/Renal Pathology Society Consensus Report on Pathologic Classification, Diagnosis, and Reporting of GN (Sethi et al., 2016) and the activity index score uses the glomerulopathy histologic score as described by Bomback et al. (Bomback et al., 2018).

For endocapillary hypercellularity/proliferation, mesangial hypercellularity, membranoproliferative morphology, and leukocyte infiltration the following scale will be used: 0 = none, 1 = 1-25%, 2 = 26-50%, 3 = >50% involvement. For crescent formation and fibrinoid necrosis, the following scale will be used: 0 = none, 1 = 1-10%, 2 = 11-25%, and 3 = >25% involvement. For interstitial inflammation, a score according to percentage of cortical tubulointerstitial area involved will be used: 0 = <10%, 1 = 10-25%, 2 = 26-50%, 3 = >50% involvement.

The C3G Histologic Index for disease activity can assume a score from 0-21 and is calculated by summing the scores from the 7 lesions.

C3G Histologic Index for Disease Chronicity

The C3G Histologic Index for disease chronicity will consider 4 lesions (Bomback et al., 2018):

1. Glomerulosclerosis (% glomeruli with global and segmental sclerosis),

2. Tubular atrophy

3. Interstitial fibrosis, and

4. Arterio- and arteriolosclerosis

Glomerulosclerosis (global plus segmental), tubular atrophy, and interstitial fibrosis will be assigned a score of 0 to 3 based on the percentage of glomeruli or cortical tubulointerstitial area involved. The following scale will be used for the chronicity index: 0 = <10%, 1 = 10-25%,

2 = 26-50%, 3 = >50% involvement. For vascular disease, a score of 0 will be assigned if intimal thickening is < thickness of media and 1 if intimal thickening is ≥ thickness of media. The C3G Histologic Index for disease chronicity can assume a score from 0-10 and is calculated by summing the scores from the 4 lesions.

eGFR

Calculation of eGFR will be based on serum creatinine using the Chronic Kidney Disease-Epidemiology Collaboration study (CKD-EPI) equation (Levey et al., 2009) in adult subjects and the modified Schwartz equation in adolescents (Schwartz et al., 2009).

CKD-EPI Equation Based on Race and Gender:

Race and Sex	Serum Creatinine, µmol/L (mg/dL)	Equation
Black		
Female	≤62 (≤0.7)	GFR = 166 x (serum creatinine/0.7)$^{-0.329}$ x (0.993)^{Age}
	>62 (>0.7)	GFR = 166 x (serum creatinine /0.7)$^{-1.209}$ x (0.993)^{Age}
Male	≤80 (≤0.9)	GFR = 163 x (serum creatinine /0.9)$^{-0.411}$ x (0.993)^{Age}
	>80 (>0.9)	GFR = 163 x (serum creatinine /0.9)$^{-1.209}$ x (0.993)^{Age}
White or Other		
Female	≤62 (≤0.7)	GFR = 144 x (serum creatinine /0.7)$^{-0.329}$ x (0.993)^{Age}
	>62 (>0.7)	GFR = 144 x (serum creatinine /0.7)$^{-1.209}$ x (0.993)^{Age}
Male	≤80 (≤0.9)	GFR = 141 x (serum creatinine /0.9)$^{-0.411}$ x (0.993)^{Age}
	>80 (>0.9)	GFR = 141 x (serum creatinine /0.9)$^{-1.209}$ x (0.993)^{Age}

Modified Schwartz: eGFR = (0.413 x Height [in cm]) / Serum creatinine (in mg/dL)

2.3.5 Pharmacokinetic Assessments

Plasma concentrations of avacopan (and its metabolite CCX168-M1) will be determined on Day 1, and Weeks 1, 2, 4, 12, 20, 26, 28, 32, 38, 52, 54, 57 and 60, using a validated analytical method. The samples on Day 1 will be collected prior to the first dose of avacopan/placebo on the same day. For subjects 12 to 17 years of age, samples will also be taken at hours 0.5, 1, 2, 3, 4, and 6 following the first dose of avacopan/placebo on Day 1 and following the morning dose of avacopan on Day 183 (Week 26). The Day 183 morning dose for these adolescent subjects should be taken in the clinic. The blood samples collected on the other study days will be single time point samples and do not need to be collected prior to the avacopan/placebo dose on those days. However, the date and time of the last dose of avacopan/placebo (or avacopan in the avacopan portion of the study) prior to the sample collections must be recorded in the electronic data capture (EDC) system.

Subjects should take avacopan at the Week 52 clinic visit either at home or in the clinic. Two days prior to this visit, the subject should be reminded with a telephone call to not take avacopan. The time of the last dose should be recorded. PK sampling from Week 52 onward (four samples total collected on Week 52, Week 54, Week 57, and on the follow-up visit, Week 60) is for the terminal PK evaluation.

Total plasma concentrations of avacopan (and its metabolite CCX168-M1) will be determined using validated analytical methods. Plasma samples collected for PK analysis may also be used to measure cytokines, complement fragments, or other markers associated with C3G.

2.3.6 Pharmacodynamic Assessments

Blood samples will be collected on Day 1, and Weeks 1, 2, 4, 12, 20, 26, 28, 32, 38, 52, 54, 57 and 60 for PD marker measurements in plasma and serum, which may include, for example, cystatin C, complement components, and inflammatory cytokine and chemokine levels. Blood samples collected will be used for lymphocyte subset counts including B cells, T cells, and natural killer cells. The complete blood cell (CBC) count results from the hematology samples will also be included in the PD assessments. The PK plasma samples may also be used for PD marker measurements.

Urine samples will be collected according to the same schedule as for blood samples with the exception of Weeks 54 and 57 for biomarker assessments including, for example, soluble CD163, complement fragments, and inflammatory cytokine and chemokine levels.

Details of the PK and PD analysis will be described in a separate analysis plan and will be reported in a separate report.

2.3.7 Safety Endpoints

2.3.7.1 Adverse Events

Safety endpoints include subject incidence of treatment-emergent serious adverse events, treatment emergent non-serious adverse events, and withdrawals from the study drug or clinical trial due to adverse events.

An adverse event will be considered treatment-emergent (TEAE) if the start date of the event is on or after the date of administration of the first dose of study medication. All reported adverse events will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) (version 19.1). Treatment-emergence will also be determined based on the Safety Populations defined in Section 3.2.3.

The relationship to avacopan/placebo will be determined by the Investigator. The sponsor will perform a safety analysis based on an aggregate analysis across the safety database as well as the assessment of individual cases of interest.

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires or prolongs hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, or is an important and significant medical event that, based on appropriate medical judgment, may jeopardize the subject and/or may require medical or surgical intervention to prevent one of the other outcomes defining serious.

In addition, specific TEAEs of interest will be presented by treatment group (see Section 6.3).

2.3.7.2 Clinical Laboratory Assessments

Safety endpoints related to clinical laboratory assessments include change from baseline and shifts from baseline in all safety laboratory parameters, including blood chemistry, hematology, and urinalysis.

Clinical laboratory assessments will be performed at the visits identified in the Time and Events Table in the protocol:

- Hematology: hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential, platelet count, mean cell hemoglobin, mean cell hemoglobin concentration, mean corpuscular volume
- Serum Chemistry: liver panel (total and fractionated bilirubin, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase), renal panel (blood urea nitrogen, creatinine), creatine phosphokinase (CPK), albumin, sodium, potassium, magnesium, bicarbonate, chloride, calcium, inorganic phosphorus, glucose, total protein, alkaline phosphatase, total cholesterol, uric acid, serum amylase, and serum lipase
- Coagulation: Prothrombin time (PT) and International normalize ratio (INR) if retest is performed because of ALT and/or AST >3x ULN

- Urinalysis: At the central laboratory, blood, nitrite, and protein, will be tested. If positive for blood, nitrite or protein, microscopy examination will be performed
- Virology (measured only at screening and may be measured at the local laboratory): hepatitis B surface antigen, hepatitis C antibodies, HIV 1 and 2 antibodies; virology tests done within 6 weeks prior to screening are acceptable for eligibility assessment. Results from prior tests performed at the local laboratory must be recorded in the EDC system
- TB screen: only one of the following is needed: interferon γ release assay (IGRA), tuberculin purified protein derivative (PPD) skin test, or chest radiograms (X rays or CT scan); chest radiography done within 6 weeks prior to screening is allowed for eligibility assessment

Specific laboratory abnormalities that would prompt pausing or permanently discontinuing study drug (avacopan or placebo) including white blood cell count, neutrophil count, lymphocyte count, AST or ALT and other lab abnormalities of impaired liver function of hepatic toxicity, CPK increase, creatinine or proteinuria increase may be summarized.

2.3.7.3 Complement Panel

The following panel will be measured in all subjects at baseline based on recommendations from a consensus panel (Pickering et al., 2013):

- Plasma C3a, C5a, C5b-9, and C5;
- Serum C3 and C4;
- Serum C3 nephritic factor;
- Plasma complement factor H and factor B;
- Serum factor H auto-antibody;
- Serum paraprotein detection;
- CFHR5 mutation

Results from tests performed within 4 weeks prior to screening will be allowed for the study. For CFHR5 mutation, results from tests performed any time in the past will be allowed. If these tests have not been performed previously in a subject, samples need to be collected prior to Day 1 for measurement either at the local laboratory (if capabilities exist) or at the central laboratory. Results from these tests do not need to be available prior to start of dosing on Day 1, except for C5b-9 which is needed for eligibility assessment. Results from tests performed at the local laboratories need to be recorded in the EDC.

2.3.7.4 Vital Signs

Individual vital sign values including temperature, blood pressure and heart rate, and change from baseline will be calculated. Visits to be listed and summarized include Screening, Day 1, and Weeks 1, 2, 4, 8, 12, 16, 20, 26, 28, 32, 38, 44 and 52 during the treatment period and Weeks 54, 57 and 60 during the follow-up.

Height and weight are to be measured as part of the vital signs. Height is to be recorded at screening only, except for adolescents (12-17 years old) in whom height is also to be included as part of all vital signs. Body mass index (BMI) will be calculated from the body weight and

height measurements. Height, weight and BMI will be listed and weight and BMI will be summarized.

2.3.7.5 ECG

ECG Interpretation (normal/abnormal), clinical significance (yes/no) and description of abnormality will be listed. Visits to be listed include Screening, Day 1, and Weeks 1, 26, 28, 32 and 52 during the treatment period and Weeks 54, 57 and 60 during the follow-up. Clinically significant findings at screening should be reported as Medical History and abnormal changes compared to baseline should be recorded as adverse events as appropriate.

2.3.7.6 Physical Exam

A complete physical examination (including evaluation of general appearance/mental status, HEENT [head, eyes, ears, nose, throat], and the following body systems: dermatologic, cardiovascular, respiratory, gastrointestinal, musculoskeletal and neurologic) for safety will be performed at Screening, Day 1, Weeks 1, 2, 4, 8, 12, 16, 20, 26, 28, 32, 38, 44 and 52 during the treatment period and Weeks 54, 57 and 60 during the follow-up. Overall assessment (normal/abnormal) and clinical significance (yes/no) will be listed. Clinically significant findings should be reflected in Medical History or recorded as adverse events as appropriate.

3 STATISTICAL METHODOLOGY

3.1 General Considerations

For efficacy analysis, to control for the Type I error rate, a gate-keeping procedure will be applied for the analysis of the primary efficacy endpoint (percent change in C3G Histologic Index for disease activity). The primary endpoint will be tested in the elevated C5b-9 stratum first with a two-sided $\alpha = 0.05$. If this test reaches statistical significance, then the primary endpoint will be tested in the combined C5b-9 strata (including both elevated and non-elevated C5b-9 strata) with a two-sided $\alpha = 0.05$. If the test in the elevated stratum fails to reach statistical significance, then the test in the combined C5b-9 strata will only be performed as an exploratory analysis. The statistical analysis for the secondary endpoint (C3G Histologic Index for disease chronicity) will be tested at a 0.05 α-level only if the primary endpoint in the same stratum reaches statistical significance.

Data will be summarized descriptively by treatment group as well as separately for the elevated C5b-9 stratum and combined strata. For continuous variables, numbers, means, medians, ranges, standard deviations, and standard error of means will be calculated. Geometric means will be calculated for UACR and urinary MCP-1:creatinine ratio, and other data that are not normally distributed. Frequency counts and percentages will be presented for categorical variables. Listings of raw and derived data will be included as part of an appendix to the CSR.

In analysis tables and listings, the two treatment groups will be referred to as

- '**Placebo**', referenced in the protocol as Group A (placebo)
- '**Avacopan'**, referenced in the protocol as Group B (avacopan)

3.1.1 Study Day

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

3.1.2 Analysis Visits for Efficacy

Scheduled visits will be assigned to analysis visits as recorded in the EDC system. If a scheduled visit is not available, unscheduled and early termination visits will be assigned to analysis visits using analysis visit windows based on the actual date the assessment took place. The start day of the analysis window will be calculated as the midpoint between the scheduled assessment and previously scheduled assessment for that parameter. The end day of the analysis window will be calculated as the midpoint between the scheduled assessment and the next scheduled assessment for that parameter. Where multiple measurements for a particular parameter appear within an analysis visit, the scheduled visit will be used. If no scheduled visit appears in the analysis window, the result closest to the target day will be used. If equidistant and both are unscheduled and/or early termination visits, the later result will be used for the summary measure. Note that scheduled visits may appear outside of the analysis day window due to factors such as COVID-19 and related factors which could have limited the ability for subjects to visit the study site. Due to specific study procedures performed at these visits, the scheduled study visit will be used in these cases. Individual adjustments may be made for subsequent unscheduled or early termination visits that occur after this visit should they appear in an analysis day window prior to the scheduled visit.

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

Analysis Visit	Analysis Day Target	Analysis Day Window [1]
Week 1	8	2 - 11
Week 2	15	12 - 22
Week 4	29	23 - 43
Week 8	57	44 - 71
Week 12	85	72 - 99
Week 16	113	100 - 127
Week 20	141	128 - 152
Week 23	162	153 - 173
Week 26	183	174 - 190
Week 28	197	191 - 211
Week 32	225	212 - 236
Week 35	246	237 - 257
Week 38	267	258 - 278
Week 41	288	279 - 299
Week 44	309	300 - 323
Week 48	337	324 - 351

Analysis Visit	Analysis Day Target	Analysis Day Window [1]
Week 52	365	352 - 372
[1] Scheduled visits are being used when available and may appear outside of the analysis day window due to factors such as COVID-19 and related factors which could have limited the ability for subjects to visit the study site		

3.1.3 Definition of Baseline

Baseline is defined as the last value prior to start of dosing with study medication (typically the Day 1 pre-dose value). Renal biopsy for study eligibility could be performed within 12 weeks prior to the Screening Period or during the up to 42 day Screening Period.

3.1.4 Handling of Missing Data

Dates will be printed in ISO 8601 date format (YYYY-MM-DD). If only year and month are available, date will be displayed as YYYY-MM. If only year, then just YYYY. Dates that are missing because they are not applicable for the subjects are output as "NA", unless otherwise specified.

If data are missing after all efforts made to collect post-baseline C3G Histologic Index data, missing data will be imputed using multiple imputation methods. See Section 5.2.1 and Appendix 12.3 for further details.

No imputation will be performed for missing safety endpoints, including safety laboratory values, vital signs, electrocardiograms, etc.

Adverse events and prior/concomitant medications/procedures with incomplete start or stop dates will be imputed according to the rules stated in Section 12.2.2.

3.1.5 Other Data Handling Approaches

For continuous variables, the estimated mean and median for a set of values will be printed out to one more decimal place than the individual units of measurement, and the standard deviation will be printed out to 1 additional place. P-values will be given with 4 decimals (i.e., 0.xxxx). When a p-value is less than 0.0001, '<0.0001' will be printed.

All fractional numeric values will be printed with a zero to the left of the decimal point (e.g., 0.12, 0.3 etc.). Percentage values will be printed with 1 digit to the right of the decimal point (e.g., 52.3%, 8.9% etc.).

3.1.6 Summary Statistics

Categorical data will be summarized with counts and percentages of subjects. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation, standard error of the mean (SEM), minimum, and maximum.

3.1.7 Evaluation of Site Effect

This is a multi-center study enrolling subjects at sites across North America, Canada and Europe. Site effect will not be evaluated since the number of subjects at each site is expected to be too small.

3.1.8 Adjustments for Potential Impact of COVID-19

COVID-19 pandemic may impact the conduct of the study from different aspects including quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product, or other considerations if site personnel or trial subjects become infected with COVID-19.

Data fields to capture visit impact due to COVID-19 were added to the database including visit status (visit not completed/in-person visit partially completed/performed virtually), if visit status was due to COVID-19, whether the visit was completed outside of window due to COVID-19 and how or why participation was impacted by COVID-19 (travel restrictions, study site closed, patient chose not to attend site visit, renal biopsy not allowed at site requiring an extended randomized treatment period, patient received COVID-19 diagnosis, lack of study site personnel, lack of home nursing, local labs used instead of protocol-defined central labs and other). The data will be included in listings. Additionally, if a subject discontinued study treatment early or discontinued early from the study due to COVID-19, these data will be summarized as part of subject disposition. Local laboratory data collected due to COVID-19 will be listed.

Adjustments for missing data due to COVID-19 are incorporated into the multiple imputation analyses, completer analyses, per-protocol analyses and sensitivity analyses. Additionally, wider analysis windows are being allowed in order to capture critical data (e.g. renal biopsy data at Week 26 and Week 52) to reduce missing data. See Section 3.1.2 and Section 5 for additional details.

3.2 Analysis Populations

3.2.1 Randomized Population

The Randomized Population will include all subjects who have provided written Informed Consent/Assent and are randomized in the study.

3.2.2 Intent-to-Treat Population

The Intent-to-Treat (ITT) Population will include all randomized subjects who received at least one dose of study medication; subjects with a histologic activity score of 0 at baseline or who are ongoing and have not completed the Week 26 visit will not be included in the ITT population.

3.2.3 Safety Population

The Safety Population will include all subjects who are randomized and have received at least one dose of study drug, including all subjects who have not yet completed the Week 26 visit. All

safety data will be analyzed using the Safety Populations according to the actual treatment received.

Notations for Treatment Periods

Treatment Period A: Initial 26-week placebo-controlled, double-blind treatment period, Day 1 – Week 26

Treatment Period B: Week 26-Week 52, the Avacopan treatment period plus 8 Weeks of Follow-up, Week 26 to End of Study (EOS)

3 Safety Populations for this study:

1. The Safety Population in the Treatment Period A is defined as all subjects who received at least one dose of blinded Investigational Drug during Treatment Period A.
2. The Safety Population in Treatment Period B is defined as all subjects who received at least one dose of Avacopan during Treatment Period B.
3. The All Avacopan Treated Population is defined as all subjects who received at least one dose of Avacopan in the study.

3.2.4 Per Protocol Population

The Per Protocol (PP) Population will consist of ITT subjects who receive at least one dose of study drug and do not have protocol deviations that could significantly affect the interpretation of the results for the primary endpoints.

The following aspects will be relevant for consideration of subjects to be excluded from the PP analysis:

- Subjects with significant protocol deviations regarding inclusion and exclusion criteria that may impact evaluation of the primary endpoints.
- Subjects who did not have week 26 with renal biopsy
- Subjects with significant lack of compliance of study medication administration (avacopan /placebo) defined as: All subjects who were <75% compliant overall during the 26-week Treatment Period A based on study medication accountability records.
- Subjects with introduction of new treatment medications for C3G such as Mycophenolate mofetil (MMF) and glucocorticoids after the screening biopsy and prior to week 26 renal biopsy such that the screening renal biopsy is done off immunosuppressant medication and the week 26 renal biopsy is done on immunosuppressant medication.
- Subjects with clinically significant increase in immunosuppressant dose (MMF, Prednisone) during the study that may impact renal biopsy results significantly.
- Subjects whose data could have been significantly impacted by COVID-19.

Subjects to be excluded from the PP Population will be identified and documented prior to the database lock and unblinding for analysis. A subject's data could be partially excluded from analysis depending on when the deviation occurred. For example, if a deviation occurred during the avacopan treatment period that did not impact the data from the double-blind period, only the data during the avacopan treatment period will be excluded.

3.2.5 C5b-9 Patient Populations

3.2.5.1 C5b-9 Elevated Stratum

This population includes all subjects enrolled under the C5b-9 elevated stratum (C5b-9 >244 ng/ml), and is the primary target population for analysis.

3.2.5.2 C5b-9 Non-Elevated Stratum

This population includes all subjects enrolled under the C5b-9 non-elevated stratum (C5b-9 <=244 ng/ml). As the sample size in this stratum is small, only summary results will be provided, no test between treatment groups will be done

3.2.5.3 Combined Population

The two strata combined (including both elevated and non-elevated C5b-9 strata) will be considered the secondary population for the primary analysis.

4 ANALYSIS OF DISPOSITION AND SUBJECT CHARACTERISTICS

4.1 Disposition and Analysis Populations

Subjects who withdrew early from the study with the reasons for early withdrawal, and subjects who prematurely discontinued study drug with the reasons for discontinuation will be presented by treatment group. These treatment groups include the number of subjects who were screened, screen failed (by reason), randomized, completed Treatment Period A at Week 26, and who completed the Avacopan treatment period. Additionally, the number of subjects in each analysis population will be presented by treatment group.

4.2 Protocol Deviations

Significant protocol deviations, i.e., those pertaining to Good Clinical Practice (GCP) violations and those that may affect the efficacy evaluation, will be captured in the Study Management System as CSR Reportable deviations. These significant deviations will be listed and summarized by category for all randomized subjects. These deviations will be reviewed prior to database freeze to determine the potential impact on the interpretation of the efficacy outcomes. The effect of major protocol deviations will be assessed by conducting per-protocol analyses (see section 3.2.4). This will be determined and documented prior to unblinding the study for the primary analysis and then again at final database lock, if applicable. Deviations related to COVID-19 will be classified as such and may be summarized and/or listed separately.

4.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be described separately for all subjects who enrolled in Treatment Period A and subjects who enrolled in Treatment Period B. These will also be described separately for strata of elevated C5b-9 blood level and non-elevated C5b-9 blood level in the ITT population. This description will include subject baseline characteristics and demographic data (age, sex, race, ethnicity, weight, height, body mass index, viral test results, C3G disease type and duration [from time of first diagnosis based on renal biopsy in months], eGFR, proteinuria [UPCR], complement marker levels, and urinary MCP-1:creatinine ratio) will be listed by study center and subject number, and will also be summarized by treatment group for all randomized subjects.

4.4 Concomitant Medications

All prior and concomitant medications (including medications taken for C3G) will be listed and summarized by Anatomic Therapeutic Chemistry (ATC) classification. The numbers and percentages of subjects taking prior and concomitant medications will be summarized by treatment group, ATC class, and preferred term for the Randomized Population. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (Sep 2016E B2).

Prior medications are defined as any medication taken prior to the first dose of study medication. Concomitant medications are defined as any medication taken on or after the first dose of study medication. A medication can be classified as both prior and concomitant if it started during the screening period and continued into the treatment period. Prior medications were to be recorded for any medication taken for C3G within 12 months of screening or taken for reasons other than C3G within 6 months of screening.

4.4.1 Non-Study Supplied Treatments for C3G

Non-study specified or supplied treatments for C3G will be listed and summarized by treatment group. These treatments include, but are not limited to, non-protocol allowed or increased doses of the following medications: glucocorticoids, mycophenolate (MMF), , angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), renin-angiotensin-aldosterone system (RAAS) blockers, aldosterone, cyclosporin, calcineurin inhibitors, eculizumab and other anti-C5 antibodies, strong inducers/inhibitors of CYP3A4 enzyme (Inducers :carbamazepine, phenobarbital, and phenytoin, rifampin, or St. John's wort and Inhibitors: boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole) or other experimental or immunosuppressive drugs.

5 ANALYSIS OF EFFICACY

The overall efficacy hypothesis in this study is that avacopan treatment will be effective in treatment of subjects with C3G based on improvement in renal histology (C3G histologic index of activity).

5.1 Covariates and Subgroups

The analysis of the efficacy endpoints may be performed by the following variables in the form of covariate analysis and/or subgroup analysis:

Stratification factors [1]:

- Subjects with elevated C5b-9 levels (>244 ng/mL)
- Subjects with non-elevated C5b-9 levels (≤244 ng/mL)
- Disease type C3GN
- Disease type DDD
- Subjects who received a renal transplant
- Subjects who have not received a renal transplant

[1] The stratification factor values as collected in the electronic case report forms (eCRFs) will be used for all stratified efficacy analyses, subgroup analyses and summaries of baseline characteristics. If missing, actual stratification factor will be used. Stratification groups with low counts may be combined.

Subgroups and Covariates

- Sex
- Baseline BMI
- Age at diagnosis of C3G
- Age at randomization; a subgroup analysis will be performed in 12 to 17 year-old subjects, if feasible.
- Duration of C3G
- Subject's race and ethnicity (if plausible)
- Baseline C3G Histologic Index for disease activity
- Baseline C3G Histologic Index for disease chronicity
- Baseline eGFR
- Baseline UPCR
- Baseline urinary MCP-1:creatinine ratio
- Baseline C5b-9, C5a, and C3a
- Geographic distribution (North America vs. Rest of World)

5.2 Primary Efficacy Analysis

The primary efficacy endpoint is the percent change from baseline to Week 26 in the C3G Histologic Index for disease activity. The C3G Histologic Index for disease activity can assume a score from 0-21. See Section 2.3.4 for further details on the calculation of C3G Histologic Index for disease activity.

Statistical Hypothesis Testing and Procedure

• The null hypothesis (H0) is that the avacopan group is not different from the placebo group when comparing the percent change from baseline to Week 26 in the C3G Histologic Index for disease activity.

• The alternative hypothesis (H1) is that the avacopan group is different from the placebo group when comparing the percent change from baseline to Week 26 in the C3G Histologic Index for disease activity.

Numbers, means, median, standard deviation, standard error of means, minimum and maximum will be presented by treatment group and study visit. Avacopan and placebo groups will be compared by Analysis of Covariance (ANCOVA) with treatment group as factor and baseline C3G Histologic Index for disease activity as a covariate. The LS mean estimate and corresponding 95% confidence interval (CI) will be estimated for the treatment main effect. The heterogeneity of the treatment effect across disease diagnoses and renal transplant strata may be investigated through subgroup analyses.

As there are no data available to access the possibility of non-normality distribution of percent change or change from baseline, normality distribution tests will be performed for both percent change and change from baseline. It is possible that the normality test would not hold for percent change from baseline or change from baseline or both. In this case, the following is the analysis procedures for the primary efficacy endpoint.

• If the test for normality fails for percent change from baseline at α level of 0.10 but not change from baseline, change from baseline will be used as the primary endpoint;

• If the test for normality fails for both percent change and change from baseline at α level of 0.10, percent change from baseline will be used as the primary endpoint, but non-parametric methodology will be used for the primary endpoint analysis. The van Elteren's test will be applied to test the percent change from baseline endpoint.

The treatment effect based on the baseline complement profile of subjects may also be investigated.

The SAS code to generate the Analysis of Covariance will be similar to the following:

```
*******************************************************************************
Note:  TRT01PN = Randomized Treatment Group (1 = Placebo, 2 = Avacopan)
       PCHG = Percent Change from Baseline
```

```
       BLIndex = Baseline C3G Histologic Index for disease activity
*******************************************************************************

proc mixed data=C3GData;
       class TRT01PN;
       model PCHG= TRT01PN BLIndex / solution cl outp=resid ddfm=kr;
       LSMEANS TRT01PN / cl diff alpha=0.05;
       ODS output LSMeans=lsmean
                  Diffs=lsmdiff;
run;
```

See Appendix 12.3 for the SAS code to perform van Elteren's test to compare the two treatment groups using the imputed datasets.

5.2.1 Primary Analysis

The primary analysis will be based on the ITT population in the elevated C5b-9 stratum (>244 ng/ml). The primary analysis is based on percent change from baseline to Week 26 during the double-blind treatment period and will be analyzed using the ANCOVA analysis methods described above. Both percent change from baseline and change from baseline will be summarized and analyzed with percent change from baseline being the primary efficacy endpoint.

Multiple Imputation Method

Missing data used to calculate the primary endpoint will be handled using the Missing at Random (MAR) multiple imputation method. The multiple imputation procedure will be conducted in two parts using SAS® PROC MI and PROC MIANALYZE.

The primary analysis will be carried out by imputing missing data for the 7 lesions that comprise the Histological Index for Disease Activity. The multiple imputation model will include the two stratification factors (disease type [C3G or DDD] and kidney transplant status [Y/N]), treatment group, in addition to values at each visit from baseline through week 26. For each lesion component, 100 'complete' datasets will be generated using SAS® PROC MI. The seeds for the imputation will be specified as '12061', '36102', '94218', '20949', '60137', '80230' and '59137', for imputation of 7 lesion activity scores, respectively. Imputed individual lesion component scores will then be classified into scale scores (e.g., leukocyte infiltration % involvement = 29% would translate to a scale score of 2). The 'complete' datasets for the individual components of the lesion activity scores will be merged by imputation number and summed to calculate the Histological Index for Disease Activity and creation of 100 'complete' datasets for evaluation of activity scores.

For the subjects with missing data, continuous results of mesangial hypercellularity, endocapillary hypercellularity/proliferation, membranoproliferative morphology, leukocyte infiltration, crescent formation, fibrinoid necrosis will be imputed first and then their categorical results will be calculated in order to calculate Histological Index for Disease Activity.

The results from the 100 fitted models will be combined using SAS® PROC MIANALYZE. The estimate of the treatment difference and standard error from the analysis will be analyzed by PROC MIANALYZE to obtain the overall estimate of treatment difference, as well as the confidence interval and p-value for the hypothesis testing.

See Appendix 12.3 for additional details.

5.2.2 Secondary Analysis

The same analysis as described for the primary analysis will also be performed for the following:

- Percent change and change from baseline to Week 26 during the placebo-controlled, double-blind treatment period in the combined C5b-9 strata (subjects with elevated C5b-9 blood levels and non-elevated C5b-9 blood levels).
- Percent change and change from Week 26 to Week 52 during the avacopan treatment period in the elevated C5b-9 stratum
- Percent change and change from Week 26 to Week 52 during the avacopan treatment period in the combined C5b-9 strata (subjects with elevated C5b-9 blood levels and non-elevated C5b-9 blood levels).

For percent change and change from Week 26 to Week 52, observed data at Week 26 and Week 52 will be used in the primary analysis and will be conducted in patients who completed Week 26 and Week 52 renal biopsies. The percent change from Week 26 to Week 52 will be only analyzed for subjects for whom the Week 26 activity index score is not 0. Multiple imputation methods similar to the primary endpoint at Week 26 may be explored.

Since the placebo group in Treatment Period A will receive avacopan during the second 26 weeks of the study, the percent change from Week 26 to Week 52 in the C3G Histologic Index for activity in the placebo control group will be compared to the percent change from baseline to Week 26 in the same group. This analysis will be done by the paired t-test. Point estimates and corresponding 95% confidence intervals will be estimated for the difference between the second 26 weeks (avacopan treatment) and the first 26 weeks (placebo treatment). This same analysis will be performed in the avacopan treatment group, comparing percent change from Week 26 to Week 52 in the C3G Histologic Index for activity in the avacopan treatment group to the percent change from baseline to Week 26 in the avacopan treatment group. These analyses will be carried out in the ITT population in the elevated C5b-9 stratum (>244 ng/ml) and separately for the combined C5b-9 strata. These analyses will require non-missing data at Baseline, Week 26 and Week 52. The same analyses will be carried out for change from baseline.

The SAS code to generate the paired t-test will be similar to the following:

```
*******************************************************************************
Note:
      BL_W26 = Percent Change from Baseline to Week 26 in the C3G Histologic Index for
               activity in the randomized placebo or avacopan group
      W26_W52 = Percent Change from Week 26 to Week 52 in the C3G Histologic Index for
                activity in the randomized placebo or avacopan group
      BLIndex = Baseline C3G Histologic Index for disease activity
*******************************************************************************

proc ttest data=C3G_pair;
       paired BL_W26 * WK26_W52;
       ODS output Statistics=S_ttest ttests=T_ttest;
run;
```

The percent change from baseline to Week 52 in the C3G Histologic Index in the avacopan group will also be compared to the percent change from baseline to Week 52 in placebo control group using similar methodology as described for the primary analysis (ANCOVA). Observed data at baseline and Week 52 will used in the analysis. The same analyses will be carried out for change from baseline.

Additional sensitivity analysis may be conducted for the percent change and change from Week 26 to Week 52, by excluding

- Subjects with significant lack of compliance of study medication administration (avacopan /placebo) defined as: All subjects who were <75% compliant overall in Period B.
- Subjects with clinically significant increase in immunosuppressant dose (MMF, Prednisone) or new treatment medications for C3G during Period B

Subjects to be excluded from Period B will be identified and documented prior to the database lock and unblinding for analysis.

5.2.3 Sensitivity Analysis

Pattern Mixture Analysis

A sensitivity analysis will be performed using a pattern mixture model with multiple imputation for missing data under the missing not at random (MNAR) assumption using the same approach as described for the primary analysis in Section 5.2.1. See Appendix 12.3 for further details.

Modified Multiple Imputation Analysis

The second sensitivity analysis may be carried out imputing C3G Histological Index of Disease Activity data for subjects who had clinical significant increase or new introduction of treatments

for C3G including MMF and/or prednisone after screening biopsy and prior to week 26 renal biopsy; should any of these changes invalidate histological activity scores at week 26. Identification of these medications will be performed and impacted subjects will be identified prior to Week 26 Primary Endpoint data freeze. Similar methodology as described for the primary analysis (ANCOVA) will be carried out. The same multiple imputation as specified for the primary analysis (Section 5.2.1) may be performed imputing C3G Histological Index of Disease Activity component scores and Disease Chronicity component scores after the initiation of the restricted medication. The imputed values will be used to calculate the C3G Histological Index of Disease Activity and Disease Chronicity. See Section 2.3.4 for details on calculation of these variables. Identification of these medications will be performed and impacted subjects will be discussed and finalized prior to database lock.

Modified Multiple Imputation method may be explored for the percent change and change from Week 26 to Week 52 during the avacopan treatment period.

Additional Modified Multiple Imputation Analysis may be conducted to explore other aspects of changes of treatments for C3G, such as clinical significant dose decreases of immunosuppressants, glucocorticoids, or ACE inhibitors/ARBs in Period A.

5.2.4 Completer Analysis

A completer analysis will also be carried out requiring subjects in ITT to have valid C3G Histologic Index for disease activity scores at Baseline and Week 26. The primary analysis is based on percent change from baseline to Week 26 during the double-blind treatment period and will be analyzed using the ANCOVA analysis methods described above. The primary analysis will be based on the in the elevated C5b-9 stratum (>244 ng/ml). The same analysis will also be carried out for the combined C5b-9 strata (subjects with elevated C5b-9 blood levels and non-elevated C5b-9 blood levels). This analysis will be repeated for the change from baseline also.

5.2.5 Individual Components of C3G Histological Index Activity

Change from baseline in individual components of the C3G Histological Index Activities indices will also be summarized over time based on actual and imputed data.

5.2.6 Per-Protocol Analyses

The same analyses as described for the Primary Analysis will also be conducted in the Per-Protocol population.

Additional per-protocol analysis may be conducted to explore other aspects of changes of treatments for C3G, such as clinical significant dose decreases of immunosuppressants, glucocorticoids, or ACE inhibitors/ARBs in Period A

5.3 Secondary Efficacy Analyses

5.3.1 Percent change from baseline in UPCR during the 26 Week placebo-controlled treatment period

Urinary protein:creatinine ratio (UPCR) is computed at Baseline, Weeks 1, 2, 4, 12, 20, 26 during the 26 week double-blind treatment period and Weeks 28, 32, 38, 52 and 60 during the active treatment and follow-up periods.

5.3.1.1 Primary Analysis

The primary analysis will be based on the ITT population in the elevated C5b-9 stratum (>244 ng/ml). The primary analysis of percent change from baseline (in the form of ratio) in UPCR over 26 weeks will be performed in the subjects in ITT population whose UPCR is abnormal at baseline using a mixed effect model for repeated measures (MMRM) analysis with treatment group, visit, treatment-by-visit interaction and baseline as a covariate. The abnormal UPCR value is defined as UPCR $\geq$ 0.15 g/g. Subjects will be considered as repeated measure units over visits. Point estimates and corresponding 95% confidence intervals will be estimated for the difference between avacopan and placebo across 26 weeks using a simple contrast from the model.

To alleviate the skewness of the data, UPCR will be $\log_e$-transformed before entering into the MMRM analysis. Least squares mean differences between avacopan and the placebo group in the percent change from baseline to Week 26 log(UPCR) will be back transformed to obtain the estimate for the baseline-adjusted reduction from control in UPCR. Corresponding P-values will also be presented.

In the MMRM model, missing data will not be imputed. Toeplitz covariance matrix will be used to model within-subject variance-covariance structure for the model errors. If the model does not converge using the Toeplitz covariance matrix, AR(1) covariance matrix will be used. If convergence is still not met, then compound symmetry (CS) will be used.

The code used to generate the MMRM analysis will be similar to the following:

```
*******************************************************************************
Note:
TRT01AN = randomized treatment group (numeric): 1=Placebo, 2=Avacopan
VISITN = Visit Number
LR2BASE = Ratio of Visit Value to Baseline Value (log-transformed)
LBASE = Baseline value of response (log transformed)
      proc mixed data=lablog;
      class SUBJID VISITN TRT01AN(ref='1');
      model LR2BASE = TRT01AN VISITN TRT01AN*VISITN LBASE/
                      solution cl ddfm=kr;
      Repeated VISITN / TYPE=TOEP sub=SUBJID;
                        **use AR(1) if no convergence, then CS;
      lsmeans VISITN*TRT01AN / alpha=0.05 cl pdiff slice=VISITN;
      ods output LSMeans=LSM
```

```
                Diffs=DiffLSM;
    run;
```

5.3.1.2 Secondary Analysis

The same analysis as described for the primary analysis will also be performed for the following:

- Percent change from baseline over 26 weeks during the double-blind treatment period in the combined C5b-9 strata (subjects with elevated C5b-9 blood levels and non-elevated C5b-9 blood levels)
- Percent change from week 26 to week 28, 32, 38, 44 and 52 by prior treatment group during the Avacopan treatment period in the elevated C5b-9 stratum
- Percent change from week 26 to week 28, 32, 38, 44 and 52 by prior treatment group during the Avacopan treatment period in the combined C5b-9 strata (subjects with elevated C5b-9 blood levels and non-elevated C5b-9 blood levels).

Additionally, percent change from baseline in UPCR across the entire study including visits during the follow-up period (Weeks 54, 57 and Week 60) will be summarized by treatment group. The percent change from baseline to Week 52 in UPCR in the avacopan group will be compared to the percent change from baseline to Week 52 in the placebo control group using similar methodology as described for the primary analysis (ANCOVA) of C3G Histologic Index for disease activity. Missing data will not be imputed. Summary and analyses will be carried out in the ITT population in the elevated C5b-9 stratum (>244 ng/ml) and separately for the combined C5b-9 strata.

5.3.1.3 Subgroup Analysis

A subgroup analysis will be carried out separately based on baseline UPCR (>1 vs <= 1 g protein/g creatinine). These analyses will be the same as described in Section 5.3.1.1 for the following:

- Percent change from baseline over 26 weeks during the double-blind treatment for the elevated C5b-9 stratum
- Percent change from baseline over 26 weeks during the double-blind treatment period in the combined C5b-9 strata

5.3.1.4 Sensitivity Analysis

For subjects who had clinical significant increased doses or new introduction of ACE inhibitors/ARB post baseline, a sensitivity analysis will be performed where data is imputed after the point of ACE inhibitors/ARB treatment change. The last observation prior to the start of concomitant medication will be carried forward to subsequent time points. Note that LOCF can only be applied within a treatment period and not across periods. Sensitivity analysis will be carried

out similar to the primary and secondary analyses of UPCR as described in Sections 5.3.1.1 and 5.3.1.2:

- Percent change from baseline to Week 26 during the double-blind treatment period (separately for elevated C5b-9 stratum and combined C5b-9 strata)
- Percent change from Week 26 to Week 52 during the Avacopan treatment period (separately for elevated C5b-9 stratum and combined C5b-9 strata)
- Percent change from baseline across the entire study with comparison between treatments at Week 52 period (separately for elevated C5b-9 stratum and combined C5b-9 strata)

Additional sensitivity analysis of UPCR may be conducted to explore other aspects of changes of ACE inhibitor/ARB treatments for C3G, such as clinical significant dose decreases in Period A.

5.3.2 Change and Percent change from baseline in eGFR during the 26 Week placebo-controlled treatment period

The same analysis as described for UPCR will be carried out for estimated glomerular filtration rate (eGFR) including primary and secondary analyses. eGFR will not be $\log_e$-transformed before entering into the MMRM analysis. eGFR is computed at Baseline, Weeks 2, 4, 12, 20, 26 during the 26 week double-blind treatment period and Weeks 32, 38, 52 and 60 during the active treatment and follow-up period.

A subgroup analysis for the change and percent change from baseline in eGFR will be performed in patients with impaired renal function at baseline eGFR (<60, ≥ 60 mL/min/1.73 m^2), if there are sufficient number of subjects in these subgroups

5.3.3 Change from baseline in the C3G Histological Index for disease chronicity during the 26 Week placebo-controlled treatment period

C3G Histologic Index for disease chronicity considers 4 lesions and can assume a score from 0 to 10. See Section 2.3.4 for further details on the calculation of C3G Histologic Index for disease chronicity.

The analysis of C3G Histologic Index for disease chronicity will be carried as described in Section 5.2 for C3G Histologic Index for disease activity including all secondary, completer and sensitivity analyses.

Similar to Histological Index for Disease Activity, the primary analysis will be carried out by imputing missing data for the 4 lesions that comprise the Histological Index for Disease Chronicity. The multiple imputation model will include the two stratification factors (disease type [C3G or DDD] and kidney transplant status [Y/N]), treatment group, in addition to values at each visit from baseline through week 26. Glomerulosclerosis is calculated from % glomeruli with global and %glomeruli with segmental sclerosis which is then summed to calculate total percent of glomeruli involved. If individual values are missing, the total percent of glomeruli will be imputed.

For each lesion component, 100 'complete' datasets will be generated using SAS® PROC MI. The seeds for the imputation will be specified as '16222', '71217', '60993', and '19457', for imputation of 4 lesion chronicity scores, respectively. Imputed individual lesion component scores will then be classified into scale scores (e.g., Interstitial fibrosis = 18% would translate to a scale score of 1). The 'complete' datasets for the individual components of the lesion chronicity scores will be merged by imputation number and summed to calculate the Histological Index for Disease Chronicity and creation of 100 'complete' datasets for evaluation of chronicity scores.

For the subjects with missing data, continuous results of glomerulosclerosis and cortical tubulointerstitial area involved will be imputed first and then their categorical results will be calculated in order to calculate Histological Index for Disease Chronicity.

5.3.4 Proportion of subjects who have a histological response

Histological response is defined as a decrease (improvement) in the C3G Histological Index for disease activity of at least 35% from baseline to Week 26. See Section 2.3.4 for further details.

5.3.4.1 Primary Analysis

For the responder analysis, data of the patients who had clinical significant increase or new introduction of treatments for C3G including MMF and/or prednisone after screening biopsy and prior to week 26 renal biopsy and were identified in the Modified Multiple Imputation Analysis will be imputed as non-responder after the initiation of rescue concomitant medication. The number and proportion of subjects who have a histological response will be presented for each treatment group. Differences between avacopan and placebo will be analyzed using the Cochran-Mantel-Haenszel (CMH) chi-square test.

The code used to generate the analysis will be similar to the following:

```
*******************************************************************************
Note:  TRT01PN = Randomized Treatment Group (1 = Placebo, 2 = Avacopan)
       RESPONSE = Histological Response (1=Yes, 0=No)

proc freq data=HISTRESP;
   tables TRT01PN*RESPONSE/out=counts outpct cmh;
   ods output CMH=pvalue;
run;

*******************************************************************************
```

Additionally, the number and percent of subjects whose histological activity scores at week 26 had been invalidated because of a clinical significant dose increase or new introduction of medication to treat C3G including MMF and/or prednisone after screening biopsy and prior to week 26 renal biopsy will be summarized. For the responder analysis, data will be imputed as non-responder after the initiation of rescue concomitant medication. Concomitant medications

and other data such as adverse events will reviewed prior to database lock to determine if reason for medication use is considered to be for rescue.

Modified Multiple Imputation method may be explored for the proportion of subjects who have a histological response.

5.3.5 Change from baseline in urinary MCP-1:creatinine ratio during the 26 Week placebo-controlled treatment period

The same analysis as described for UPCR will be carried out for urinary MCP-1:creatinine ratio including primary and secondary analyses. Urinary MCP-1:creatinine ratio is computed at Baseline, Weeks 1, 2, 4, 12, 20, 26 during the 26 week double-blind treatment period and Weeks 28, 32, 38, 52 and 60 during the avacopan treatment and follow-up periods.

5.3.6 SF-36 v2 and EQ-5D-5L VAS and Index - Change from Baseline during the 26 Week placebo-controlled treatment period

The same analysis as described for eGFR will be carried out including primary and secondary analyses. This includes the physical component score, mental component score, and eight domains of the SF-36 v2, and the visual analogue scale and index of the EQ-5D-5L.

SF-36 v2 and EQ-5D-5L are computed at Baseline, Weeks 4, 12, 20, 26 during the 26 week double-blind treatment period and Weeks 32, 38, 52 and 60 during the avacopan treatment and follow-up period.

5.4 8-week Follow-Up Period Data

After the 52-week treatment period, there is an 8-week follow-up period during which subjects are not receiving any study treatment. Subjects visit the study centers at Weeks 54, 57 and Week 60 for the final study visit. Data collected at the follow up visit will be listed by subject and summarized by treatment group assignment in the double-blind period. Change and percent change in the efficacy parameters during the 8-week follow-up period will also be assessed to determine the off-treatment effect. No inferential statistical analyses will be conducted on the follow-up period data.

6 ANALYSIS OF SAFETY

6.1 Population

All safety parameters will be summarized using the Safety Population. All safety assessments will be based on actual treatments received by participants.

6.2 Study Drug Exposure and Compliance

Subject drug exposure will be calculated based on the study drug dispensing and return records (based on drug accountability). Avacopan plasma concentrations over the course of the study will also be used to assess compliance. The avacopan/placebo compliance will be calculated comparing the study drug dispensed and the study drug returned. The study drug exposure

(duration, total dose, and average daily dose) and compliance will be summarized and listed. If date of last dose is not available, the date of discontinuation from study will be used.

Duration of exposure is defined as the date of the last dose of study medication minus the date of the first dose of study medication plus 1. Duration of exposure to study medication will be summarized with descriptive statistics for the double-blind period, avacopan treatment period and both periods combined. Exposure data will be provided for the following intervals:

- < 26 weeks
- ≥ 26 weeks

Percent compliance to study drug will be summarized for double-blind, avacopan treatment period and both periods, calculated as follows:

Percent Compliance *= 100 × number of capsules taken / (6 × number of days in the specified period).*

Percent compliance to the study drug regimen will be summarized by treatment group based on the Safety Population using counts and percentages of subjects with compliance in the following categories:

- <75%
- 75-120%
- >120%

For adolescent subjects, the dose of avacopan or placebo on Day 1 of the Treatment Period A will be calculated based on the body weight determined at screening. Depending on the avacopan plasma exposure ($AUC_{0\text{-}6hr}$) from Day 1, the dose will be adjusted as shown in Table 2. These dose adjustments will be made as soon as the plasma exposure results are available.

When adolescent subjects begin Treatment Period B (avacopan treatment period), they will receive avacopan twice daily. Starting on Day 183, their dose will be recalculated based on the body weight determined on that day according to Table 2. Depending on the avacopan plasma exposure ($AUC_{0\text{-}6hr}$) from Day 183 the dose will be adjusted as shown in Table 2. These dose adjustments will be made as soon as the plasma exposure results are available. If adolescent subjects were treated with avacopan in the first 26 weeks, their dose adjustment in the avacopan treatment period may be determined based on Day 183 trough concentration rather than exposure ($AUC_{0\text{-}6hr}$).

Table 2. Avacopan/Placebo Starting Dose and Dose Adjustments Based on Avacopan Plasma Exposure in Adolescent subjects

Body weight	Avacopan/Placebo Dose on Day 1 and Day 183, respectively	Avacopan Plasma $AUC_{0\text{-}6hr}$ (ng•hr/mL) on Day 1 (or Day 183 if the subject was on placebo in the first 26 weeks)	Avacopan Dose Adjustment
<40 kg (88 lb)	10 mg (1 capsule) twice daily	≥351	None
		<351	Increase dose to 20 mg (2 capsules) twice daily
40-55 kg (88-121 lb)	20 mg (2 capsules) twice daily	351 to 699	None
		<351	Increase dose to 30 mg (3 capsules) twice daily
		>699	Decrease dose to 10 mg (1 capsule) twice daily
>55 kg (121 lb)	30 mg (3 capsules) twice daily	≤699	None
		>699	Decrease dose to 20 mg (2 capsules) twice daily

For adolescents, the formula will be altered to be consistent with the number of capsules taken daily, e.g., if the avacopan dose was 10 mg twice daily, the formula would be:

100 × number of capsules taken / (2 × number of days in the specified period).

6.3 Adverse Events

Adverse event results will be provided including number of events and percentages of subjects (subject incidence) affected for the 3 Safety Populations (see 3.2.3 for definitions) separately including the following:

- All treatment emergent serious adverse events by SOC and preferred term
- All treatment emergent serious adverse events by decreasing order of frequency by preferred term
- All treatment emergent non-serious adverse events by SOC and preferred term
- All treatment emergent non-serious adverse events by preferred term by decreasing order of frequency
- All treatment emergent serious and non-serious adverse events by SOC

- All treatment emergent serious and non-serious adverse events by decreasing order of frequency by preferred term

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1.

TEAEs for the Safety Population in each period are defined as an event with a start date on or after the first study drug treatment in each period and up to the final observation in each period. Treatment periods for analysis of adverse event are defined in Section 3.2.3. TEAEs for the All Avacopan Treated Population are defined as an event with a start date on or after the first dose of avacopan up to the final visit.

Adverse events will be listed by treatment group, including all available information of interest such as onset and resolution dates, study day of onset and resolution relative to first dosing day, duration, severity, seriousness, causal relationship to study medication per the investigator, action taken with study medication, and outcome. Separate listings will be provided for TESAEs, TESAEs and TEAEs leading to discontinuation of study drug, and TEAEs of interest.

TEAEs of interest include hepatic enzyme elevations, hypersensitivity Standardized MedDRA Queries (SMQ), infections, decrease in white blood cell count and elevations in creatine phosphokinase (CPK).

The severity of AEs was assessed by the investigator using the following protocol definitions:

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

6.4 Safety Laboratory Parameters

Laboratory parameter results and changes from baseline will be summarized by visit. Summaries will be limited to values assessed at the Central Laboratory. Laboratory values collected at local laboratories will be provided in listings, but not summarized. Shift tables from baseline to subsequent study visits will also be generated based on the Central Laboratory measurements for ALT, AST, total bilirubin, serum creatinine, urine protein:creatinine ratio, creatine phosphokinase, sodium, hematocrit, platelets, white blood count, neutrophils, and lymphocytes. Counts and percentages of laboratory values outside the normal reference range will be summarized by laboratory parameter, treatment group and visit. The denominator for percentages will be the number of subjects in the particular treatment group with measurement at a specified visit. Laboratory values outside the reference ranges will be flagged in the listings. Summaries will be presented separately for the double-blind and avacopan treatment periods, respectively.

The subject incidence of elevated laboratory values of ALT, AST, total bilirubin, alkaline phosphatase, creatinine, potassium, and creatine phosphokinase (CPK) as assessed by the Central Laboratory, will be summarized by treatment group and Grade, as defined per Common Terminology Criteria for Adverse Events (CTCAE) Version 5. Shift from baseline to highest CTCAE grade during the study period will also be produced for these laboratory parameters based on the Central Laboratory measurements. The same summary by treatment and CTCAE grade will be produced for subject incidence of low neutrophils, low lymphocytes, low leukocytes, low hemoglobin, and low platelets. Shift from baseline to highest CTCAE grade during the study period will also be produced for these laboratory parameters. A by-subject listing including all data for these laboratory parameters including CTCAE grade for subjects with any abnormality will be provided.

6.5 Vital Signs

Vital sign results and changes from baseline will be listed and summarized by study visit and treatment group separately for the double-blind and open-label periods.

6.6 ECG Parameters

Abnormal ECG findings will be listed by treatment group and study visit, and clinical significance of abnormalities indicated.

6.7 Physical Examinations

Physical examination findings will be listed by treatment group and study visit, and clinical significance of abnormalities indicated.

6.8 Pharmacokinetic and Pharmacodynamic Marker Analysis

Individual plasma concentrations of avacopan and its significant metabolite CCX168-M1 will be listed, plotted, and summarized descriptively and graphically. When possible, the mean steady state trough concentrations and the terminal elimination half-life will be calculated. PK parameters such as C_{max}, T_{max}, and $AUC_{0\text{-}6hr}$ will be calculated in adolescents for avacopan and metabolite CCX168-M1 based on plasma concentrations for samples collected on Day 1 and on Day 183. Plasma and urinary PD markers will be summarized and may be analyzed using methods analogous to the efficacy parameters. The relationship between PK parameters and renal function based on eGFR will also be evaluated. The data may also be used to evaluate the PK/PD relationship of avacopan treatment. To this end, the change and/or percent change from baseline in C3G Histologic Index for disease activity, C3G Histologic Index for disease chronicity, eGFR, UPCR, urinary MCP-1:creatinine ratio, or other biomarkers may be used as PD markers.

Details of the PK and PD analysis will be described in a separate analysis plan and will be reported in a separate report

7 DATA MONITORING COMMITTEE

In addition to continuous safety monitoring by the Medical Monitor and clinical staff, an external Data Monitoring Committee (DMC) has been established to monitor the safety of subjects over the course of the study. The DMC consists of external physicians and a biostatistician. A DMC charter was developed before start of the study and the DMC functions according to the charter. The DMC has regular meetings, once every 3 to 6 months, depending on study enrollment rate. Ad hoc meetings may be scheduled if unanticipated safety events occur. After review of data at each meeting, the DMC makes recommendations about further conduct of the study.

8 ANALYSIS TIMING

Per the protocol, the earliest time point at which the primary efficacy analysis can occur is when the last enrolled subject in the primary population (subjects in the elevated C5b-9 stratum) has completed the Week 26 visit. The second (follow-up) analysis will be performed when all subjects have completed the full study after Week 60. No Type I error adjustment will be made for the second analysis since the endpoints for the second analysis are different from the first analysis and it is considered to be supportive.

Additionally, enrollment for the stratum with C5b-9 levels ≤244 ng/ml could terminate early, if subject enrollment in the elevated stratum (C5b-9 level >244 ng/mL) reaches target enrollment first. Further, both strata can be analyzed separately and independently. The stratum with elevated levels (primary population) will be analyzed first should the stratum with C5b-9 ≤244ng/ml (secondary population) continue a blinded follow up.

8.1 Week 26 Primary Analysis

The Week 26 Primary Efficacy Analysis will be performed including all subjects who reach Week 26 or discontinued the study by 01-Oct-2020. The data beyond Week 26 will also be summarized for data collected and cleaned at the time of the data cutoff. As of 01-Oct-2020, there are four subjects (2 patients in each of the two C5b-9 stratum) who are ongoing and will not reach Week 26 at the time of data cutoff of the primary analysis. Details of subjects who had major protocol deviations that could affect the primary efficacy outcome will be documented in a memo along with other patient population decisions at the conclusion of blinded data review prior to the data freeze.

The final analysis will be performed when all subjects have completed the full study after Week 60. The final analysis will repeat the primary analysis on all subjects' data, including patients who are ongoing for the week 26 renal biopsies now and enrolled in the future. The final results will be consider as supportive of the primary analysis. All study results will be included in a single Clinical Study Report.

9 SAMPLE SIZE AND POWER CONSIDERATIONS

A sample size of 22 patients per treatment group (avacopan and placebo, respectively) in each of the C5b-9 level strata is based on the between-treatment difference of -35% in the C3G

Histologic Index for activity at Week 26, standard deviation (SD) 34%, power 90%, and 2-sided $\alpha = 0.05$.

The sample size of 22 per group also provides approximately 90% power to detect a delta of -35% in the C3G Histologic Index for activity between the percent change from baseline in the first 26 weeks and in the second 26 weeks, assuming an SD of 34% for each change.

The mean treatment effect size of 35% is considered reasonable based of the following:

- Of the 5 patients with histologic data in the study by Herlitz et al., 2012 with eculizumab, an anti-C5 antibody, 2 patients had a 67% decrease (improvement) in histologic score, 1 had a 43% decrease, and 2 had no change from baseline; the mean decrease for the 5 patients was 35%;
- An improvement in the histologic score of at least 35% is considered clinically meaningful by clinical and histology experts;
- The SD for the percent change from baseline in C3G Histologic Index of activity was 34% in the Herlitz study; a change of 35% of greater will be above the observed variance for this parameter.

10 CHANGES FROM PROTOCOL–SPECIFIED STATISTICAL ANALYSES

- The protocol specified 3 analysis populations for the study including the primary elevated C5b-9 population, the non-elevated C5b-9 population and the combined population. Due to the small sample size in the non-elevated C5b-9 stratum, the primary elevated C5b-9 population will remain as the primary population and the two strata combined (including both elevated and non-elevated C5b-9) will be considered the secondary population for analysis. Data from the non-elevated C5b-9 stratum will only be summarized.
- ITT population definition change to exclude subjects who had baseline C3G Histologic Index of activity score of 0.
- Secondary efficacy endpoint order rearranged.

11 REFERENCES

1. Bomback AS, et al. C3 glomerulonephritis and dense deposit disease share a similar disease course in a large United States cohort of patients with C3 glomerulopathy. Kidney Int. 2018
2. Herlitz LC, et al. Pathology after eculizumab in Dense Deposit Disease and C3 GN. J Am Soc Nephrol. 2012; 23(7):1229–1237
3. Levey AS, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009; 150(9):604–612.
4. Pickering MC, et al. C3 glomerulopathy: consensus report. Kidney Int. 2013; 84(6):1079–1089. 14

5. 14. Schwartz GJ, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol. 2009; 20(3):629–637.
6. Sethi S, et al. Mayo Clinic/Renal Pathology Society Consensus Report on Pathologic Classification, Diagnosis, and Reporting of GN. J Am Soc Nephrol. 2016; 27(5):1278–1287.

12 APPENDICES

12.1 Data Derivation Details

12.1.1 EQ-5D-5L

Crosswalk value sets used in the calculation of the EQ-5D-5L Index Score are available for the following countries: Denmark, France, Germany, Japan, the Netherlands, Spain, Thailand, UK, US and Zimbabwe. For countries not listed above, reference data will used according to the following:

Country	EQ-5D-5L Crosswalk Value Country Set
US, Canada	US
Denmark, Sweden	Denmark
France, Switzerland	France
Germany, Czech Republic, Austria	Germany
Japan	Japan
Netherlands, Belgium	Netherlands
Spain, Italy	Spain
UK, Ireland, Australia, New Zealand,	UK

12.2 Imputation for Missing/Partially Missing Adverse Event and Concomitant Medication Dates

12.2.1 Incomplete Adverse Event Start Date:

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

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

Missing day and month

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

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

Missing day only

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

Missing day, month, and year

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

12.2.2 Incomplete AE Stop Date:

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

Missing day and month

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

Missing day only

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

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

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

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

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

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

12.3 Analysis Methods for Missing C3G Histological Index of Disease Activity and Disease Chronicity

Primary Analysis Method for Missing C3G Histological Index of Disease Activity and Disease Chronicity at Week 26

The primary imputation model for this study will impute missing Week 26 C3G Histological Index of Disease Activity using Missing at Random (MAR) multiple imputation approach.

The multiple imputation method will be conducted in two parts: PROC MI and PROC MIANALZE.

Multiple imputation will be used to impute missing data and will be implemented using SAS® PROC MI: Missing data may be the result of missing lesion components for calculation of C3G Histological Index of Disease Activity or Disease Chronicity or due to subjects discontinuing the study prior to Week 26 or Week 52. Missing at random (MAR) will be assumed. The primary analysis will be carried out by imputing missing data for the 7 lesions that comprise the Histological Index for Disease Activity and separately for the 4 lesions that comprise the Histological Index for Disease Chronicity. The multiple imputation model will include the two stratification factors (disease type [C3G or DDD] and kidney transplant status [Y/N]), treatment group, in addition values at each visit from baseline through week 26. If the model fails to converge, exclusion of stratification factors may be considered.

For each lesion component, 100 ‘complete’ datasets will be generated using SAS® PROC MI. Imputed individual lesion component scores will then be classified into scale scores (e.g.,

leukocyte infiltration % involvement = 29% would translate to a scale score of 2). The 'complete' datasets for the individual components specific to disease activity and disease chronicity separately, will be merged by imputation number and summed to calculate the Histological Index for Disease Activity and Disease Chronicity and creation of 100 'complete' datasets for evaluation of activity and chronicity scores.

The results from the 100 fitted models will be combined using SAS® PROC MIANALYZE. The estimate of the treatment difference and standard error from the analysis will be analyzed by PROC MIANALYZE to obtain the overall estimate of treatment difference, as well as the confidence interval and p-value for the hypothesis testing. This will be done separately for Histological Index for Disease Activity and Histological Index for Disease Chronicity

The steps to carry out the primary multiple imputation and analysis are described below:

```
*******************************************************************************
Note:
      W26 = Week 26 continuous result
      BL = Baseline continuous result
      DISTYPE  = Disease Type (C3GN or DDD)
      RENTRANS = Renal Transplant Status (Y/N)
      TRT01PN = Treatment Group (Placebo/Avacopan)
*******************************************************************************


*******************************************************************************
```

The 6 lesions in disease activity and 2 lesions in disease chronicity with continuous results will be imputed using SAS code below.

```
*******************************************************************************

/* Imputation at Week 26 */
Proc MI Data= num_org Seed= Seedno nimpute= 100
       minimum= . . . 0
       maximum= . . . 100
       Out= mum_mi26;
       by TRT01PN;
       class DISTYPE RENTRANS;
       var DISTYPE RENTRANS BL W26;
       monotone reg(W26/details) ;
Run;

/* Note: In the code above, remove minimum and maximum when imputed value is out of
range; replace percentage <0 to be 0 and replace percentage >100 to be 100 for imputed
values */

proc sort data= mum_mi26;
       by _imputation_ TRT01PN;
run;
```

If imputation at Week 52 is explored, code similar to the following will be used.

```
/* Imputation at Week 52 */
Proc MI Data= mum_mi26 Seed= Seedno nimpute= 1
       minimum= . . . . 0
       maximum= . . . . 100
       Out= mum_mi52;
       by _imputation_ TRT01PN;
       class DISTYPE RENTRANS;
       var DISTYPE RENTRANS BL W26 W52;
       monotone reg(W52/details) ;
Run;

/* Note:  In the code above, if the model is not able to be fit, remove Renal
Transplant Status (RENTRANS) */

*******************************************************************************
```

The 1 classification variable in disease activity and 2 classification variables in disease chronicity will be imputed using SAS code below.

```
*******************************************************************************

/* Imputation at Week 26 */
Proc MI Data= cat_org Seed= Seedno nimpute=100
       out= cat_mi26;
       by TRT01PN;
       class DISTYPE RENTRANS BL;
       var DISTYPE RENTRANS BL;
       monotone logistic(W26= DISTYPE RENTRANS BL/ Details Likelihood=AUGMENT) ;
run;

proc sort data= cat_mi26;
       by _imputation_ TRT01PN;
run;
```

If imputation at Week 52 is explored, code similar to the following will be used.

```
/* Imputation at Week 52 */
Proc MI Data= cat_mi26 Seed= Seedno nimpute=1
       out= cat_mi52;
       by _imputation_ TRT01PN;
       class DISTYPE RENTRANS BL W26 W52;
       var DISTYPE RENTRANS BL W26 W52;
       monotone logistic(W52= DISTYPE RENTRANS BL W26/ Details Likelihood=AUGMENT) ;
       fcs logistic(W52= DISTYPE RENTRANS BL W26/ Details Likelihood=AUGMENT) ;
run;

*******************************************************************************
If there are no patients randomized to Avacopan with missing data at Week 26 in
observed dataset, 100 datasets will be created from observed dataset to combine with
the 100 imputed datasets from the Placebo group; similarly, for no missing in Placebo
group.
*******************************************************************************
```

The Summary Statistics, such as Mean and Standard Errors for Imputed dataset are obtained as follows:

```
*******************************************************************************
Note:
      EFFI = Imputed efficacy analysis dataset
      AVAL = Variable analyzed
      Imputation = Imputed number
      TRT01PN = Treatment Group (Placebo/Avacopan)
*******************************************************************************

*** Proc Univariate to generate sample means and standard errors for the variables in
each imputed data set

Proc Univariate Data= EFFI;
       By _Imputation_;
       Class TRT01PN;
       Var AVAL;
       Output Out= SumStat_MI
              Mean= AVAL
              Stderr= SAVAL;
Run;

Proc sort data= SumStat_MI; By TRT01PN; Run;

*** Proc MIANALYZE;
PROC MIANALYZE DATA = SumStatMI;
       By TRT01PN;
       Modeleffects AVAL;
       Stderr SAVAL;
       ODS Output
              ParameterEstimates = SumStat_Mian;
RUN;


Note: If variables not requested imputation, the above procedure won't be appropriate.
Using PROC MEANS to summary one single imputation to get summary statistics.
```

The ANCOVA analysis will be carried out using the following:

```
*******************************************************************************
Note:
      EFFI = Imputed efficacy analysis dataset
      Response = CHG/PCHG
      CHG = Change from baseline in C3G Disease Activity or Chronicity
      PCHG = Percent change from baseline in C3G Disease Activity or Chronicity
      Base = Baseline value
      TRT01PN = Treatment Group (Placebo/Avacopan)
*******************************************************************************

***  Perform ANCOVA;
PROC MIXED DATA= EFFI;
       By _Imputation_;
       Class TRT01AN(ref='1');
       Model Response = TRT01AN Base / solution cl ddfm = KR
                        residual OUTP = ano_res ;      * studentized residual ;
       Lsmeans TRT01AN / Alpha=0.05 cl diff ;
       ODS Output LSMEANS = ano_lsm
                        Diffs = ano_diff;
RUN;

*** Combine result;
PROC MIANALYZE DATA = ano_lsm;
       By TRT01AN;
       Modeleffects Estimate;
       Stderr;
       ODS Output
              ParameterEstimates = miana_lsm;
RUN;

PROC MIANALYZE DATA = ano_diff;
       By TRT01AN;
       Modeleffects Estimate;
       Stderr;
       ODS Output
              ParameterEstimates = miana_diff;
RUN;

*** Normality Test;
PROC UNIVARIATE DATA = ano_res Normaltest;
       Class _Imputation_;
       Var StudentResid;
       ODS Output
              TestsForNormality = res_SW (Where=(Test="Shapiro-Wilk"));
Run;

*** Select the minimum P-value from Shapiro-Wilk test among all imputation;
```

For the primary analysis of change from baseline to Week 26 in C3G Histological Index of Disease Activity and Disease Chronicity, the normality test is performed on the imputed data using the Shapiro-Wilk test where the lowest p-value is selected. If the p-value is < 0.01, normality is rejected, van Elteren's test is used for the treatment comparison. The steps to carry out the analysis are detailed below.

```
*******************************************************************************
Note:
       EFFI = Efficacy Analysis Dataset with multiple imputation
       Response = categorical variable of interest in analysis
       DISTYPE  = Disease Type (C3GN or DDD)
       RENTRANS = Renal Transplant Status (Y/N)
       TRT01PN = Treatment Group (Placebo/Avacopan)

*******************************************************************************

*** Van Elteren's Test by each Imputation;
Proc Freq Data= EFFI;
       By _Imputation_;
       Table DISTYPE*RENTRANS*TRT01PN*Response / CMH Scores= modridit;
       Ods Output
              CMH= cmh_RMS (Where=(AltHypothesis="Row Mean Scores Differ"));
Run;


*** Apply Wilson-Hilferty transformation to the CMH statistic and standardize the
resulting normal variable;
DATA cmh_wh;
       SET cmh_RMS;

       cmh_value_wh = ((VALUE/DF)**(1/3) - (1-2/(9*DF)))/SQRT(2/(9*DF));
       cmh_sterr_wh = 1.0;

RUN;


*** Proc MIANALYZE;
PROC MIANALYZE DATA = cmh_wh;
       Modeleffects cmh_value_wh;
       Stderr cmh_sterr_wh;
       ODS Output
              ParameterEstimates = cmh_miana;
RUN;
```

A sensitivity analysis will be performed using a pattern mixture model with multiple imputation for missing data under the missing not at random (MNAR) assumption using the same approach as described for the primary analysis. The steps to carry out the multiple imputation and analysis are described below:

```
*******************************************************************************
Note:
      W26 = Week 26 result
      BL = Baseline result
      DISTYPE  = Disease Type (C3GN or DDD)
      RENTRANS = Renal Transplant Status (Y/N)
      TRT01PN = Treatment Group (Placebo/Avacopan)
*******************************************************************************

*******************************************************************************
```

The 6 lesions in disease activity and 2 lesions in disease chronicity with continuous results will be imputed using SAS code below, using the same seed numbers as specified for the primary imputation method.

```
*******************************************************************************
*** Imputation at Week 26, Continuous variable;
Proc MI Data= ERT (Where=(PARAMCD=" ")) Seed= ##### Nimpute= 100
       Minimum= . . . 0
       Maximum= . . . 100
       OUT= PMMnum_IM26;
       Class TRT01PN DISTYPE RENTRANS;
       Var DISTYPE RENTRANS BL W26;
       Monotone Reg(W26/Details) ;
       MNAR Model(W26/ modelobs=(TRT01PN='1')) ;
 Run;

*******************************************************************************
```

The 1 classification variable in disease activity and 2 classification variables in disease chronicity will be imputed using SAS code below using the same seed numbers as specified for the primary imputation method.

```
*******************************************************************************

*** Week 26, Classification variable;
Proc MI Data= ERT (Where=(PARAMCD=" ")) Seed= ##### Nimpute= 100
       OUT= PMMcat_IM26;
       Class DISTYPE RENTRANS TRT01PN BL W26;
       Var DISTYPE RENTRANS TRT01PN BL W26;
       Monotone Logistic(W26= DISTYPE RENTRANS TRT01AN BL / Details
likelihood=AUGMENT);
       MNAR Model(W26/ modelobs=(TRT01PN='1')) ;
 Run;
```

The ANCOVA analysis will be performed as detailed above for the primary imputation method using the imputation datasets.

12.4 Preferred Terms of Adverse Events Potentially Associated with Liver Injury

Alanine aminotransferase increased

Aspartate aminotransferase increased

Alcohol withdrawal syndrome

12.5 Preferred Terms of Adverse Events Indicating WBC Count Decrease

Leukopenia

Lymphopenia

Neutropenic sepsis

Lymphocyte count decreased

Neutrophil count decreased