PROTOCOL

Protocol Amendment 4.0

TITLE PAGE

Study Title:	A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study to Evaluate the Safety and Efficacy of Avacopan (CCX168) in Patients with C3 Glomerulopathy
Protocol Number:	CL011_168
Investigational Product:	Avacopan (formerly CCX168)
Indication:	Treatment of patients with C3 glomerulopathy
Sponsor:	ChemoCentryx, Inc.
Development Phase:	2
IND number	132321
EudraCT number	2017-001821-42
Sponsor's Responsible Medical Officer:	[redacted] ChemoCentryx, Inc. Mountain View, California 94043, USA
Sponsor Signatory:	[redacted]
Approval Date:	**29 June 2017** **13 September 2017 – Protocol Amendment 1.0** **16 April 2018 – Protocol Amendment 2.0** **10 September 2018 – Protocol Amendment 3.0** **20 March 2019 – Protocol Amendment 4.0**

INVESTIGATOR SIGNATORY PAGE

Protocol Number: CL011_168

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I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by ChemoCentryx, Inc.
- Not to implement any deviations from or changes to the protocol without agreement from the Sponsor and prior review and written approval from the Institutional Review Board (IRB)/Ethics Committee (EC), except where necessary to eliminate an immediate hazard to the patients, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- That I am thoroughly familiar with the appropriate use of the investigational drug(s), as described in this protocol, and any other information provided by the Sponsor including, but not limited to the following: the current version of the Investigator's Brochure prepared by ChemoCentryx, Inc. and approved product label, if applicable.
- That I am aware of and will comply with current International Conference on Harmonisation ICH/ Food and Drug Administration (FDA) good clinical practices guidelines (GCP) and all regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the investigational drug(s) and their study-related duties and function as described in the protocol.

_____ _____
Principal Investigator Date

_____
Printed Name

Address*_____

_____

Phone Number* _____

* If the address or phone number needs to be changed during the course of the study, this will be done by the Investigator, with written notification to the Sponsor, and will not require (a) protocol amendment(s).

SPONSOR CONTACT INFORMATION

Protocol Number: CL011_168

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

Medical Officer [redacted]

Vice President, Clinical Development and Translational Medicine

ChemoCentryx, Inc.

850 Maude Avenue

Mountain View, CA 94043 USA

Tel: [redacted]

Fax: [redacted]

Email: [redacted]

Clinical Operations Manager [redacted]

Director of Clinical Operations, [redacted]

ChemoCentryx, Inc.

850 Maude Avenue

Mountain View, CA 94043 USA

Mobile telephone number: [redacted]

Fax number: [redacted]

Email: [redacted]

SPONSOR SIGNATURE FOR APPROVAL

Protocol Number: CL011_168

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

[redacted]

Vice President, Clinical Development and Translational Medicine

March 20, 2019

Date

SUMMARY OF CHANGES: PROTOCOL AMENDMENT 3.0 TO 4.0

1. The protocol Title Page was updated with the new amendment number and date.
2. Changed subject(s) to patient(s) throughout the document for consistency.
3. Protocol updated to specify that the study drug or study medication is blinded throughout the document, where applicable.
4. Details on the study drug or medication updated to be avacopan or placebo throughout the document.
5. SYNOPSIS: study period increased from 26 months to 32 months to reflect previous increase of sample size and slower than expected enrollment.
6. SYNOPSIS – Methodology, Section 3.2 Randomization and Section 8.9 Interim Analysis have been updated to specify the earliest timepoint for the primary efficacy analysis and to clarify that the primary analysis of the primary population (elevated C5b-9 stratum) can occur at a timepoint independent of the secondary population.
7. SYNOPSIS – Methodology has been updated:
    a. To increase the frequency of hematology testing based on the recommendation of the DMC.
    b. To clarify the time allowed to differentiate between common fluctuations of renal function and true deterioration of renal function and to prevent unnecessary discontinuation.
8. SYNOPSIS – Test Product has been updated to clarify that the medication will be administered orally and that placebo contains no active ingredient.
9. Hematology testing was added to study weeks 23, 35, 41 and 48 to increase the testing frequency based on the recommendation of the DMC. The following sections have been updated: Time & Events Table, Section 6.10. Study Week 23, Section 6.14. Study Week 35, 6.16. Study Week 41 and Section 6.18. Study Week 48.
10. Study Schema simplified for better overview and to present duration of individual treatments and to eliminate redundancies (Visit days, Study procedures) and to align with the Time and Events Table.
11. LIST OF ABBREVIATIONS AND ACRONYMS has been updated to include missing acronyms.
12. Section 1.2 Previous Clinical Studies has been updated to include current status of clinical studies and additional details on the review of safety data.
13. Section 3.3.2. Adolescent Patients – Study Treatments, added a statement to clarify the procedure to keep study team blinded.
14. Section 3.4 Study Flow has been updated:
    a. To increase the frequency of hematology testing based on the recommendation of the DMC.

b. To make statement more concise and reduce redundancies within the protocol; the reader is directed to "Section 4.4 Removal of Patients from Therapy" where important lab observations are presented that would cause pausing or discontinuation of study drug (avacopan or placebo).

15. Section 4.4 Removal of Patients From Therapy have been updated:
    a. To ensure that liver function tests are repeated in a timely manner, that study drug (avacopan or placebo) dosing is paused during investigation into the causality of abnormal liver tests and to permanently discontinue study drug when applicable.
    b. To ensure that study drug (avacopan or placebo) dosing is paused during investigation into the causality of abnormal hematology and serum chemistry tests.
    c. To relocate paragraph from Section 3.4 to Section 4.4 to ensure that study drug (avacopan or placebo) dosing is permanently discontinued if a patient experiences deteriorating renal function; for clarification of time allowed to differentiate between common fluctuations of renal function and true deterioration of renal function, and to prevent unnecessary discontinuation.
    d. To relocate text for laboratory abnormalities from 7.2.4.6. Laboratory Abnormalities and consolidate in "Section 4.4 Removal of Patients from Therapy"
16. Section 5.6 Blinding has been updated to clarify that the actual value, if within normal range, will be blinded and reported as "normal" but that values outside the normal range will be made available for safety monitoring.
17. Section 5.9 Concomitant Medications and Restrictions has been updated relocate text to "Section 4.4 Removal of Patients from Therapy" where its presentation is more appropriate.
18. Section 7.2.1. Physical Examinations, Vital Signs and 12-lead ECGs has been updated to clarify that only clinically significant changes will be recorded as Adverse Events.
19. Section 7.2.2 Clinical Safety Laboratory Assessments has been updated:
    a. To clarify that safety laboratory assessments are performed through a central laboratory for safety monitoring of lab thresholds.
    b. To specify the components of the bilirubin test
    c. To add coagulation test in the case of elevated ALT and ASN
20. Section 7.2.4.6. Laboratory Abnormalities has been update to make statement more concise and reduce redundancies within the protocol. The reader is directed to Section 4.4 Removal of Patients from Therapy where important lab observations are presented that would cause pausing or discontinuation of study drug.
21. Section 12.3.2 Clinical Evaluation has been updated to include current clinical status, clarify patient safety information and to include the clinical safety information based on DMC review of safety data from all completed and ongoing studies of avacopan.

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LIST OF TABLES

PROTOCOL SYNOPSIS

Name of Sponsor ChemoCentryx, Inc.	**Name of Active Ingredient** Avacopan (CCX168)	**Study number:** CL011_168
Title A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study to Evaluate the Safety and Efficacy of Avacopan (CCX168) in Patients with C3 Glomerulopathy		
Investigators Several		
Study centers Multi-center		
Study period 32 months (first patient enrolled to last patient last study visit)	**Phase of development** Phase 2	

Aim

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).

Objectives

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.

The secondary objectives of this study include evaluation of:

1. The safety of avacopan compared to placebo based on the incidence of adverse events, changes in clinical laboratory measurements and changes in vital signs;
2. Changes in laboratory parameters of renal disease including estimated glomerular filtration rate (eGFR), proteinuria, and urinary excretion of monocyte chemoattractant protein-1 (MCP-1) with avacopan compared to placebo;
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.

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

Rationale

C3G is characterized by evidence of alternative complement activation based on C3 deposition in the glomeruli. There are two forms of the disease: dense deposit disease (DDD, formerly

called membranoproliferative glomerulonephritis [MPGN] Type II) and C3 glomerulonephritis (C3GN, formerly called idiopathic MPGN). Genetic mutations leading to defective complement regulation, including reduced-function mutations of complement factor H (CFH), have been described in some of these patients. Patients with C3G often have progressive deterioration in renal function, ultimately leading to end-stage renal disease.

There is no approved treatment for patients with C3G. Immunosuppressive drugs such as cyclophosphamide, mycophenolate mofetil, and glucocorticoids, as well as biologics such as rituximab have been used with limited success. The anti-C5 antibody eculizumab previously showed evidence of improvement in some patients with C3G. Eculizumab blocks the formation of C5a and C5b-9 (membrane attack complex) from C5. Evidence from animal models suggests that inhibition of C5a may be more important than inhibition of C5b-9 in C3G, because deletion of C6 (which is part of the C5b-9 complex) in CFH knockout mice failed to protect the mice from developing symptoms of C3G (Pickering et al., 2006). This provides support for testing drugs that target C5aR, such as avacopan.

Avacopan is an orally administered, selective inhibitor of the complement 5a receptor (C5aR) which is in Phase 3 clinical development for treatment of patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Phase 2 study data with avacopan in patients with AAV indicate efficacy with 30 mg avacopan given twice daily based on improvement in disease activity (Birmingham Vasculitis Activity Score), a significant anti-proteinuric effect, and improvement in quality of life among other improved disease parameters (Jayne et al., 2017). This treatment effect was observed in patients receiving avacopan plus cyclophosphamide or rituximab, but without oral glucocorticoids.

One patient with treatment refractory C3GN, one of the subtypes of C3G, has been treated successfully with 30 mg avacopan twice daily from September 2015 until Lost to Follow up in December 2016 under a “Special Needs” program in the UK. This patient had progressive decline in renal function despite previous treatment with immunosuppressants, rituximab, and glucocorticoids, as well as a kidney transplant.

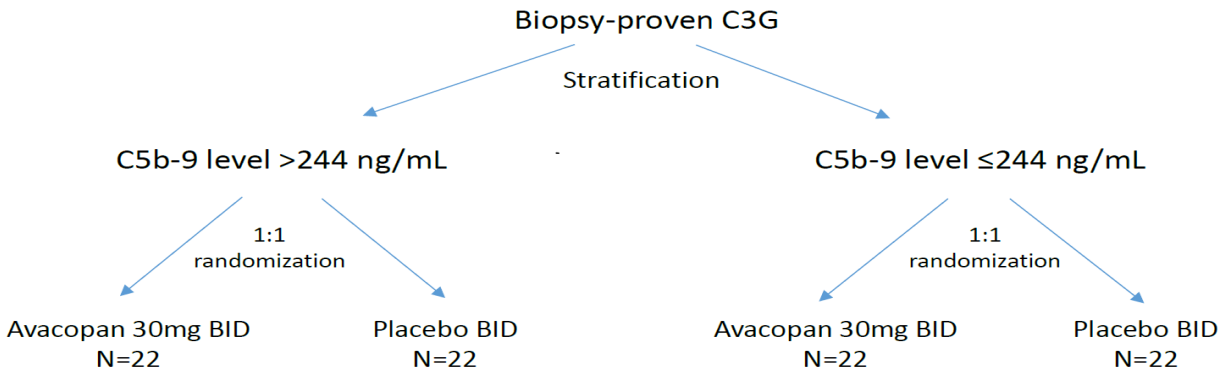
Kidney histology prior to treatment with avacopan showed endocapillary hypercellularity and abundance of CD68-positive cells (macrophages) in the glomeruli. After 2 months of treatment with avacopan, histology showed no evidence of endocapillary hypercellularity and only a small number of CD68-positive cells in the glomeruli. A renal biopsy conducted approximately 6 months after starting avacopan treatment showed no hypercellularity and no crescents, and very few CD68-positive cells in the glomeruli. There was attenuation of eGFR decline. The patient’s quality of life showed a significant improvement since starting avacopan treatment until the patient was lost for follow up.

Based on the results in the patient with C3GN and the Phase 2 study in AAV, testing avacopan more broadly in patients with C3G is indicated.

Methodology

This is a clinical trial to test the efficacy, safety, and tolerability of avacopan in patients with C3G, including both C3GN and DDD.

Patients with biopsy-proven C3G (biopsy has occurred within 12 weeks prior to signing informed consent or is to occur after consenting during the screening period), with or without a renal transplant, will be stratified by elevated or normal levels of C5b-9 and then will be randomized 1:1 using a minimization algorithm to receive 30 mg avacopan BID or placebo BID for 26 weeks in a double-blind manner:



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

Eligible patients within each of the C5b-9 level strata will be further stratified based on two factors:

1. C3GN or DDD, and
2. Whether the patient has received a kidney transplant or not.

The earliest timepoint at which the primary efficacy analysis can occur is when the last enrolled patient in the elevated stratum has completed the Week 26 visit. After the 26-week double-blind period, the avacopan group will continue receiving avacopan for another 26 weeks and the placebo group patients will be switched over in a blinded manner to receive 30 mg avacopan twice daily treatment, instead of placebo, for another 26 weeks.

Patients will be screened for enrollment based on biopsy-proven C3G (i.e., ≥2 levels of magnitude greater staining of C3 than any combination of IgG, IgM, IgA, kappa and lambda light chains, and C1q) and evidence of proliferative glomerulonephritis (mesangial hypercellularity and/or endocapillary hypercellularity based on the Mayo Clinic/Renal Pathology Society Consensus Report on Pathologic Classification, Diagnosis, and Reporting of GN; Sethi et al., 2016).

The screening period will be up to 42 days (6 weeks). Screening procedures will include written Informed Consent/Assent, demographics, medical history, medication history (medication given prior to Day 1 of dosing is considered medication history), physical examination and vital signs, 12-lead ECGs, serum pregnancy test for women of childbearing potential, serum chemistry (including serum creatinine), hematology, urinalysis, urinary albumin creatinine ratio (UACR) and protein: creatinine ratio (UPCR), viral and TB screening. If a patient did not have a renal biopsy in the past 12 weeks, a renal biopsy needs to be done prior to dosing. Prior to starting blinded study drug treatment (avacopan or placebo), blood samples will be collected for the following measurements to create a baseline profile for all patients:

3. Plasma C3a, C5a, C5b-9, and C5;
4. Serum C3 and C4;
5. Serum C3 nephritic factor;
6. Plasma complement factor H and factor B;
7. Serum factor H autoantibody;
8. Serum paraprotein detection;
9. Complement factor H related protein 5 (CFHR5) mutation.

Results obtained within 4 weeks prior to screening, or any time in the past for CFHR5 mutation, will be acceptable for the study. Patients who do not provide consent for genetic evaluation are allowed to participate in the study without the collection of genetic information.

Patients meeting eligibility criteria will start blinded study drug treatment on Day 1. Patients will take avacopan 30 mg or matching placebo orally twice daily. The placebo-controlled treatment period is 26 weeks (182 days). This placebo-controlled treatment period will be followed by an open-label 26-week treatment period during which all patients will receive avacopan. Thereafter, all patients will be followed for 8 weeks (56 days) without study drug treatment.

At post-Day 1 study visits, blood and urine samples will be collected for safety, efficacy, and pharmacokinetic and biomarker measurements. A serum pregnancy test for women of childbearing potential will be done regularly during the 52-week treatment period and at the end of the 8-week follow-up period. Physical examinations and vital signs assessments and 12-lead ECGs will be performed throughout the study. Liver function and hematology including differential blood work will be monitored at least every 4 weeks throughout the study. Health-related quality of life using the EQ-5D-5L and SF-36 v2 surveys will be assessed periodically over the course of the study. Blinded study drug will be dispensed and drug accountability will be done. Concomitant medication and adverse event assessments will be made at every study visit. A follow-up renal biopsy will be performed at the following time points:

1. Within 2 weeks of the Week 26 visit, and completed before dosing with open-label treatment;
2. If a patient is withdrawn early from the study, and
3. After the 52-week treatment period.

The Week 52 biopsy is optional in adolescent patients.

If a patient is on other immunosuppressive treatment at the start of dosing, the dose(s) of concomitant immunosuppressive treatment may not be increased during the study. Treatment with these other drugs may be reduced or stopped during the study at the discretion of the Investigator, if the patient's condition justifies it. Adjustments of tacrolimus and cyclosporine doses to ensure these medications are at goal trough levels for maintenance of immunosuppression in transplant patients will be allowed during the study. No new treatments for C3G, except for renin-angiotensin-aldosterone system (RAAS) blockers, may be added during the study period (52-week treatment period or 8-week follow up), unless the patient's condition deteriorates to the extent that the investigator deems it in the best interest of the patient to do so. Addition of new treatments for C3G during the treatment period will be considered a treatment failure.

Patients who experience deteriorating renal function based on an increase in serum creatinine of at least 50% (confirmed by a repeat measurement after at least 2 weeks) which is otherwise not explained (e.g., dehydration, new medication), or an increase in proteinuria of >3 g/g creatinine (confirmed by a repeat measurement after at least 2 weeks) from Screening or baseline during the 52-week treatment period, will exit the treatment phase of the study and be treated at the discretion of their physician. The increase of serum creatinine or proteinuria will be calculated from the higher value that is measured either at Screening or baseline. They will remain in the study and complete the remaining study visits and procedures. If a patient refuses further study participation, the Early Termination visit procedures will be performed, if possible. These patients will be considered treatment failures.

Dose strengths given to study patients will differ for adult and adolescents. Adolescent patients (12 to 17 years old) are allowed to be enrolled only in countries and at study centers for which approval by Regulatory Authorities and IRBs/ECs was granted.

All adults will receive an avacopan dose of 30 mg twice daily or matching placebo twice daily in the initial 26-week, placebo-controlled treatment period. When they enter the open-label 26-week treatment period, all study patients regardless of their prior treatment will receive avacopan 30 mg twice daily.

For study centers where enrollment of adolescent patients (12 to 17 years old) is approved, the dose of avacopan or placebo dose will be given based on their body weight and avacopan plasma exposure ($AUC_{0\text{-}6hr}$) or avacopan trough concentrations. This is further specified in the main protocol.

Patients will visit the study center for Screening and on Day 1 (baseline) and on Weeks 1, 2, 4, 8, 12, 16, 20, 23 26, 28, 32, 35**,** 38, 41**,** 44, 48, 52, 54, 57 and 60.

Patients will be discharged from the study when all the Week 60 visit procedures have been completed. The patient'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 patients as needed.

Number of Patients

Approximately 88 male or female patients with C3G will be enrolled in this study with approximately 44 patients in each of the two C5b-9 level strata. Patients who drop out early will not be replaced.

Main Criteria for Inclusion

1. Biopsy-proven C3G, either DDD or C3GN, with or without a renal transplant, and with the following observations upon renal biopsy taken within 12 weeks prior to screening or during screening:
   a. ≥2 levels of magnitude greater staining of C3 than any combination of IgG, IgM, IgA, kappa and lambda light chains, and C1q by immunohistochemistry, and
   b. Evidence of proliferative glomerulonephritis (mesangial hypercellularity of greater than 3 mesangial cells per mesangial area and/or endocapillary hypercellularity defined as an increased number of cells within glomerular capillary lumina, causing luminal narrowing) based on light microscopy, and
   c. Confirmation of the presence of electron dense deposits in the glomeruli on electron microscopy corresponding with the C3 immunofluorescence positivity.

   The site will use their site-specific standard technique for taking the biopsy, which can include ultrasound guidance.
2. Male or female patients, aged at least 18 years; where approved, adolescents (12 to 17 years old) may be enrolled; female patients of childbearing potential (i.e., those who have experienced menarche and who are not permanently sterile or postmenopausal, defined as at least 12 consecutive months with no menses without an alternative medical cause) may participate if adequate contraception is used during and for at least the three months after study completion; male patients with partners of childbearing potential may participate in the study if they had a vasectomy at least 6 months prior to randomization or if adequate contraception is used during and for at least the 3 months after study completion; male patients with partners of childbearing potential must be excluded if they plan to father a child during the study. Adequate contraception is defined as resulting in a failure rate of less than 1% per year (combined estrogen and progestogen [oral, intravaginal, or transdermal], or progestogen-only hormonal contraception (oral, injectable, or implantable), intra-uterine device, intra-uterine hormone releasing system, bilateral tubal occlusion, vasectomized partner, or true sexual abstinence, i.e., in line with the preferred and usual lifestyle of the patient); In addition, a barrier method (i.e., cervical cap, diaphragm or condom) must be used during intercourse between a male patient and a female of child-bearing potential.
3. Willing and able to give written Informed Consent and to comply with the requirements of the study protocol; written Assent and Informed Consent must be obtained from the legal guardian in accordance with regional laws or regulations for patients 12 to 17 years of age; and
4. Judged to be otherwise fit for the study by the Investigator, based on medical history, physical examination, and clinical laboratory assessments. Patients with clinical laboratory values that are outside of normal limits (other than those specified in the Exclusion Criteria) and/or with other abnormal clinical findings that are judged by the Investigator not to be of clinical significance, may be entered into the study.

Main Criteria for Exclusion

1. Pregnant or nursing;
2. Tubulointerstitial fibrosis appears to be more than 50% based on standard assessment using trichrome staining of the renal biopsy;
3. Use of eculizumab or another anti-C5 antibody within 26 weeks prior to dosing;
4. Secondary C3 disease, e.g., infection-associated disease, or associated with another systemic or autoimmune disease; presence of a monoclonal spike on serum or urine protein electrophoresis or immunofixation assay;
5. Currently on dialysis or likely will require dialysis within 7 days after screening;
6. History or presence of any form of cancer within the 5 years prior to screening, with the exception of excised basal cell or squamous cell carcinoma of the skin, or carcinoma in situ such as cervical or breast carcinoma in situ that has been excised or resected completely and is without evidence of local recurrence or metastasis;
7. Positive HBV, HCV, or HIV viral screening test indicative of acute or chronic infection;
8. Evidence of tuberculosis based on interferon γ release assay (IGRA), tuberculin purified protein derivative (PPD) skin test, or chest radiography done at screening or within 6 weeks prior to screening; a CT scan or chest X-ray are not mandatory if evidence of tuberculosis was excluded by any of the other methods specified above;
9. Active uncontrolled infection;
10. WBC count less than 3500/μL, or neutrophil count less than 1500/μL, or lymphocyte count less than 500/μL before start of dosing;
11. Evidence of hepatic disease; AST, ALT, alkaline phosphatase, or bilirubin >3x the upper limit of normal before start of dosing;
12. Currently using a strong inducer of the cytochrome P450 3A4 (CYP3A4) enzyme, such as carbamazepine, phenobarbital, phenytoin, rifampin, or St. John's wort;
13. Known hypersensitivity to ava opan o inactive ingredients of the avacopan capsules (including [redacted] or inability to swallow the capsules;
14. Participated in any clinical study of an investigational product within 30 days prior to screening or within 5 half-lives after taking the last dose; and
15. History or presence of any medical condition (for example, contraindication to local anesthesia required for renal biopsy, or recurring serious infections) or disease which, in the opinion of the Investigator, may place the patient at unacceptable risk for study participation.

Test Product

Avacopan will be administered orally as hard gelatin capsules containing 10 mg avacopan. The avacopan capsules will be supplied to the study centers in plastic bottles containing 180 capsules.
Matching placebo will be administered orally as matching hard gelatin capsules containing no avacopan but inactive ingredients. The placebo capsules will be supplied to the study centers in plastic bottles containing 180 capsules.

Patients will receive one bottle of avacopan or placebo capsules on Day 1 and Weeks 4, 8, 12, and 16, and two bottles at Weeks 20, 26, 32, 38, and 44.

Patients will be asked to take 3 capsules every morning and 3 capsules every evening orally with water, approximately 12 hours after the morning dose, as instructed. Study medication (avacopan or placebo) should be taken preferably with food. If a patient misses a dose, the next dose should be taken as soon as possible. If it is close to the time for their next dose (within 3 hours), the missed dose should not be taken and the next dose should be taken at the regular time.

Duration of Treatment and Observation

Patients will be screened within a period not to exceed 42 days prior to Day 1. The total treatment period is 52 weeks (364 days) and all patients will be followed for 8 weeks (56 days) after the dosing period.

To the extent possible, any adverse events that are deemed study drug-related and are ongoing at discharge will be followed-up to resolution or until a determination is made that the unresolved event is stable. The patient's condition will be evaluated by the Investigator at the end of the clinical trial and appropriate standard of care medical treatment will be provided to all patients as needed.

Safety Assessments

Safety assessments include adverse events, physical examination abnormalities, vital signs, 12-lead ECG, and clinical laboratory tests (including blood chemistry, hematology, and urinalysis).

Efficacy Assessments

Efficacy assessments include:

1. Renal biopsy to perform light microscopy, immunohistochemistry, and electron microscopy; light microscopy and immunohistochemistry will be used to determine the C3G Histologic Index for disease activity and chronicity;
2. eGFR calculated from serum creatinine using the Chronic Kidney Disease-Epidemiology Collaboration study (CKD-EPI) equation (Levey et al., 2009) in adult patients and the modified Schwartz equation in adolescents (Schwartz et al., 2009);
3. Urinary protein:creatinine ratio (UPCR);
4. Urinary MCP-1:creatinine ratio;
5. Health-related quality of life based on the EQ-5D-5L and SF-36 v2.

Pharmacokinetic Assessments

Concentrations of avacopan and its metabolite CCX168-M1 will be determined in plasma according to the Time and Events Table, using a validated analytical method.

Exploratory Pharmacodynamic Markers

Plasma/serum samples will be collected according to the Time and Events Table for pharmacodynamic marker measurements, which may include, for example, complement fragments, and inflammatory cytokine and chemokine levels. Urine samples will also be collected according to the Time and Events Table for biomarker assessments including, for example, complement fragments, sCD163, and inflammatory cytokine and chemokine levels.

Renal Histology

For eligibility assessment, renal biopsy samples taken within 12 weeks prior to screening or during screening will be assessed by immunofluorescence staining for C3 and immunoglobulins, as well as electron microscopy to confirm the presence of electron dense deposits. Eligibility assessment will be made by the Investigator based on their local pathologist's evaluation. Patients must have biopsy-proven C3G, either DDD or C3GN, with ≥2 levels of magnitude greater staining of C3 than any combination of IgG, IgM, IgA, kappa and lambda light chains, and C1q, and with evidence of proliferative glomerulonephritis (mesangial hypercellularity and/or endocapillary hypercellularity).

All renal biopsies will be analyzed with the routine panel of stains which includes hematoxylin-eosin (H&E), periodic acid–Schiff (PAS), trichrome, and Jones methenamine silver. A minimum of 4 (preferably 6) unstained slides from paraffin-embedded renal tissue will be provided by study centers to the central histopathology laboratory for additional immunostaining (e.g., CD45, CD68, MPO, C5a, C5aR, etc.).

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.

The central reader will determine the degree of disease activity and chronicity based on the C3G Histologic Index. A semi-quantitative scale of 0 to 3 will be used, indicating either the proportion (%) of glomeruli involved or the proportion of cortex involved (for tubular atrophy and interstitial fibrosis).

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.

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, and
3. Interstitial fibrosis
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.

Electron microscopy will be performed to evaluate the treatment effect of avacopan on electron microscopic features of the disease such as dense deposits.

Immunohistochemistry evaluation will be performed by the central pathologist to evaluate the treatment effect of avacopan on specific immune cell populations, such as total leukocytes, macrophages, and neutrophils.

Statistical Methods

This study will enroll and treat two patient populations: patients in the elevated stratum of C5b-9 levels (i.e., >244 ng/mL) and patients in the non-elevated stratum of C5b-9 levels (i.e., ≤244 ng/mL). Data summaries and statistical analyses will be presented for each of the two strata as well as combined. The elevated stratum will be considered as the primary population, the non-elevated stratum will be considered as the secondary population, and the two strata combined will be considered the exploratory population. Enrollment for the stratum with C5b-9 levels ≤244 ng/mL could terminate early, if patient enrollment in the other 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 ≤244 ng/mL (secondary population) continue a blinded follow up – further details will be provided in the statistical analysis plan (SAP).

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 stratum first with a two-sided $\alpha = 0.05$. If this test reaches statistical significance, then the primary endpoint will be tested in the non-elevated stratum with a two-sided $\alpha = 0.05$. If the test in the elevated stratum fails to reach statistical significance, then the test in the non-elevated stratum 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.

Demographics and Baseline Characteristics

All patient 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], eGFR, proteinuria [UPCR], complement marker levels, urinary MCP-1:creatinine ratio, physical examination abnormalities, medical history, previous [within 6 months of screening] and concomitant medications [including other treatments for C3G] at study entry) will be listed by study center and patient number, and will also be summarized.

Efficacy Analysis

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

The avacopan and placebo groups will be compared by ANCOVA with treatment group as factor and baseline C3G Histologic Index for disease activity as covariate. A point estimate and corresponding 95% confidence interval will be estimated for the treatment main effect. The heterogeneity of the treatment effect across disease diagnoses and renal transplant strata will be investigated through subgroup analyses. The treatment effect based on the baseline complement profile of patients will also be investigated. If data are not normally distributed, in addition to the ANCOVA for the percent change in C3G Histologic Index for disease activity and chronicity, the Cochran-Mantel-Haenszel (CMH) test will be applied to the percent change results and ANCOVA will be applied to the change in C3G Histologic Index disease activity and chronicity scores.

Data from patients who are treatment failures, i.e., requiring treatment rescue measures such as high dose glucocorticoids during the treatment period, will be excluded from efficacy analysis after the point of rescue treatment. Missing data will be imputed with the last observation carried forward (LOCF). Multiple-imputation using Markov Chain Monte Carlo (MCMC) or other statistical method may also be performed.

Since the placebo group will receive avacopan during the second 26 weeks of the study, the change from Week 26 to Week 52 in the C3G Histologic Index in the placebo control group will be compared to the change from baseline to Week 26 in this 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).

The change from baseline to Week 52 in the C3G Histologic Index in the avacopan group will also be compared to the change from baseline to Week 26 in placebo control group using similar methodology as described for the primary efficacy endpoint.

Other efficacy endpoints include:

1. The proportion of patients 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;
2. The percent change from baseline in the C3G Histologic Index for disease chronicity over the placebo-controlled 26-week treatment period;
3. The change and percent change from baseline in eGFR over the placebo-controlled 26-week treatment period;
4. The percent change from baseline in UPCR over the placebo-controlled 26-week treatment period;
5. The percent change from baseline in urinary MCP-1:creatinine ratio over the placebo-controlled 26-week treatment period;
6. 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.

Continuous variables, including eGFR, UPCR, urinary MCP-1: creatinine ratio, EQ-5D-5L, and SF-36 v2 will be analyzed using a mixed effects model for repeated measures (MMRM) with treatment group, visit, and treatment-by-visit interaction as factors, and baseline as covariate. Patients will be considered as repeated measure units over visits. The interaction term may be dropped if it is not significant at $\alpha = 0.25$ level. Point estimates and corresponding 95% confidence intervals will be estimated for the difference between the avacopan group and the control group at Week 26 using simple contrast from the model.

Similar to the primary endpoint, the second 26 weeks will be compared to the first 26 weeks for the placebo group. Changes in the efficacy parameters across 52 weeks will also be assessed.

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.

Change from baseline in individual components of the C3G Histologic Index for disease activity and chronicity as well as glomerular leukocytes and leukocyte subsets based on immunohistochemistry will be summarized and, where appropriate, analyzed using similar methodologies as describe above.

The endpoint of the proportion of patients who have a histologic response will be analyzed by the CMH chi-square test. Data from patients who are treatment failures, i.e., require rescue medication during the treatment period, will be summarized.

Summary statistics will be calculated for each of the efficacy endpoints. For continuous variables, numbers of patients, means, medians, minimum, maximum, standard deviations, standard errors, and 95% confidence intervals will be calculated. Geometric means will be calculated for UPCR and MCP-1: creatinine, and other measurements that are not normally distributed. For the categorical variable of histologic response, the number and percentage of patients, as well as the 95% confidence intervals will be calculated.

The primary efficacy analysis will be based on the intent-to-treat (ITT) population, defined as all patients who are randomized. If data are still missing after all efforts made to collect post-baseline C3G Histologic Index data, missing data will be imputed using the last observation

carried forward method. This method may impute Week 26 missing data with the baseline value if there are no unscheduled data from visits prior to the missing time point.

Safety Analysis

Safety endpoints include:

1. Patient incidence of treatment-emergent serious adverse events, adverse events, and study withdrawals due to adverse events;
2. Change from baseline and shifts from baseline in all safety laboratory parameters;
3. Change from baseline in vital signs.

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

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

All reported adverse events will be coded using MedDRA and listed by System Organ Class, preferred term, and verbatim term.

Treatment-emergent adverse events will be listed and summarized by treatment group by System Organ Class and Preferred Term, by relatedness and by maximum severity.

Treatment-emergent serious adverse events and adverse events leading to study withdrawal will be summarized by treatment group.

Individual vital signs and change from baseline in vital signs will be listed by treatment group, patient, and study visit, and summarized by treatment group.

Laboratory data (actual values and change from baseline) will be listed by treatment group, patient, and study visit. Abnormal laboratory values will be flagged. Laboratory data will also be summarized by treatment group and study visit. Shift tables will be generated for shifts in laboratory parameters by study visit.

Sample Size Assumptions

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 disease activity at Week 26, standard deviation (SD) 34%, power 90%, and 2-sided $\alpha = 0.05$. The sample size also provides approximately 90% power to detect a delta of -35% in the C3G Histologic Index for disease 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.

Pharmacokinetic and Exploratory Pharmacodynamic Marker Analysis

Individual plasma concentrations of avacopan (and 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.

The following parameters will be determined, where possible, in 12-17 year-old patients:

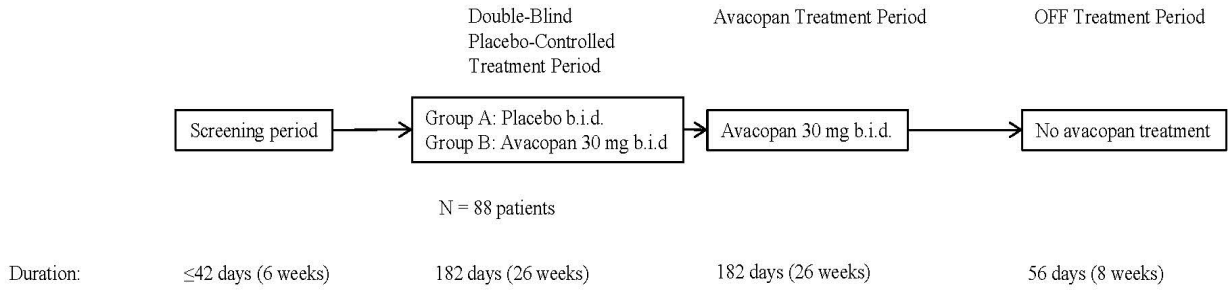
C_{max} Maximum plasma concentration

t_{max}	Time of maximum plasma concentration
$AUC_{0\text{-}6hr}$	Area under the plasma concentration-time curve from Time 0 to Hour 6 on Day 1 and Day 183
C_{min}	Trough level plasma concentrations at post-Day 1 visits

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 be evaluated. The data may also be used to evaluate the PK/PD relationship of avacopan treatment for both C5b-9 level strata separately as well as combined. To this end, the change and/or percent change from baseline in the C3G Histologic Index, UPCR, eGFR, urinary MCP-1: creatinine ratio, and other biomarkers may be used as PD markers.

STUDY SCHEMA



TIME AND EVENTS TABLE

	Screening	Double-Blind Treatment										Active Treatment								Follow-up		
Study Day[a]	**≤42 days**	**1**	**8**	**15**	**29**	**57**	**85**	**113**	**141**	**162**	**183**	**197**	**225**	**246**	**267**	**288**	**309**	**337**	**365**			
Study Week[1]	**≤6**		**1**	**2**	**4**	**8**	**12**	**16**	**20**	**23**	**26**	**28**	**32**	**35**	**38**	**41**	**44**	**48**	**52**	**54**	**57**	**60**
Informed Consent/Assent	X																					
Demographics, medical history, prior medications	X																					
Physical examination[b]	X	X[c]	X	X	X	X	X	X	X		X	X	X		X		X		X	X	X	X
Vital signs	X	X[c]	X	X	X	X	X	X	X		X	X	X		X		X		X	X	X	X
12-lead ECG	X	X[c]	X								X	X	X						X	X	X	X
Serum pregnancy test for women of childbearing potential	X	X[c]			X	X	X	X	X		X	X	X		X		X		X	X	X	X
HIV, HBV, HCV testing	X																					
Screening for tuberculosis[d]	X																					
Serum chemistry	X	X[c]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X[c]	X	X	X	X	X	X	X		X	X	X		X		X		X	X	X	X
Urine albumin, protein and creatinine	X	X[c]	X	X	X	X	X	X	X		X	X	X		X		X		X	X	X	X
Renal biopsy for light and electron microscopy, immunostaining, morphometry, and C3G Histologic Index calculation[e,f]	X[e]										X[e]								X			

	Screening	Double-Blind Treatment										Active Treatment								Follow-up		
Study Day[a]	**≤42 days**	**1**	**8**	**15**	**29**	**57**	**85**	**113**	**141**	**162**	**183**	**197**	**225**	**246**	**267**	**288**	**309**	**337**	**365**			
Study Week[l]	**≤6**		**1**	**2**	**4**	**8**	**12**	**16**	**20**	**23**	**26**	**28**	**32**	**35**	**38**	**41**	**44**	**48**	**52**	**54**	**57**	**60**
Complement profiling[g]	X																					
Stratification and randomization		X																				
Urine MCP-1 and creatinine		X[c]	X	X	X		X		X		X	X	X		X				X			X
EQ-5D-5L and SF-36 v2		X[c]			X		X		X		X		X		X				X			X
Avacopan/Placebo dispensing		X[c]			X	X	X	X	X													
Avacopan dispensing											X		X		X		X					
Avacopan/Placebo double-blind dosing		X→	→	→	→	→	→	→	→		→X											
Avacopan dosing											X[h]	→	→	→	→	→	→	→	X[i]			
Avacopan/Placebo accountability					X	X	X	X	X		X		X		X		X		X			X
PD plasma/serum sample collection[j]		X[c]	X	X	X		X		X		X	X	X		X				X	X	X	X
Blood sample for lymphocyte subset analysis[k]		X[c]	X	X	X		X				X				X				X			X
PD urine sample collection		X[c]	X	X	X		X		X		X	X	X		X				X			X
PK plasma sample collection		X[c]	X	X	X		X		X		X	X	X		X				X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] Week 1 through 20 visits may occur within a ± 2 day window. Week 26 through 60 visits may occur within a ± 7 day window.

[b] Physical examination will include body weight measurements. Height will be measured only at Screening in adults, but at all visits for adolescents.

[c] These procedures must be performed before taking the first dose of avacopan.

[d] Any one of the following may be done for TB screening: Interferon γ release assay (IGRA), tuberculin purified protein derivative (PPD) skin test, or chest radiography (done within 6 weeks prior to Screening or done during Screening).

[e] Renal biopsy required for eligibility if not performed within 12 weeks prior to screening; renal biopsy -2 weeks prior to the Week 26 visit, and should be completed before open-label medication is started.

[f] In adolescents, only the baseline and one follow-up renal biopsy (at Week 26) are required; the 52-week biopsy is optional.

[g] Plasma C3a, C5, C5a, and C5b-9; serum C3, C4, and C3 nephritic factor; plasma complement Factor H and factor B; serum factor H auto-antibody; serum paraprotein detection; CFHR5 mutation. Results obtained within 4 weeks prior to screening or any time in the past for CFHR5 mutation will be acceptable for the study.

[h] Only in adolescent patients, plasma samples for avacopan measurements will be taken at pre-dose, 0.5, 1, 2, 3, 4, and 6 hours after dosing on Day 1 and on Day 183 (Week 26). For all other visits, single time point samples approximately 12 hours post the most recent dose and immediately prior to the dose on the visit day will be taken. The date and time of the last dose of study drug prior to the PK sample collection will be recorded. *Note: For adolescents only - it is important that on Day 183 (Week 26) the adolescent patients take the dose when instructed at the study center, NOT at home, and they should be reminded through a telephone call two days before the Day 183 (Week 26) visit.*

[i] For both adults and adolescents, the final dose of avacopan should NOT be taken on the morning of the scheduled Week 52 visit. *Note: Patients should be reminded through a telephone call two days before the scheduled Week 52 visit.*

[j] Blood samples will be put in wet ice immediately after collection, centrifuged in a refrigerated centrifuge and plasma or serum stored at ≤ -70 °C.

[k] For T cell, B cell, and natural killer T cell counts.

LIST OF ABBREVIATIONS AND ACRONYMS

AAV	ANCA-Associated Vasculitis
AE	adverse event
aHUS	atypical Hemolytic Uremic Syndrome
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
ANCA	Anti-Neutrophil Cytoplasmic Autoantibody
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Chemistry
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}6hr}$	Area under the plasma concentration-time curve for 0 to 6 hours after dosing
b.i.d. or BID	Twice daily
BVAS	Birmingham Vasculitis Activity Score
C1q	Complement component C1q
C3	Complement component 3
C3G	C3 glomerulopathy
C3GN	C3 glomerulonephritis
C3NeF	C3 nephritic factor
C4	Complement component 4
C5a	Complement component 5a fragment
C5aR	Receptor for C5a
C5b-9	Membrane attack complex or terminal complement complex
C6	Complement 6
CA	Competent Authority
CBC	Complete Blood Count
CD11b	Cluster of differentiation 11b
CD45	Cluster of differentiation 45
CD60	Cluster of differentiation 60
CD68	Cluster of differentiation 68
CD163	A protein that in humans is encoded by the CD163 gene
CFH	Complement factor H
CFR	Code of Federal Regulations
CFHR5	Complement factor H related protein 5
C_{max}	Maximum (maximal) plasma concentration
C_{min}	Minimum plasma concentration
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMH	Cochran-Mantel-Haenszel
CPK	Creatine phosphokinase
CRA	Clinical Research Associate
CRF/eCRF	Case Report File
CRO	Clinical Research Organization
CSR	Clinical Study Report

CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	Cytochrome P450 3A4 enzyme
DDD	Dense Deposit Disease
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
eGFR	estimated Glomerular Filtration Rate
EQ-5D-5L	EuroQuality of Life-5 Domains-5 Levels
EU	European Union
FDA	Food and Drug Administration
g	gram
GCP	Good Clinical Practices
GMP	Good Manufacturing Practices
GFR	Glomerular Filtration Rate
H or hr	Hour
H&E	Hematoxylin-eosin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDPE	High Density Polyethylene
hERG	Potassium channel encoded by the human ether-à-gogo related gene
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
IHC	Immunohistochemistry
IC_{50}	Concentration associated with 50% inhibition
Ig	Immunoglobulin
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IgAN	Immunoglobulin A Nephropathy
IGRA	Interferon γ Release Assay
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-To-Treat
IV	Intravenous(ly)
kD	kilodalton
kg	kilogram
lbs.	Pound (weight)
LOCF	Last observation carried forward
LVFS	Swedish Medical Products Agency's Code of Statues

MAC	Membrane Attack Complex
MCMC	Markov Chain Monte Carlo (statistical method)
MCP-1	Monocyte Chemoattractant Protein-1, also known as CCL2
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
MMRM	Mixed effects Model for Repeated Measures
MPGN	Membranoproliferative Glomerulonephritis
MPO	myeloperoxidase
N	Number
PAS	periodic acid Schiff
PD	Pharmacodynamics(s)
PK	Pharmacokinetic(s)
PP	Per Protocol
PPD	Purified Protein Derivative
QT/QTc	Q-T interval on ECG; corrected Q-T interval
RAAS	Renin-Angiotensin-Aldosterone System
RBC	Red Blood Cell(s)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD	Standard Deviation
SEM	Standard Error of the Mean
SF-36 v2	Short Form-36 version 2.0
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TCC	Terminal Complement Complex, also known as membrane attack complex
T_{max}	Time of Maximal Concentration
UACR	Urinary Albumin:Creatinine Ratio
UPCR	Urinary Protein:Creatinine Ratio
UK	United Kingdom
WBC	White Blood Cell
WHODD	World Health Organization Drug Dictionary

1. INTRODUCTION

1.1. Complement and Avacopan

The activation of the complement pathway generates biologically active fragments of complement proteins, e.g., C3a, C4a and C5a anaphylatoxins, and the C5b-9 membrane attack complex (MAC) or terminal complement complex (TCC), all of which mediate inflammatory responses by inducing leukocyte chemotaxis, activating macrophages, neutrophils, platelets, mast cells and endothelial cells, and by increasing vascular permeability, cytolysis, and tissue injury.

C5a is one of the most potent pro-inflammatory mediators of the complement system, being at least 100 times more potent than C3a. This 12 to 14.5 kD polypeptide, along with a C5b fragment, is produced by enzymatic cleavage of a C5 precursor during activation of any of the 3 complement pathways. C5a induces expression of adhesion molecules and chemotactic migration of neutrophils, eosinophils, basophils, and monocytes. It also mediates inflammatory reactions by causing smooth muscle contraction, increasing vascular permeability, inducing basophil and mast cell degranulation, and inducing release of lysosomal proteases and oxidative free radicals. The anaphylactic and chemotactic effects of C5a are mediated through its interaction with the C5aR, a G protein-coupled receptor expressed on human neutrophils, monocytes, basophils, eosinophils, renal glomerular tissues, and lung smooth muscle and endothelial cells.

Avacopan (formerly CCX168) is an orally administered, small molecule, selective inhibitor of the complement 5a receptor (C5aR).

As measured in vitro, avacopan functionally inhibits C5a-mediated chemotaxis, displaces [^{125}I]-C5a from human C5aR, and inhibits C5a-mediated increase in cytoplasmic calcium levels with a potency (IC_{50}) of 0.2 to 0.9 nM in buffer (Bekker et al., 2016).

Avacopan was also evaluated for its ability to inhibit the C5a-mediated chemotaxis of neutrophils in freshly collected human whole blood. Avacopan produced 50% inhibition (IC_{50}) of C5a-mediated neutrophil migration at a concentration of 1.7 nM; 90% inhibition (A_{10} value) occurred at an avacopan concentration of 15.4 nM. Avacopan also inhibits C5aR in cynomolgus monkeys and hamsters at potencies similar to that observed with human whole blood. However, avacopan possesses moderate potency for rabbit C5aR (IC_{50} ~ 1.4 µM) and lacks affinity for mouse, rat, or dog C5aR (IC_{50} >10 µM).

The efficacy of avacopan was assessed using genetically modified mice where the mouse C5aR coding region was substituted for the human C5aR coding region. In these studies, intravenous injection of mouse anti-myeloperoxidase (anti-MPO) IgG into the human C5aR knock-in mice caused glomerulonephritis in a manner mimicking ANCA disease in humans. At daily oral doses of 30 mg/kg avacopan, a marked inhibition of anti-MPO induced glomerulonephritis was documented histologically, as assessed by the number of necrotic and crescent-containing glomeruli. These results were consistent with reduced protein, leukocytes, and red blood cells in the urine, and reduced serum blood urea nitrogen and creatinine in mice receiving avacopan (Xiao et al, 2014).

Studies assessing the effects of avacopan upon the central nervous, respiratory, and renal systems did not reveal any adverse findings following the oral administration of avacopan. Additionally, in vitro data suggest that avacopan and its only major metabolite CCX168-M1 are unlikely to pose a pro-arrhythmic risk in humans. Nonclinical toxicity studies of up to 26 weeks and 44 weeks in duration (in rats and cynomolgus monkeys, respectively) involving exposures higher than those expected in the clinic did not identify any safety concerns with avacopan. No adverse effects upon fertility or embryo-fetal development were seen in reproductive toxicity studies conducted in hamsters and rabbits. No evidence of any immunotoxicity was noted as immunological, clinical, and anatomical pathological parameters were, with limited exceptions (e.g., minor clinical pathology changes in rats in the 26-week study), unaffected by treatment. An in vitro study indicated that avacopan was not phototoxic. Thus, results from these nonclinical studies support chronic oral dosing of 30 mg avacopan twice daily to humans. Refer to the Investigator's Brochure for details of these studies.

1.2. Previous Clinical Studies

Five Phase 1 studies and four Phase 2 studies with avacopan have previously been completed. A Phase 3 study in patients with AAV previously completed enrollment but follow up is ongoing and the study remains blinded. A total of 182 healthy volunteers participated in the five Phase 1 studies; 153 of these patients received avacopan at doses ranging from 1 mg up to 100 mg (CL001_168, CL004_168, CL007_168, and CL008_168, and Japanese Phase 1 study CCX1101). Avacopan was generally well tolerated in these studies.

Following oral administration, avacopan was absorbed rapidly and reached peak plasma levels after a median time of approximately 2.5 hours. After reaching the peak plasma level, avacopan appears to have a biphasic elimination profile (as observed from the log-linear concentration-time profiles), with a rapid early phase followed by a long terminal phase, a moderate to high apparent clearance in humans, and a large apparent volume of distribution. Despite the long observed terminal half-life, repeat administration for 7 days resulted in only modest accumulation (~2-fold) at the higher dose levels. Co-administration with a high fat, high calorie meal did not affect C_{max} but increased the plasma exposure (AUC) approximately 72% and delayed t_{max} by approximately 3 hours (study CL007_168).

Avacopan dose-dependently inhibited the C5a-induced upregulation of CD11b in patients' neutrophils in study CL001_168. At a mean avacopan plasma concentration of 150.9 ng/mL, C5a-induced upregulation of CD11b was inhibited by ~95% (Bekker et al., 2016). In Phase 2 studies in patients with AAV, an average steady state plasma trough concentration of ~200 ng/mL was observed with the therapeutic dose of 30 mg avacopan given twice daily.

Results from a mass balance study (CL004_168) showed that avacopan was mostly metabolized in the liver by cytochrome P450 3A4 (CYP3A4).

Avacopan did not show evidence of a detrimental effect on QT/QTc based on results from an intensive ECG study (CL007_168).

Co-administration of the strong CYP3A4 enzyme inducer, rifampicin, in study CL008_168 resulted in an approximately 93% reduction of systemic exposure of avacopan; this reduction may result in a loss of efficacy of avacopan. Therefore, the use of strong CYP3A4 enzyme inducers with avacopan is an exclusion criterion for the study. Co-administration of the strong

CYP3A4 enzyme inhibitor itraconazole resulted in a 119% increase of systemic exposure of avacopan. This approximate doubling of the avacopan plasma concentrations indicates a modest interaction and should not pose a safety concern, given that the safety margins for 30 mg avacopan twice daily in humans compared to animals are at least 6 to 19-fold, respectively, based on the long-term cynomolgus monkey and rat toxicology studies. Nevertheless, strong CYP3A4 enzyme inhibitors with avacopan should be used with caution.

Two Phase 2 clinical trials in 109 patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) were conducted. The first study in 67 patients (CL002_168) included three dose groups: 30 mg avacopan twice daily plus low dose prednisone (20 mg/day), 30 mg avacopan twice daily plus no prednisone, and placebo plus full dose prednisone (60 mg/day). All patients received either IV cyclophosphamide or rituximab as standard of care treatment. Avacopan, alone or with low dose prednisone, was associated with a rapid onset of action based on a global disease activity index, the Birmingham Vasculitis Activity Score (BVAS), renal parameters such as albuminuria, and health-related quality of life measurements over a 12-week treatment period (Jayne et al., 2017). The steady state mean avacopan plasma concentration was approximately 204 ng/mL in these patients, corresponding to >95% projected inhibition of the C5aR in the circulation. Avacopan also showed a favorable safety profile.

The second study in 42 patients (CL003_168) included three dose groups: 10 mg avacopan twice daily plus full dose prednisone (60 mg), 30 mg avacopan twice daily plus full dose prednisone, and placebo plus full dose prednisone. All patients received either IV cyclophosphamide or rituximab as standard of care treatment. Avacopan appeared to be safe when added on top of full dose prednisone plus cyclophosphamide or rituximab and the efficacy data support 30 mg avacopan twice daily as the therapeutic dose in AAV. There was no rebound effect when avacopan treatment was stopped. Refer to the Investigator's Brochure for more details.

A Phase 3 clinical trial with patients with AAV previously completed enrollment of >300 patients and follow up is ongoing **(**ADVOCATE, CL010_168). In this study in patients with AAV, avacopan (or placebo) is being compared with standard of care glucocorticoids as added medications to background therapy of either cyclophosphamide followed by azathioprine, or of rituximab. The study remains blinded.

The Data Monitoring Committee (DMC) for that study has commented on a [redacted]. The DMC further commented on a potential risk of [redacted] ter an unblinded review of safety data from [redacted] enrolled patients because [redacted]

Specifically, [redacted] patients receiving blinded study drug had Grade 2 (>3-5 times upper limit of normal [ULN]), and [redacted] patients receiving blinded study drug had Grade 3 transaminase elevations (>5 to 20 times ULN). In one patient, the transaminase elevation recurred when study drug was restarted. The interpretation was confounded by use of other immunosuppressive agents and other drugs known to be liver irritants including Sulfamethoxazole-Trimethoprim.

The Reference Safety Information section of the Investigator's Brochure has been updated to include the potential risk of [redacted], [redacted], and [redacted] and to state that general gastrointestinal adverse events (e.g., nausea, diarrhea) as previously observed in Phase 2 AAV

studies have been observed in the ongoing Phase 3 CL010_168 study at approximately the same frequency and severity.

An open-label Phase 2 clinical trial in 7 patients with IgA nephropathy (IgAN) has been conducted (CL005_168). Results showed that avacopan was effective in improving proteinuria over a 12-week treatment period; 3 of 7 patients showed approximately 50% decrease in either urinary protein:creatinine ratio (UPCR) or albumin:creatinine ratio (UACR). An open-label Phase 2 clinical trial in 6 patients with atypical hemolytic uremic syndrome (aHUS) was conducted (CL006_168). Results showed that serum collected from patients dosed with avacopan caused a mean percent reduction of 82% in thrombus size compared to baseline in an ex vivo assay.

A benefit and risk assessment of avacopan is presented in Section 12.3; detailed information about non-clinical and clinical trials with avacopan is presented in the Investigator's Brochure. Results from nonclinical and clinical studies conducted to date showed a positive risk-benefit profile of avacopan in treatment of patients with AAV (Section 12.3.1 and Section 12.3.2).

1.3. Rationale for the Study

C3 glomerulopathy (C3G) is characterized by evidence of alternative complement activation based on C3 deposition in the glomeruli. There are two forms of the disease: dense deposit disease (DDD, formerly called membranoproliferative glomerulonephritis [MPGN] Type II) and C3 glomerulonephritis (C3GN, formerly called idiopathic MPGN).

The major defect underlying C3G is excessive activation of the alternative complement pathway, resulting in the deposition of multiple complement components in the glomerulus, including components of C3 and C5 (Pickering et al., 2013), in the absence of antibody or immune complex deposition. The mechanism by which complement deposition leads to renal damage is not well understood, but likely involves chemotaxis of leukocytes resulting from cleavage of C5 to generate C5a, as well as the cytolytic effects of C5b-9 (Hou et al., 2014).

There is no approved treatment for patients with C3G. Immunosuppressive drugs such as cyclophosphamide, mycophenolate mofetil, and glucocorticoids, as well as biologics such as rituximab have been used with limited success. The anti-C5 antibody eculizumab has shown evidence of improvement in some patients with C3G (Bomback et al., 2012; Herlitz et al., 2012). Eculizumab blocks the formation of C5a and C5b-9 (membrane attack complex) from C5. Evidence from animal models suggests that inhibition of C5a may be more important than inhibition of C5b-9 in C3G because deletion of C6 (which is part of the C5b-9 complex) in complement factor H (CFH) knockout mice failed to protect the mice from developing symptoms of C3G (Pickering et al., 2006). This provides support for testing drugs such as avacopan that target C5aR.

We used mice deficient in complement factor H (CFH) which develop spontaneous glomerulonephritis resembling C3G in humans (Pickering et al., 2002; Pickering et al., 2006) to evaluate the effect of avacopan. These CFH-deficient mice, carrying human C5aR, were treated with avacopan from 3 months of age. Plasma and urine were collected periodically and plasma creatinine, blood urea nitrogen, and urine albumin to creatinine ratio were measured. At 7 months of age, CFH deficient mice that have been treated with vehicle showed elevated plasma creatinine comparing to CFH wild-type mice treated with vehicle (CFH deficient mice 1038 ±

15.48 µg/mL vs. CFH wild-type mice 863.5 ± 13.50 µg/mL; mean ± SEM; p = 0.002 for comparison of the two groups). The avacopan-treated CFH deficient mice had lower plasma creatinine compared to vehicle-treated CFH deficient mice (avacopan 843.0 ± 23.43 µg/mL vs. vehicle 1038 ± 15.48 µg/mL mean ± SEM, p = 0.0003 for comparison of the two groups). These data indicate that administration of avacopan to CFH-deficient mice protects renal function and provides a strong rationale for blocking the C5a receptor with a drug such as avacopan as a novel therapeutic approach for patients with C3G.

One patient with treatment refractory C3GN, one of the subtypes of C3G, has been treated with 30 mg avacopan twice daily from September 2015 until Lost to Follow up in December 2016 under a "Special Needs" program in the UK (CL009_168). This patient had progressive decline in renal function despite previous treatment with immunosuppressants, rituximab, and glucocorticoids, as well as a kidney transplant. Kidney histology prior to treatment with avacopan showed endocapillary hypercellularity and abundance of CD68-positive cells (macrophages) in the glomeruli. After 2 months of treatment with avacopan, histology showed no evidence of endocapillary hypercellularity and only a small number of CD68-positive cells in the glomeruli. A renal biopsy conducted approximately 6 months after starting avacopan treatment showed no hypercellularity and no crescents, and very few CD68-positive cells in the glomeruli. There was attenuation of eGFR decline with avacopan treatment. Refer to the Investigator's Brochure for more detail.

Based on the results in mice, the patient with C3GN, and the Phase 2 studies in AAV, IgAN, and aHUS, testing avacopan more broadly in patients with C3G is indicated.

For more detail regarding the pharmacology and toxicology, and in-depth descriptions of clinical studies conducted with avacopan, please refer to the Investigator's Brochure.

This clinical trial will be conducted in compliance with the protocol, good clinical practice (GCP), and applicable regulatory requirements.

2. OBJECTIVES

2.1. 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.

2.2. Secondary Objectives

The secondary objectives of this study include evaluation of:

1. The safety of avacopan compared to placebo based on the incidence of adverse events, changes in clinical laboratory measurements, and vital signs;
2. Changes in laboratory parameters of renal disease including estimated glomerular filtration rate (eGFR), proteinuria, and urinary excretion of monocyte chemoattractant protein-1 (MCP-1) with avacopan compared to placebo;
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.

2.3. Exploratory Objectives

Additionally, 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.

3. STUDY DESIGN

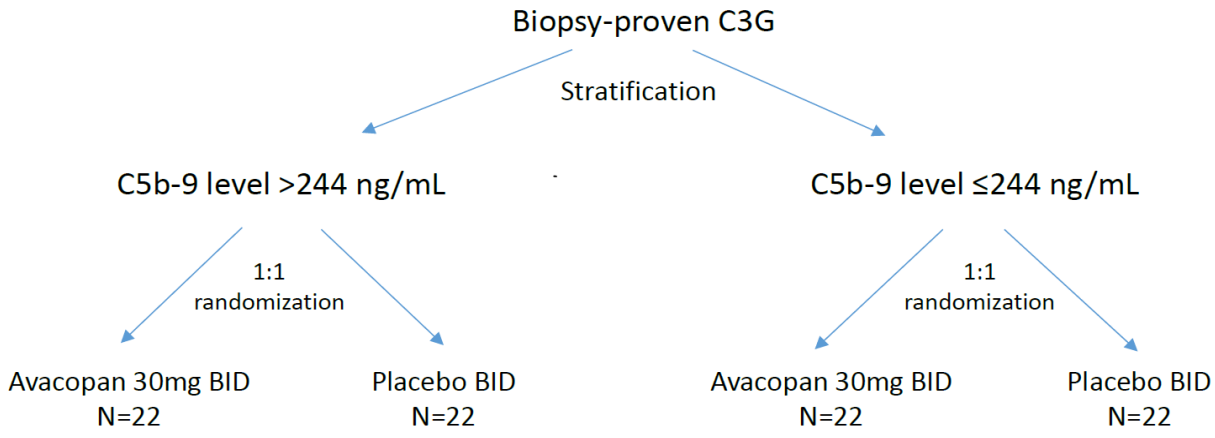
There is no approved treatment for patients with C3G. Immunosuppressive drugs such as cyclophosphamide, mycophenolate mofetil, and glucocorticoids, as well as biologics such as rituximab have been used but with limited success. The anti-C5 antibody eculizumab has shown evidence of improvement in some patients with C3G.

Based on results both from preclinical studies and clinical results from treatment of a patient with C3GN in a "Special Needs" protocol, avacopan has the potential to be an effective therapy for patients with C3G. The safety and efficacy of avacopan will be evaluated in this randomized, double-blind, placebo-controlled clinical trial in approximately 88 patients with C3G.

3.1. Stratification

This is a clinical trial to test the efficacy, safety, and tolerability of avacopan in patients with C3G, including both C3GN and DDD.

Patients with biopsy-proven C3G (within 12 weeks prior to signing informed consent or after consenting during screening or during screening), with or without a renal transplant, will be stratified by elevated or normal levels of C5b-9, and then will be 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 patients; each level will have approximately 22 patients 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 patient enrollment in the other stratum (C5b-9 level >244 ng/mL) reaches target enrollment first.

To obtain balance across treatment groups, eligible patients within each of the C5b-9 level strata will be further stratified based on two factors:

1. C3GN or DDD, and
2. Whether the patient has received a kidney transplant or not.

3.2. Randomization

Patients will be randomized using an interactive response technology (IRT) system and a minimization algorithm, using the stratification factors, in a 1:1 ratio to one of two treatment groups:

Group A: avacopan-matching placebo twice daily

Group B: avacopan 30 mg twice daily

The earliest timepoint at which the primary efficacy analysis can occur is when the last enrolled patient in the primary population (patients in the elevated C5b-9 stratum, see Section 8.2.1) has completed the Week 26 visit. After the 26-week double-blind period, the avacopan group will continue receiving avacopan for another 26 weeks, and the avacopan-matching placebo group 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.

3.3. Study Treatments

Treatments for each group are shown in Table 1 and Table 2.

The treatment period is 52 weeks (364 days).

Study drug (avacopan or placebo) will be taken as described in Section 5.3.

Dose strengths given to study patients will differ for adults and adolescents. Adolescent patients (12 to 17 years old) are allowed to be enrolled only in countries and at study centers for which approval by Regulatory Authorities and IRBs/ECs was granted.

3.3.1. Adult Patients - Study Treatments

All adults will receive an avacopan dose of 30 mg twice daily or avacopan-matching placebo twice daily in the initial 26-week, placebo-controlled treatment period (Table 1).When they enter the open-label 26-week treatment period, all study patients regardless of their prior treatment will receive avacopan 30 mg twice daily.

Table 1: Dosing Groups in the First and Last 26 Weeks of Treatment in Adults

	First 26 Weeks (Placebo-controlled treatment period)		Last 26 Weeks (Open-label treatment period)	
Group	**Avacopan Active**	**Avacopan-Matching Placebo**	**Avacopan Active**	**Avacopan-Matching Placebo**
A	None	3 placebo capsules orally twice daily	3 x 10 mg avacopan capsules orally twice daily	None
B	3 x 10 mg avacopan capsules orally twice daily	None	3 x 10 mg avacopan capsules orally twice daily	None

3.3.2. Adolescent Patients - Study Treatments

For study centers where enrollment of adolescent patients (12 to 17 years old) is approved, the dose of avacopan or placebo on Day 1 of the placebo-controlled period will be given 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 they enter the open-label 26-week treatment period, all adolescent patients will receive avacopan twice daily. Starting on Day 183, their dose will be reset 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 patients were treated with avacopan in the first 26 weeks, their dose adjustment in the open-label treatment period may be determined based on Day 183 trough concentration rather than exposure ($AUC_{0\text{-}6hr}$).

In all adolescents, blood samples will be taken at pre-dose and at 0.5, 1, 2, 3, 4, and 6 hours after the first avacopan dose on Day 1 and Day 183, respectively, to determine the avacopan plasma exposure ($AUC_{0\text{-}6hr}$). Plasma samples will be sent to the central laboratory for expeditious measurement of avacopan and CCX168-M1 in these patients.

These $AUC_{0\text{-}6hr}$ thresholds are based on the mean avacopan plasma exposure (525 ng•hr/mL) and one standard deviation (174 ng•hr/mL) above or below the mean in adult patients from Phase 2 study CL002_168 in AAV.

In order to maintain the blind in the first 26 weeks of the study, some patients on placebo will also be instructed to modify the number of placebo capsules taken. The laboratory personnel conducting the PK assays will communicate the dosage changes, without sharing the PK results with the study site personnel or study team (see Section 5.6).

Table 2: Avacopan/Placebo Starting Dose and Dose Adjustments Based on Avacopan Plasma Exposure in Adolescent Patients

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 patient was on placebo in the first 26 weeks)	Avacopan Dose Adjustment
<40 kg (88 lbs.)	10 mg (1 capsule) twice daily	≥351	None
		<351	Increase dose to 20 mg (2 capsules) twice daily
40-55 kg (88-121 lbs.)	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 lbs.)	30 mg (3 capsules) twice daily	≤699	None
		>699	Decrease dose to 20 mg (2 capsules) twice daily

3.4. Study Flow

Patients will be screened for enrollment based on biopsy-proven C3G (i.e., ≥2 levels of magnitude greater staining of C3 than any combination of IgG, IgM, IgA, kappa and lambda light chains, and C1q) and evidence of proliferative glomerulonephritis (mesangial hypercellularity and/or endocapillary hypercellularity based on the Mayo Clinic/Renal Pathology Society Consensus Report on Pathologic Classification, Diagnosis, and Reporting of GN; Sethi et al., 2016).

The screening period will be up to 42 days (6 weeks). Screening procedures will include written Informed Consent/Assent, demographics, medical history, medication history (medication given prior to Day 1 of dosing is considered medication history), physical examination, 12-lead ECG, and vital signs, serum pregnancy test for females of childbearing potential, serum chemistry (including serum creatinine), hematology, urinalysis, urinary protein:creatinine ratio (UPCR) and albumin:creatinine ratio (UACR), viral and tuberculosis (TB) screening. If a patient did not have a renal biopsy in the past 12 weeks, a renal biopsy is required prior to Day 1. Prior to starting blinded study drug treatment, blood samples will be collected for the following measurements to create a baseline profile for all patients:

1. Plasma C3a, C5a, C5b-9 and C5;
2. Serum C3 and C4;
3. Serum C3 nephritic factor;
4. Plasma complement factor H and factor B;

5. Serum factor H autoantibody;
6. Serum paraprotein detection;
7. Complement factor H related protein 5 (CFHR5) mutation.

Results obtained within 4 weeks prior to screening, or any time in the past for CFHR5 mutation, will be acceptable for the study. Patients who do not provide consent for genetic evaluation will not be excluded from the study.

Patients meeting eligibility criteria will start blinded study drug treatment on Day 1. Patients will take avacopan 30 mg or matching placebo orally twice daily. The placebo-controlled treatment period is 26 weeks (182 days). This will be followed by 26 weeks during which all patients will receive avacopan.

Thereafter, all patients will be followed for 8 weeks (56 days) without study drug treatment.

As specified in the Time and Events Table, blood and urine samples will be collected for safety, efficacy, and pharmacokinetic and biomarker measurements. A serum pregnancy test for women of childbearing potential will be done regularly during the 52-week treatment period and at the end of the 8-week follow-up period. Liver function and hematology including differential blood work will be monitored at least every 4 weeks throughout the study. Physical examinations and vital signs assessments will be performed throughout the study. Health-related quality of life using the EQ-5D-5L and SF-36 v2 surveys will be assessed periodically over the course of the study. Study drug (avacopan or placebo) will be dispensed and drug accountability will be done. Concomitant medication and adverse event assessments will be made at every study visit. A follow-up renal biopsy will be performed at the following time points:

1. Within 2 weeks prior to the Week 26 visit, and should be completed before open-label medication is started;
2. If a patient is withdrawn early from the study, and
3. After the 52-week treatment period.

The Week 52 biopsy is optional in adolescent patients.

If a patient is on other immunosuppressive or glucocorticoid treatment at the start of dosing, the dose(s) of concomitant immunosuppressive or glucocorticoid treatment may not be increased during the study (see Section 5.9). Treatment with these other drugs may be reduced or stopped during the study at the discretion of the Investigator, if the patient's condition justifies it. Adjustments of tacrolimus and cyclosporine doses to ensure these medications are at goal trough levels for maintenance of immunosuppression in transplant patients will be allowed during the study. No new treatments for C3G, except for renin-angiotensin-aldosterone system (RAAS) inhibitors, may be added during the study period (52-week treatment period or 8-week follow up), unless the patient's condition deteriorates to the extent that the investigator deems it in the best interest of the patient to do so. Addition of new treatments for C3G during the treatment period will be considered a treatment failure.

Patients who experience deteriorating renal function based on an increase in serum creatinine of at least 50%, or an increase in proteinuria of >3 g/g creatinine from Screening or baseline during

the 52-week treatment period, will be considered treatment failures (see Section 4.4. Removal of Patients from Therapy).

Patients will visit the study center for Screening and on Day 1 (baseline) and Weeks 1, 2, 4, 8, 12, 16, 20, 23, 26, 28, 32, 35, 38, 41, 44, 48, 52, 54, 57, and 60 (follow-up visit).

Patients will be discharged from the study when all the Week 60 visit procedures have been completed. The patient'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 patients as needed.

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

4. STUDY POPULATION

4.1. Size of the Population

The aim is to enroll approximately 88 patients in this clinical trial with approximately 44 patients in each of the two C5b-9 level strata. Patients who drop out early will not be replaced.

4.2. Inclusion Criteria

Patients must meet all of the following inclusion criteria in order to enter the study:

1. Biopsy-proven C3G, either DDD or C3GN, with or without a renal transplant, and with the following observations upon renal biopsy taken within 12 weeks prior to screening or during screening:
    a. ≥2-levels of magnitude greater staining of C3 than any combination of IgG, IgM, IgA, kappa and lambda light chains, and C1q by immunohistochemistry, and
    b. Evidence of proliferative glomerulonephritis (mesangial hypercellularity of greater than 3 mesangial cells per mesangial area and/or endocapillary hypercellularity defined as an increased number of cells within glomerular capillary lumina, causing luminal narrowing) based on light microscopy, and
    c. Confirmation of the presence of electron dense deposits in the glomeruli on electron microscopy corresponding with the C3 immunofluorescence positivity.

    The site will use their site-specific standard technique for taking the biopsy, which can include ultrasound guidance.
2. Male or female patients, aged at least 18 years; where approved, adolescents (12-17 years old) may be enrolled; female patients of childbearing potential (i.e., those who have experienced menarche and who are not permanently sterile or postmenopausal, defined as at least 12 consecutive months with no menses without an alternative medical cause) may participate if adequate contraception is used during, and for at least the three months after study completion; Male patients with partners of childbearing potential may participate in the study if they had a vasectomy at least 6 months prior to randomization or if adequate contraception is used during, and for at least the 3 months after study completion; male

patients with partners of childbearing potential must be excluded if they plan to father a child during the study. Adequate contraception is defined as resulting in a failure rate of less than 1% per year (combined estrogen and progestogen [oral, intravaginal, or transdermal], or progestogen-only hormonal contraception (oral, injectable, or implantable), intra-uterine device, intra-uterine hormone releasing system, bilateral tubal occlusion, vasectomized partner, or true sexual abstinence, i.e., in line with the preferred and usual lifestyle of the patient). In addition, a barrier method (i.e., cervical cap, diaphragm or condom) must be used during intercourse between a male patient and a female of child-bearing potential.

3. Willing and able to give written Informed Consent and to comply with the requirements of the study protocol; written Assent and Informed Consent must be obtained from the legal guardian in accordance with regional laws or regulations for patients 12 to 17 years of age; and
4. Judged to be otherwise fit for the study by the Investigator, based on medical history, physical examination, and clinical laboratory assessments. Patients with clinical laboratory values that are outside of normal limits (other than those specified in the Exclusion Criteria) and/or with other abnormal clinical findings that are judged by the Investigator not to be of clinical significance, may be entered into the study. At sites in which adolescents are allowed to be enrolled, the Investigator assures that the adolescent patient is willing and able to ingest the size "0" study drug.

4.3. Exclusion Criteria

1. Pregnant or nursing;
2. Tubulointerstitial fibrosis appears to be more than 50% based on standard assessment using trichrome staining of the renal biopsy;
3. Use of eculizumab or another anti-C5 antibody within 26 weeks prior to dosing;
4. Secondary C3 disease, e.g., infection-associated disease, or associated with another systemic or autoimmune disease; presence of a monoclonal spike on serum or urine protein electrophoresis or immunofixation assay;
5. Currently on dialysis or likely will require dialysis within 7 days after screening;
6. History or presence of any form of cancer within the 5 years prior to screening, with the exception of excised basal cell or squamous cell carcinoma of the skin, or carcinoma in situ such as cervical or breast carcinoma in situ that has been excised or resected completely and is without evidence of local recurrence or metastasis;
7. Positive hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) viral screening test indicative of acute or chronic infection;
8. Evidence of tuberculosis based on interferon γ release assay (IGRA), tuberculin purified protein derivative (PPD) skin test, or chest radiography done at screening or within 6 weeks prior to screening; a CT scan or chest X-ray are not mandatory if evidence of tuberculosis was excluded by any of the other methods specified above;
9. Active uncontrolled infection;

10. WBC count less than 3500/μL, or neutrophil count less than 1500/μL, or lymphocyte count less than 500/μL before start of dosing;
11. Evidence of hepatic disease; AST, ALT, alkaline phosphatase, or bilirubin >3x the upper limit of normal before start of dosing;
12. Currently using a strong inducer of the CYP3A4 enzyme, such as carbamazepine, phenobarbital, phenytoin, rifampin, or St. John's wort;
13. Known hypersensitivity to avacopan or inactive ingredients of the avacopan capsules (including [redacted]) or inability to swallow the capsules;
14. Participated in any clinical study of an investigational product within 30 days prior to screening or within 5 half-lives after taking the last dose; and
15. History or presence of any medical condition (for example: contraindication to local anesthesia required for renal biopsy, or recurring serious infections) or disease which, in the opinion of the Investigator, may place the patient at unacceptable risk for study participation.

4.4. Removal of Patients from Therapy

Investigators must clearly distinguish between discontinuation of study drug treatment (avacopan or placebo) and withdrawal from the study. Patients who discontinue study drug treatment or who initiate medication changes (including those prohibited by the protocol that comprise treatment failure) will not be automatically withdrawn from the study, but all efforts must be made to continue to follow the patients for all regularly scheduled visits.

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

Patients may be withdrawn from the study for only one of the following two reasons:

1. Patient withdrawal of consent to contribute additional outcome information;
2. Loss to follow-up.

Patients may discontinue study drug treatment for any of the following reasons:

1. Patient withdrawal of consent;
2. The Investigator may discontinue study drug treatment if, in his/her clinical judgment, it is in the best interest of the patient;
3. The Sponsor may request discontinuation of study drug treatment for safety reasons. If a patient develops any of the following lab abnormalities:

If a patient develops ALT or AST >3x ULN, additional testing should be performed immediately and repeated in one week to assay for total and fractionated serum bilirubin concentration, serum albumin concentration, and prothrombin time or INR, in addition to repeat transaminase (ALT, AST) testing. In addition, if a patient develops Grade 3 or greater increased hepatic transaminases (>5 times the upper limit of normal), or if a patient develops Grade 2 or greater increased transaminases (>3 times the upper limit of normal) with elevation of bilirubin to >2 times the upper limit of normal, dosing with study drug must be paused in this patient.

Study medication must be permanently discontinued (FDA Guidance 2009) if any of the following markers of hepatic injury and/or impaired liver synthetic function are observed, and cannot be attributed to a reversible etiology unrelated to study medication (e.g., cholelithiasis):

- ALT or AST >8x ULN
- ALT or AST >5x ULN for more than 2 weeks
- ALT or AST >3x ULN and (Total Bilirubin >2x ULN or INR >1.5)
- ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

If a patient develops Grade 3 or greater leukopenia (WBC count <2 x 10^9/L) or neutropenia (<1 x 10^9/L), or Grade 4 lymphopenia (<0.2 x 10^9/L), then study drug (avacopan or placebo) must be paused in this patient. In addition, if a patient develops Grade 2 leukopenia (WBC count <3 x 10^9/L, but ≥2 x 10^9/L), the patient must be followed closely for infection and for further significant reduction (reduction by an additional 0.5 x 10^9/L or more, or to <2 x 10^9/L) in WBC count; if either occurs, then study drug must be paused in this patient. Study drug may be resumed only if the abnormal value returns to normal and the Investigator deems resumption to be appropriate.

If a patient develops Grade 3 or worse CPK increase (>5 times the upper limit of normal), dosing with study drug must be paused in this patient. Study drug may be resumed only if the CPK returns to normal levels.

Patients who experience deteriorating renal function based on an increase in serum creatinine of at least 50% (confirmed by a repeat measurement after at least 2 weeks) which is otherwise not explained (e.g., dehydration, new medication), or an increase in proteinuria of >3 g/g creatinine (confirmed by a repeat measurement after at least 2 weeks) from Screening or baseline during the 52-week treatment period, will exit the treatment phase of the study and be treated at the discretion of their physician. The increase of serum creatinine or proteinuria will be calculated from the higher value that is measured either at Screening or baseline. They will remain in the study for follow up and complete the remaining study visits and procedures. If a patient refuses further study participation, the Early Termination visit procedures will be performed, if possible. These patients will be considered treatment failures.

In the event of early withdrawal from the study, the tests and evaluations listed for the Early Termination visit in Section 6.23 will be performed, whenever possible. Data collected at this visit will be designated as an “Early Termination” visit in the EDC. The Sponsor should be notified of all study drug treatment and study withdrawals in a timely manner.

5. STUDY MEDICATION/TREATMENT

5.1. Product Characteristics

Avacopan will be administered orally as hard gelatin capsules containing 10 mg avacopan. The capsules are manufactured under current good manufacturing practices. All doses of study medication will be administered orally. The avacopan capsules will be supplied to the study centers in plastic bottles containing 180 capsules. This is sufficient for 30 days of dosing at 30 mg avacopan twice daily.

Avacopan-matching placebo will be administered orally as matching hard gelatin capsules containing no avacopan but inactive ingredients. The capsules are manufactured under current good manufacturing practices. All doses of study medication will be administered orally. The placebo capsules will be supplied to the study centers in plastic bottles containing 180 capsules. This is sufficient for 30 days of twice daily dosing.

5.2. Randomization and Method of Treatment Assignment

Eligible patients with biopsy-proven C3G (within 12 weeks prior to signing Informed Consent or after consenting during screening or during screening), with or without a renal transplant, will be stratified by elevated or normal plasma levels of C5b-9 and then further stratified based on two stratification factors (C3GN or DDD and renal transplant or no renal transplant), and eventually randomized to one of the two treatment groups in a ratio of 1 placebo: avacopan.

Randomization will be performed centrally via an interactive response technology (IRT) system and minimization algorithm, using the stratification factors. In order to protect the blinding, the randomization schedule will not be accessible to study personnel who have contact with study centers or who are involved in data management and analysis.

5.3. Doses and Regimens

Treatments for each group are shown in Table 1. Adult patients will receive 30 mg avacopan or avacopan-matching placebo twice daily. For patients who are 12 to 17 years old, initial avacopan or avacopan-matching placebo doses will be selected based on body weight and further refined based on avacopan plasma exposure according to Table 2.

The treatment period is 52 weeks (364 days), followed by an 8-week (56 days) follow-up period.

Study drug (avacopan or placebo) within each of the C5b-9 level strata will be taken as follows by study patients:

Group A (placebo):

- Three avacopan-matching placebo capsules in the morning, preferably with food, and three in the evening, preferably with food, approximately 12 hours after the morning dose, daily for 26 weeks (182 days).
- This will be followed by three avacopan capsules in the morning, preferably with food, and three in the evening, preferably with food, approximately 12 hours after the morning dose, daily for the next 26 weeks (182 days).

Group B (avacopan):

- Three 10 mg avacopan capsules in the morning, preferably with food, and three 10 mg avacopan capsules in the evening, preferably with food, approximately 12 hours after the morning dose, daily for 52 weeks (364 days).

The placebo capsules will be identical in appearance to the avacopan capsules.

Patients in Group A will receive one bottle of avacopan-matching placebo capsules on Day 1 and Weeks 4, 8, 12, and 16, and two bottles at the Week 20 visit. These patients will then receive 2 bottles of avacopan capsules at the Week 26, 32, 38, and 44 visits. Patients will be asked to take 3 capsules every morning, preferably with food, and 3 capsules every evening, preferably with food, as instructed. Patients will be asked to bring all bottles, whether empty or not, to the study center at each study visit. Capsules will be taken with water.

Patients in Group B will receive one bottle of avacopan capsules on Day 1 and Weeks 4, 8, 12, and 16, and two bottles of avacopan capsules at the Week 20, 26, 32, 38, and 44 visits. Patients will be asked to take 3 capsules every morning, preferably with food, and 3 capsules every evening, preferably with food, as instructed. Patients will be asked to bring all bottles, whether empty or not, to the study center at each study visit. Capsules will be taken with water.

If a patient misses a dose, the next dose should be taken as soon as possible. If it is close to the time for their next dose (within 3 hours), the missed dose should not be taken and the next dose should be taken at the regular time.

5.4. Rationale for Dose Selection

Single doses of 1 mg up to 100 mg avacopan were studied in a Phase 1 study (CL001_168) in 48 healthy volunteers; once daily doses of 1, 3, and 10 mg avacopan and twice daily doses of 30 mg and 50 mg for up to 7 days were studied in the multiple dose period of this study. Doses from 3 mg up to 100 mg twice daily for 7 days were tested in 16 healthy volunteers in Phase 1 study CL007_168; 30 mg single doses and 30 mg twice daily doses were tested for 17 days in 32 healthy volunteers in Phase 1 study CL008_168. The various avacopan doses given in these studies were found to be safe.

A dose of 30 mg avacopan twice daily given for 12 weeks was studied in clinical trial CL002_168 in patients with AAV. This dose regimen was shown to be effective and well tolerated in study CL002_168. Doses of 10 mg and 30 mg avacopan twice daily given for 12 weeks were studied in clinical trial CL003_168 in patients with AAV and found to be well tolerated. Refer to the Investigator's Brochure for details.

An avacopan dose regimen of 30 mg twice daily was well tolerated in a patient with C3GN in a "Special Needs" study (CL009_168); this patient had been dosed continuously from September 2015 until Lost to Follow-up in December 2016.

A dose of 30 mg avacopan twice daily has been selected for adults in this study, which is lower than the maximum dose of 100 mg twice daily tested in study CL007_168. Adolescent patients may receive a lower starting dose, depending on their body weight (see Table 2). A dose regimen of 30 mg avacopan twice daily provides steady state trough (C_{min}) a plasma avacopan concentration of approximately 200 ng/mL. This concentration was shown to provide at least 95% C5aR blockade of blood neutrophils continuously throughout the day; the blockade level is

based on ex vivo C5a-induced CD11b upregulation assays conducted in whole blood samples obtained from patients in Phase 1 clinical trial CL001_168. This level of C5aR coverage is deemed appropriate to achieve optimal pharmacology.

Based on the favorable safety profile observed in the long-term toxicology studies (26 weeks in rats and 44 weeks in cynomolgus monkeys; see Investigator's Brochure), and on the safety and tolerability results from the clinical trials conducted to date, 30 mg avacopan twice daily is considered an appropriate dose to test in adults in this study.

5.5. Drug Supply

5.5.1. Packaging and Labeling

Avacopan capsules containing 10 mg avacopan and identical appearing placebo capsules will be packaged in high density polyethylene (HDPE) bottles with child-resistant screw caps and provided to the study sites for dispensing. Each bottle will contain 180 capsules.

5.5.2. Storage

Avacopan and avacopan-matching placebo capsules will be stored according to label instructions. Access should be restricted to pharmacy staff or to the designated responsible member of the Investigator's staff, and to the study monitor. The Investigator agrees that neither s/he nor any of the study staff will supply study medication to any persons other than those enrolled in the study.

5.6. Blinding

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

1. The blinded study drug bottles and capsule appearance for avacopan and its matching placebo will be identical;
2. Limited access to the randomization code; Sponsor personnel, study site personnel, study patients, personnel responsible for study monitoring, and biostatisticians and data managers involved in data analysis of the study will remain blinded to treatment assignment for the duration of the study;
3. While laboratory personnel conducting the PK assays will not be blinded to treatment assignment, unblinded avacopan plasma concentration results will not be shared with the study site personnel or study staff who have direct contact with study sites during the study;
4. Data that could potentially be unblinding, i.e., UPCR, UACR, and WBC and neutrophil count data within the normal range (i.e., values outside the normal range will be made available for safety monitoring), histology results from the central pathologist analysis, and urinary MCP-1:creatinine ratio will not be made available to study site personnel, study patients, personnel responsible for study monitoring, biostatisticians and data managers during the study unless required for safety monitoring. Investigators, however, will be provided with safety laboratory data reports, flagging abnormally high and low values in order to make informed decisions regarding patient care.

Treatment assignments for individual patients will remain blinded to the study team, investigators, and patients until after the study database has been cleaned and locked. Designated study staff will be provided with instructions regarding how to unblind an individual patient treatment assignment. An individual patient treatment assignment may be unblinded only in the case of an adverse event that requires knowledge of the study medication received by the patient in order to provide appropriate treatment or management of the adverse event. The study monitor and Sponsor should be notified as soon as possible in the event that unblinding of an individual patient's treatment assignment occurs prior to study completion.

An external data monitoring committee (DMC) will be constituted prior to start of the study (see Section 7.6). The DMC members will review data periodically over the course of the study in an unblinded manner. The DMC will provide recommendations to the Sponsor regarding further conduct of the study. The DMC will operate according to a charter developed prior to study initiation.

5.7. Drug Accountability

The study pharmacist and Investigator must maintain accurate records of dates and quantities of product(s) received, to whom dispensed (patient-by-patient accounting), and accounts of any product accidentally or deliberately destroyed. The Investigator must retain all unused and/or expired study supplies until the study monitor has confirmed the accountability data. All remaining study medication will be returned to the central depots for destruction.

5.8. Treatment Compliance

The avacopan and avacopan-matching placebo capsules will be self-administered by participating study patients. The morning dose of blinded study drug on Day 1 will be taken in the presence of study site personnel. Patients will be provided with dosing instructions at the start of the study and will be encouraged by study site personnel to take the study medication according to the instructions for the duration of the study. Patients will be instructed to bring the assigned bottles of study medication to the site staff at each study visit, whether empty or not. The study drug dispensed will be checked and a capsule count will be done from Week 4 through Week 52 of any remaining avacopan or placebo capsules. This information will be recorded and entered into the EDC system.

Avacopan plasma concentration measurements over the course of the study may also be used to assess patient compliance. Any events of non-compliance to the protocol will be documented in the study records.

5.9. Concomitant Medications and Restrictions

In order not to disrupt patient care, the protocol will allow initial continuation of treatment with glucocorticoids, immunosuppressants, calcineurin inhibitors, or RAAS inhibitors at the start of the study, at the same or lower dose than what was given prior to the study. Treatment with these other drugs may be reduced or stopped during the study if, in the opinion of the treating physician, the patient's condition justifies it. Adjustments of tacrolimus and cyclosporine doses to ensure these medications are at goal trough levels for maintenance of immunosuppression in transplant patients will be allowed during the study.

With the exception of RAAS inhibitors, dose increases of these concomitant treatments, or introduction of new treatments for C3G, will not be allowed during the study period (active treatment period) unless the patient's condition deteriorates to the extent that the Investigator deems it in the best interest of the patient to do so. This will be considered a treatment failure.

Eculizumab (and other anti-C5 antibodies) and investigational drugs will not be allowed during the study. The rationale for excluding anti-C5 antibodies is that these drugs act on the same branch of the complement pathway (C5), even though avacopan is selective for the C5aR. Therefore, eculizumab may interfere with the safety and efficacy assessment of avacopan. Investigational drugs have unknown effects and will therefore be excluded from the study.

Plasma exchange or infusion during the study will also not be allowed, since these may interfere with the efficacy and safety evaluation of avacopan.

Drugs that are strong inducers of the CYP3A4 enzyme, such as carbamazepine, phenobarbital, and phenytoin, rifampin, or St. John's wort are prohibited during the study because these drugs may substantially reduce the plasma concentrations of avacopan and reduce its effectiveness. If a patient requires one of these drugs, the Medical Monitor needs to be contacted to discuss the situation.

Substances that are strong inhibitors of CYP3A4, such as boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole, and grapefruit juice should be avoided during the study because these may modestly increase (~2-fold) the plasma concentrations of avacopan. However, these substances are not absolutely contraindicated. In case it is unavoidable that these substances are used concomitantly with avacopan, patients should be monitored carefully for any untoward side effects.

All concomitant medications taken during the course of the study must be recorded meticulously on the concomitant medication pages of the CRF.

6. STUDY PROCEDURES

6.1. Screening and Enrollment

Informed Consent (and Assent, if relevant) must be obtained prior to performance of any study-specific tests or evaluations. Within a period not to exceed 42 days prior to randomization, patients will undergo the following evaluations to determine their eligibility for study participation:

- Recording of demographic data and relevant medical history in the EDC;
- Recording of all prior medications for C3G for the 12-month period prior to screening in the EDC;
- Recording of all other prior medications for the 6-month period prior to screening in the EDC;

- Recording of all other concomitant medications on the screening day(s) in the EDC, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or special diets;
- A physical examination will be performed; body weight and height will be measured;
- Vital signs (temperature, sitting blood pressure, heart rate) will be measured after at least 3 minutes of rest;
- A 12-lead ECG will be performed after at least 3 minutes of rest in a supine position;
- Serum pregnancy test (in women of childbearing potential);
- Virology assessments as detailed in Section 7.2.2, unless done within 6 weeks prior to screening;
- At least one of the following tests to exclude tuberculosis: interferon γ release assay (IGRA), tuberculin purified protein derivative (PPD) skin test, or chest radiography (X rays or CT scan); tests performed within 6 weeks prior to screening are allowed to assess eligibility;
- Serum chemistry and hematology tests (results from tests done within 72 hours prior to screening may be used for eligibility assessment);
- A clean catch, midstream urine sample will be collected for urinalysis, and urine protein, urine albumin and urine creatinine measurement for UPCR and UACR;
- A renal biopsy will be taken if renal histology has not been performed within 12 weeks prior to screening;
- Complement profiling as detailed in Section 7.2.3. Results obtained within 4 weeks prior to screening, or any time in the past for CFHR5 mutation, will be acceptable for the study. Also, the results from these tests do not need to be available before start of dosing on Day 1, except for the C5b-9 levels that are needed for eligibility assessment.

Results from tests that have been performed prior to screening may be used to determine study eligibility if these tests were performed as part of the practice of medicine and were done whether or not study entry was contemplated, such as for diagnosis or treatment of the patient's condition. Results from the prior tests must be recorded in the EDC.

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

6.2. Study Day 1

If eligible for the study, the patient will visit the study center on Day 1. The following procedures will be performed before taking the first dose of avacopan or placebo:

- Stratification and randomization in the IRT system;
- A physical examination including body weight; height will also be measured in 12 to 17 year-old patients;
- Vital signs (temperature, sitting blood pressure, heart rate) after at least 3 minutes of rest;

- A 12-lead ECG will be performed after at least 3 minutes of rest in a supine position;
- Blood samples will be collected for shipment to the central laboratory for serum chemistry, hematology, serum pregnancy test (in women of childbearing potential), lymphocyte subset analysis, and PK and PD baseline measurements;
- A clean catch, midstream urine sample will be collected, aliquoted, and sent to the central laboratory for urinalysis (including blood, protein, and nitrites; if positive for blood, protein, or nitrites, a microscopic assessment for RBC count will be performed), albumin, protein, MCP-1, and creatinine measurement (for UACR, UPCR and MCP-1:creatinine ratio), and urinary PD markers related to inflammation and the complement system;
- Patients will be asked to complete the SF-36 v2 and EQ-5D-5L;
- Any pre-treatment adverse events (from time of the screening visit) will be recorded;

The patient will be stratified and randomized, and the following procedures will be performed:

- Blinded study medication (1 bottle of avacopan or avacopan-matching placebo) will be provided to the patient with dosing instructions (see Section 5.3);
- The patient will be asked to take the first dose of blinded study medication while at the study center;
- The time of the dosing of avacopan or avacopan-matching placebo will be recorded;
- If the patient is 12 to 17 years old, blood samples will be taken before dosing and at Hour 0.5, 1, 2, 3, 4, and 6 after the first dose of avacopan or avacopan-matching placebo; plasma samples will be frozen and sent to the central laboratory for expeditious measurement of avacopan and metabolite plasma concentrations. Precise dosing and sampling times need to be recorded;
- Any changes in concomitant medication use will be recorded, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or special diets;
- Any post-dosing adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 1 study visit;
  - Store the blinded study medications in a cool and dry place according to label instructions for the duration of the study;
  - Take the avacopan or avacopan-matching placebo, as instructed, and
  - Continue taking all their other concomitant medications as usual.

6.3. Study Week 1 (Day 8)

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

- A physical examination including body weight; height will also be measured in 12 to 17 year-old patients;

- Vital signs (temperature, sitting blood pressure, heart rate) after at least 3 minutes of rest;
- A 12-lead ECG will be performed after at least 3 minutes of rest in a supine position;
- Blood samples will be collected for shipment to the central laboratory for hematology, lymphocyte subset analysis, and for PK and PD measurements. Record the date and time of blood draw;
- The date and time of the last dose of avacopan/ avacopan-matching placebo prior to collection of the PK sample will be recorded;
- If the patient has not yet taken the morning dose of avacopan/placebo for this day, the patient will be asked to take the dose;
- A clean catch, midstream urine sample will be collected for urinalysis, for PD assessment, and for urine protein, urine albumin, urinary MCP-1 and urine creatinine measurement for calculation of UPCR, UACR and urinary MCP-1:creatinine ratio; the sample will be sent to the central laboratory;
- The bottle of blinded study medication will be checked to make sure the patient is taking the blinded study medication as instructed;
- Any changes in concomitant medication use will be recorded, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or special diets;
- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 2 study visit;
  - Store the blinded study medications in a cool and dry place according to label instructions for the duration of the study;
  - Take the avacopan or avacopan-matching placebo as instructed, and
  - Continue taking all their other concomitant medications as usual.

6.4. Study Week 2 (Day 15)

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

- A physical examination including body weight; height will also be measured in 12 to 17 year-old patients;
- Vital signs (temperature, sitting blood pressure, heart rate) after at least 3 minutes of rest;
- Blood samples will be collected for shipment to the central laboratory for serum chemistry, hematology, lymphocyte subset analysis, and for PK and PD measurements. Record the date and time of blood draw;
- The date and time of the last dose of avacopan/ avacopan-matching placebo prior to collection of the PK sample will be recorded;

- If the patient has not yet taken the morning dose of avacopan/ avacopan-matching placebo for this day, the patient will be asked to take the dose;
- A clean catch, midstream urine sample will be collected for urinalysis, for PD assessment, and for urine protein, urine albumin, urinary MCP-1 and urine creatinine measurement for calculation of UPCR, UACR and urinary MCP-1:creatinine ratio; the sample will be sent to the central laboratory;
- The bottle of blinded study medication will be checked to make sure the patient is taking the blinded study medication as instructed;
- Any changes in concomitant medication use will be recorded, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or special diets;
- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 4 study visit;
  - Store the blinded study medications in a cool and dry place according to label instructions for the duration of the study;
  - Take the avacopan or avacopan-matching placebo as instructed, and
  - Continue taking all their other concomitant medications as usual.

6.5. Study Week 4 (Day 29)

The Study Week 4 visit must occur within ± 2 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination including body weight; height will also be measured in 12 to 17 year-old patients;
- Vital signs (temperature, sitting blood pressure, heart rate) after at least 3 minutes of rest;
- Blood samples will be collected for shipment to the central laboratory for serum chemistry, hematology, serum pregnancy test (in women of childbearing potential), lymphocyte subset analysis, and PK and PD measurements. Record the date and time of blood draw;
- The date and time of the last dose of avacopan/ avacopan-matching placebo prior to collection of the PK sample will be recorded;
- If the patient has not yet taken the morning dose of avacopan/avacopan-matching placebo for this day, the patient will be asked to take the dose;
- A clean catch, midstream urine sample will be collected for urinalysis, for PD assessment, and for urine protein, urine albumin, urinary MCP-1 and urine creatinine measurement for calculation of UPCR, UACR and urinary MCP-1:creatinine ratio; the sample will be sent to the central laboratory;
- Patients will be asked to complete the SF-36 v2 and EQ-5D-5L;
- Drug accountability will be performed on the returned avacopan/placebo bottle;

- A new bottle of avacopan/avacopan-matching placebo will be dispensed;
- Any changes in concomitant medication use will be recorded, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or special diets;
- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 8 study visit;
  - Store the blinded study medications in a cool and dry place according to label instructions for the duration of the study;
  - Take the avacopan or avacopan-matching placebo as instructed, and
  - Continue taking all their other concomitant medications as usual.

6.6. Study Week 8 (Day 57)

The Study Week 8 visit must occur within ± 2 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination including body weight; height will also be measured in 12 to 17 year-old patients;
- Vital signs (temperature, sitting blood pressure, heart rate) after at least 3 minutes of rest;
- Blood samples will be collected for shipment to the central laboratory for serum chemistry, hematology, and serum pregnancy test (in women of childbearing potential). Record the date and time of blood draw;
- If the patient has not yet taken the morning dose of avacopan/avacopan-matching placebo for this day, the patient will be asked to take the dose;
- A clean catch, midstream urine sample will be collected for urinalysis and for urine protein, urine albumin, and urine creatinine measurement for calculation of UPCR and UACR; the sample will be sent to the central laboratory;
- Drug accountability will be performed on the returned avacopan/avacopan-matching placebo bottle;
- A new bottle of avacopan/placebo will be dispensed;
- Any changes in concomitant medication use will be recorded, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or special diets;
- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 12 study visit;
  - Store the blinded study medications in a cool and dry place according to label instructions for the duration of the study;
  - Take the avacopan or avacopan-matching placebo as instructed, and

- Continue taking all their other concomitant medications as usual.

6.7. Study Week 12 (Day 85)

The Study Week 12 visit must occur within ± 2 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination including body weight; height will also be measured in 12 to 17 year-old patients;
- Vital signs (temperature, sitting blood pressure, heart rate) after at least 3 minutes of rest;
- Blood samples will be collected for shipment to the central laboratory for a serum pregnancy test (in women of childbearing potential), serum chemistry, hematology, lymphocyte subset analysis, and PK and PD measurements. Record the date and time of blood draw;
- The date and time of the last dose of avacopan/ avacopan-matching placebo prior to collection of the PK sample will be recorded;
- If the patient has not yet taken the morning dose of avacopan/ avacopan-matching placebo for this day, the patient will be asked to take the dose;
- A clean catch, midstream urine sample will be collected for urinalysis, for PD assessment, and for urine protein, urine albumin, urinary MCP-1 and urine creatinine measurement for calculation of UPCR, UACR and urinary MCP-1:creatinine ratio; the sample will be sent to the central laboratory;
- Patients will be asked to complete the SF-36 v2 and EQ-5D-5L;
- Drug accountability will be performed on the returned avacopan/ avacopan-matching placebo bottle;
- A new bottle of avacopan/ avacopan-matching placebo will be dispensed;
- Any changes in concomitant medication use will be recorded, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or special diets;
- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 16 study visit;
  - Store the blinded study medications in a cool and dry place according to label instructions for the duration of the study;
  - Take the avacopan/ avacopan-matching placebo as instructed, and
  - Continue taking all their other concomitant medications as usual.

6.8. Study Week 16 (Day 113)

The Study Week 16 visit must occur within ± 2 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination including body weight; height will also be measured in 12 to 17 year-old patients;
- Vital signs (temperature, sitting blood pressure, heart rate) after at least 3 minutes of rest;
- Blood samples will be collected for shipment to the central laboratory for serum chemistry, hematology, and serum pregnancy test (in women of childbearing potential). Record the date and time of blood draw;
- If the patient has not yet taken the morning dose of avacopan/ avacopan-matching placebo for this day, the patient will be asked to take the dose;
- A clean catch, midstream urine sample will be collected for urinalysis and for urine protein, urine albumin, and urine creatinine measurement for calculation of UPCR and UACR; the sample will be sent to the central laboratory;
- Drug accountability will be performed on the returned avacopan/ avacopan-matching placebo bottle;
- One new bottle of avacopan/ avacopan-matching placebo will be dispensed;
- Any changes in concomitant medication use will be recorded, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or special diets;
- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 20 study visit;
  - Store the blinded study medications in a cool and dry place according to label instructions for the duration of the study;
  - Take the avacopan/ avacopan-matching placebo as instructed, and
  - Continue taking all their other concomitant medications as usual.

6.9. Study Week 20 (Day 141)

The Study Week 20 visit must occur within ± 2 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination including body weight; height will also be measured in 12 to 17 year-old patients;
- Vital signs (temperature, sitting blood pressure, heart rate) after at least 3 minutes of rest;
- Blood samples will be collected for shipment to the central laboratory for a serum pregnancy test (in women of childbearing potential), serum chemistry, hematology, and PK and PD measurements. Record the date and time of blood draw;
- The date and time of the last dose of avacopan/ avacopan-matching placebo prior to collection of the PK sample will be recorded;

- If the patient has not yet taken the morning dose of avacopan/ avacopan-matching placebo for this day, the patient will be asked to take the dose;
- A clean catch, midstream urine sample will be collected for urinalysis, for PD assessment, and for urine protein, urine albumin, urinary MCP-1 and urine creatinine measurement for calculation of UPCR, UACR and urinary MCP-1:creatinine ratio; the sample will be sent to the central laboratory;
- Patients will be asked to complete the SF-36 v2 and EQ-5D-5L;
- Drug accountability will be performed on the returned avacopan/ avacopan-matching placebo bottle;
- Two new bottles of avacopan/ avacopan-matching placebo will be dispensed;
- Any changes in concomitant medication use will be recorded, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or special diets;
- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
- Come to the study center for the Week 23 study visit;
  - Store the blinded study medication in a cool and dry place according to label instructions for the duration of the study;
  - Take the avacopan/avacopan-matching placebo as instructed, and
  - Remember not to take the morning dose of avacopan or /avacopan-matching placebo at home on the morning of the next visit at the study center, and
  - Continue taking all their other concomitant medications as usual.

6.10. Study Week 23 (Day 162)

The Study Week 23 visit must occur within ± 7 days of the scheduled date. During this visit, the following study procedures will be performed:

- A blood sample will be collected for measurement of serum chemistry and hematology. Record the date and time of blood draw.
- Any changes in concomitant medication use will be recorded, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or changes to a special diet;
- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 26 study visit
  - Take the avacopan/ avacopan-matching placebo as instructed, and
  - Remember not to take the morning dose of avacopan or avacopan-matching placebo at home on the morning of the next visit at the study center, and

– Continue taking all their other concomitant medications as usual.

6.11. Study Week 26 (Day 183)

The Study Week 26 visit must occur within ± 7 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination including body weight; height will also be measured in 12 to 17 year-old patients;
- Vital signs (temperature, sitting blood pressure, heart rate) after at least 3 minutes of rest;
- A 12-lead ECG will be performed after at least 3 minutes of rest in a supine position;
- Blood samples will be collected before the morning dose for shipment to the central laboratory for a serum pregnancy test (in women of childbearing potential), serum chemistry, hematology, lymphocyte subset analysis, and PK and PD measurements. Record the date and time of blood draw;
- The date and time of the last dose of avacopan/ avacopan-matching placebo prior to collection of the PK sample will be recorded;
- The patient will be asked to take the morning dose of avacopan while at the study center;
- The time of the dosing of avacopan will be recorded;
- If the patient is 12 to 17 years old, blood samples will be taken before dosing and at Hour 0.5, 1, 2, 3, 4, and 6 after the morning dose of avacopan; plasma samples will be frozen and sent to the central laboratory for expeditious measurement of avacopan and metabolite plasma concentrations. *Note: it is important that on Day 183 the adolescent patients take the dose when instructed at the study center, NOT at home, and they should be reminded through a telephone call two days before the Day 183 visit.*
- A clean catch, midstream urine sample will be collected for urinalysis, for PD assessment, and for urine protein, urine albumin, urinary MCP-1 and urine creatinine measurement for calculation of UPCR, UACR and urinary MCP-1:creatinine ratio; the sample will be sent to the central laboratory;
- Renal biopsy, performed within -2 weeks prior to the Week 26 visit and BEFORE patient is started on open-label treatment;
- Patients will be asked to complete the SF-36 v2 and EQ-5D-5L;
- Drug accountability will be performed on the returned avacopan/ avacopan-matching placebo bottles;
- Two new bottles of avacopan will be dispensed;
- For adolescents, two new bottles of avacopan will be provided to the patient with dosing instructions according to body weight (see Section 5.3);
- Any changes in concomitant medication use will be recorded, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or special diets;

- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 28 study visit;
  - Store the study medication in a cool and dry place according to label instructions for the duration of the study;
  - Take the avacopan as instructed, and
  - Continue taking all their other concomitant medications as usual.

6.12. Study Week 28 (Day 197)

The Study Week 28 visit must occur within ± 2 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination including body weight; height will also be measured in 12 to 17 year-old patients;
- Vital signs (temperature, sitting blood pressure, heart rate) after at least 3 minutes of rest;
- A 12-lead ECG will be performed after at least 3 minutes of rest in a supine position;
- Blood samples will be collected for shipment to the central laboratory for a serum pregnancy test (in women of childbearing potential), serum chemistry, hematology, and PK and PD measurements. Record the date and time of blood draw;
- If the patient has not yet taken the morning dose of avacopan for this day, the patient will be asked to take the dose;
- The date and time of the last dosing of avacopan prior to the collection of the PK sample will be recorded;
- A clean catch, midstream urine sample will be collected for urinalysis, for PD assessment, and for urine protein, urine albumin, urinary MCP-1 and urine creatinine measurement for calculation of UPCR, UACR and urinary MCP-1:creatinine ratio; the sample will be sent to the central laboratory;
- Any changes in concomitant medication use will be recorded, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or special diets;
- Any adverse events will be recorded;
- The dose for this visit and doses forward for adolescent patients may be adjusted based on the PK result of Day 183, per directions from the Sponsor;
- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 32 study visit;
  - Store the study medication in a cool and dry place according to label instructions for the duration of the study;
  - Take the avacopan as instructed, and

- Continue taking all their other concomitant medications as usual.

6.13. Study Week 32 (Day 225)

The Study Week 32 visit must occur within ± 7 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination including body weight; height will also be measured in 12 to 17 year old patients;
- Vital signs (temperature, sitting blood pressure, heart rate) after at least 3 minutes of rest;
- A 12-lead ECG will be performed after at least 3 minutes of rest in a supine position;
- Blood samples will be collected for shipment to the central laboratory for a serum pregnancy test (in women of childbearing potential), serum chemistry, hematology, and PK and PD measurements. Record the date and time of blood draw;
- If the patient has not yet taken the morning dose of avacopan for this day, the patient will be asked to take the dose;
- The date and time of the last dose of avacopan prior to collection of the PK sample will be recorded;
- A clean catch, midstream urine sample will be collected for urinalysis, for PD assessment, and for urine protein, urine albumin, urinary MCP-1 and urine creatinine measurement for calculation of UPCR, UACR and urinary MCP-1:creatinine ratio; the sample will be sent to the central laboratory;
- Patients will be asked to complete the SF-36 v2 and EQ-5D-5L;
- Drug accountability will be performed on the returned avacopan bottles;
- Two new bottles of avacopan will be dispensed;
- Any changes in concomitant medication use will be recorded, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or special diets;
- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 35 study visit;
  - Store the study medication in a cool and dry place according to label instructions for the duration of the study;
  - Take the avacopan as instructed, and
  - Continue taking all their other concomitant medications as usual.

6.14. Study Week 35 (Day 246)

The Study Week 35 visit must occur within ± 7 days of the scheduled date. During this visit, the following study procedures will be performed:

- A blood sample will be collected for measurement of serum chemistry and hematology. Record the date and time of blood draw.
- Any changes in concomitant medication use will be recorded, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or changes to a special diet;
- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 38 study visit
  - Take the avacopan/ avacopan-matching placebo as instructed, and
  - Remember not to take the morning dose of avacopan or avacopan-matching placebo at home on the morning of the next visit at the study center, and
  - Continue taking all their other concomitant medications as usual.

6.15. Study Week 38 (Day 267)

The Study Week 38 visit must occur within ± 7 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination including body weight; height will also be measured in 12 to 17 year old patients;
- Vital signs (temperature, sitting blood pressure, heart rate) after at least 3 minutes of rest;
- Blood samples will be collected for shipment to the central laboratory for a serum pregnancy test (in women of childbearing potential), serum chemistry, hematology, lymphocyte subset analysis, and PK and PD measurements. Record the date and time of blood draw;
- If the patient has not yet taken the morning dose of avacopan for this day, the patient will be asked to take the dose;
- The date and time of the last dose of avacopan prior to collection of the PK sample will be recorded;
- A clean catch, midstream urine sample will be collected for urinalysis, for PD assessment, and for urine protein, urine albumin, urinary MCP-1 and urine creatinine measurement for calculation of UPCR, UACR and urinary MCP-1:creatinine ratio; the sample will be sent to the central laboratory;
- Patients will be asked to complete the SF-36 v2 and EQ-5D-5L;
- Drug accountability will be performed on the returned avacopan bottles;
- Two new bottles of avacopan will be dispensed;
- Any changes in concomitant medication use will be recorded, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or special diets;
- Any adverse events will be recorded;

- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 41 study visit;
  - Store the study medication in a cool and dry place according to label instructions for the duration of the study;
  - Take the avacopan as instructed, and
  - Continue taking all their other concomitant medications as usual.

6.16. Study Week 41 (Day 288)

The Study Week 41 visit must occur within ± 7 days of the scheduled date. During this visit, the following study procedures will be performed:

- A blood sample will be collected for measurement of serum chemistry and hematology. Record the date and time of blood draw.
- Any changes in concomitant medication use will be recorded, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or changes to a special diet;
- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 44 study visit
  - Take the avacopan as instructed, and
  - Remember not to take the morning dose of avacopan at home on the morning of the next visit at the study center, and
  - Continue taking all their other concomitant medications as usual.

6.17. Study Week 44 (Day 309)

The Study Week 44 visit must occur within ± 7 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination including body weight; height will also be measured in 12 to 17 year-old patients;
- Vital signs (temperature, sitting blood pressure, heart rate) after at least 3 minutes of rest;
- Blood samples will be collected for shipment to the central laboratory for a serum pregnancy test (in women of childbearing potential), serum chemistry, and hematology. Record the date and time of blood draw;
- If the patient has not yet taken the morning dose of avacopan for this day, the patient will be asked to take the dose;
- The date and time of the last dose of avacopan prior to collection of the PK sample will be recorded;

- A clean catch, midstream urine sample will be collected for urinalysis and for urine protein, urine albumin, and urine creatinine measurement for calculation of UPCR and UACR; the sample will be sent to the central laboratory;
- Drug accountability will be performed on the returned avacopan bottles;
- Two new bottles of avacopan will be dispensed;
- Any changes in concomitant medication use will be recorded, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or special diets;
- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 48 study visit;
  - Store the study medication in a cool and dry place according to label instructions for the duration of the study;
  - Take the avacopan as instructed
  - Continue taking all their other concomitant medications as usual.

6.18. Study Week 48 (Day 337)

The Study Week 48 visit must occur within ± 7 days of the scheduled date. During this visit, the following study procedures will be performed:

- A blood sample will be collected for measurement of serum chemistry and hematology. Record the date and time of blood draw**.**
- Any changes in concomitant medication use will be recorded, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or changes to a special diet;
- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 52 study visit
  - NOT take any study medication the morning of the Week 52 visit

6.19. Study Week 52 (Day 365)

The Study Week 52 visit must occur within ± 7 days of the scheduled date. Two days prior to the expected visit, the Investigator must telephone the patient (this applies to both adults and adolescents) to remind him or her to NOT take any avacopan in the morning of this visit. The dose will also NOT be taken at the study center on this day. During this visit, the following study procedures will be performed:

- A physical examination including body weight; height will also be measured in 12 to 17 year-old patients;
- Vital signs (temperature, sitting blood pressure, heart rate) after at least 3 minutes of rest;

- A 12-lead ECG will be performed after at least 3 minutes of rest in a supine position;
- Blood samples will be collected for shipment to the central laboratory for a serum pregnancy test (in women of childbearing potential), serum chemistry, hematology, lymphocyte subset analysis, and PK and PD measurements. Record the date and time of blood draw;
- The date and time of the last dose of avacopan prior to collection of the PK sample will be recorded;
- A clean catch, midstream urine sample will be collected for urinalysis, for PD assessment, and for urine protein, urine albumin, urinary MCP-1 and urine creatinine measurement for calculation of UPCR, UACR and urinary MCP-1:creatinine ratio; the sample will be sent to the central laboratory;
- Renal biopsy, performed within ± 2 weeks of the Week 52 visit; this procedure is optional for adolescent patients;
- Patients will be asked to complete the SF-36 v2 and EQ-5D-5L;
- Drug accountability will be performed on the returned avacopan bottles;
- Any changes in concomitant medication use will be recorded, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or special diets;
- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 54 study visit, and
  - Continue taking all their other concomitant medications as usual.

6.20. Study Week 54 (Day 379)

The Study Week 54 visit must occur within ± 7 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination including body weight; height will also be measured in 12 to 17 year-old patients;
- Vital signs (temperature, sitting blood pressure, heart rate) after at least 3 minutes of rest;
- A 12-lead ECG will be performed after at least 3 minutes of rest in a supine position;
- Blood samples will be collected for shipment to the central laboratory for a serum pregnancy test (in women of childbearing potential), serum chemistry, hematology, and PK and PD measurements. Record the date and time of blood draw;
- A clean catch, midstream urine sample will be collected for urinalysis and for urine protein, urine albumin, and urine creatinine measurement for calculation of UPCR and UACR; the sample will be sent to the central laboratory;
- Any changes in concomitant medication use will be recorded, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or special diets;

- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 57 study visit, and
  - Continue taking all their other concomitant medications as usual.

6.21. Study Week 57 (Day 400)

The Study Week 57 visit must occur within ± 7 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination including body weight; height will also be measured in 12 to 17 year-old patients;
- Vital signs (temperature, sitting blood pressure, heart rate) after at least 3 minutes of rest;
- A 12-lead ECG will be performed after at least 3 minutes of rest in a supine position;
- Blood samples will be collected for shipment to the central laboratory for a serum pregnancy test (in women of childbearing potential), serum chemistry, hematology, and PK and PD measurements. Record the date and time of blood draw;
- A clean catch, midstream urine sample will be collected for urinalysis and for urine protein, urine albumin, and urine creatinine measurement for calculation of UPCR and UACR; the sample will be sent to the central laboratory;
- Any changes in concomitant medication use will be recorded, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or special diets;
- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be reminded to:
  - Come to the study center for the Week 60 study visit, and
  - Continue taking all their other concomitant medications as usual.

6.22. Study Week 60 (Day 421)

The Study Week 60 visit (follow-up visit) must occur within ± 7 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination including body weight; height will also be measured in 12 to 17 year-old patients;
- Vital signs (temperature, sitting blood pressure, heart rate) after at least 3 minutes of rest;
- A 12-lead ECG will be performed after at least 3 minutes of rest in a supine position;
- Blood samples will be collected for shipment to the central laboratory for a serum pregnancy test (in women of childbearing potential), serum chemistry, hematology, lymphocyte subset analysis, and PK and PD measurements. Record the date and time of blood draw;

- A clean catch, midstream urine sample will be collected for urinalysis, for PD assessment, and for urine protein, urine albumin, urinary MCP-1 and urine creatinine measurement for calculation of UPCR, UACR and urinary MCP-1:creatinine ratio; the sample will be sent to the central laboratory;
- Patients will be asked to complete the SF-36 v2 and EQ-5D-5L;
- Any changes in concomitant medication use will be recorded, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or special diets;
- Any adverse events will be recorded;
- After all study procedures have been completed, the patient will be discharged from the study. The patient'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 patients as needed.

6.23. Early Termination Visit

If a patient is withdrawn early from the study, the following termination procedures must be completed whenever possible:

- A physical examination including body weight; height will also be measured in 12 to 17 year-old patients;
- Vital signs (temperature, sitting blood pressure, heart rate) after at least 3 minutes of rest;
- A 12-lead ECG will be performed after at least 3 minutes of rest in a supine position;
- Blood samples will be collected for shipment to the central laboratory for serum chemistry, hematology, lymphocyte subset analysis and serum pregnancy test (in women of childbearing potential) measurement. Record the date and time of blood draw;
- A clean catch, midstream urine sample will be collected for urinalysis at the central laboratory;
- Drug accountability will be performed on the returned avacopan/avacopan-matching placebo bottles;
- Any changes in concomitant medication use will be recorded, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or special diets;
- Any adverse events will be recorded. If an adverse event remains unresolved at the conclusion of the study, a clinical assessment will be made by the Investigator and the Sponsor's Medical Monitor to determine whether continued follow-up of the adverse event is warranted.
- A follow-up renal biopsy will be performed if a patient is withdrawn early from the study.

7. STUDY ASSESSMENTS

7.1. Efficacy Assessments

7.1.1. Renal Histology

For eligibility assessment, renal biopsy samples taken within 12 weeks prior to screening or during screening will be assessed by immunofluorescence staining for C3 and immunoglobulins, as well as electron microscopy to confirm the presence of electron dense deposits. Eligibility assessment will be made by the Investigator based on their local pathologist's evaluation. Patients must have biopsy-proven C3G, either DDD or C3GN, with ≥2-levels of magnitude greater staining of C3 than any combination of IgG, IgM, IgA, kappa and lambda light chains, and C1q, and with evidence of proliferative glomerulonephritis (mesangial hypercellularity and/or endocapillary hypercellularity).

All renal biopsies will be analyzed with the routine panel of stains which includes hematoxylin-eosin (H&E), periodic acid–Schiff (PAS), trichrome, and Jones methenamine silver. A minimum of 4 (preferably 6) unstained slides from paraffin-embedded renal tissue will be provided by study centers to the central histopathology laboratory for additional immunostaining (e.g., CD45, CD68, MPO, C5a, C5aR, etc.).

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.

The central reader will determine the degree of disease activity and chronicity based on the C3G Histologic Index. A semi-quantitative scale of 0 to 3 will be used, indicating either the proportion (%) of glomeruli involved or the proportion of cortex involved (for tubular atrophy and interstitial fibrosis).

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 and colleagues (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.

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.The primary endpoint is based on the percent change from baseline in the C3G Histologic Index for disease activity. Percent change from baseline in C3G Histologic Index for disease chronicity will be a secondary endpoint.

Electron microscopy will be performed to evaluate the treatment effect of avacopan on electron microscopic features of the disease such as dense deposits.

Immunohistochemistry evaluation will be performed by the central pathologist to evaluate the treatment effect of avacopan on specific immune cell populations such as total leukocytes, macrophages, neutrophils, etc.

7.1.2. Urinary Measurements

A clean catch midstream urine sample needs to be collected at the clinic according to instructions provided separately. The urine samples will be sent to the central laboratory for analysis. The following analyses will be performed according to the Time and Events Table:

- Urinalysis including blood, protein, and nitrites; if positive for blood, protein, or nitrites, a microscopic assessment for RBC casts and RBC count will be performed;
- Quantitative albumin, protein and creatinine measurements to calculate the urinary albumin:creatinine ratio (UACR) and protein:creatinine ratio (UPCR);
- Quantitative MCP-1 measurements to calculate the MCP-1:creatinine ratio;
- Other urinary markers related to inflammation and the complement system may also be measured.

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

Proteinuria will be assessed by measuring the protein and creatinine concentrations and calculating the UPCR. Results will be expressed as mg protein/g creatinine.

Albuminuria will be assessed by measuring the albumin and creatinine concentrations and calculating the UACR. Results will be expressed as mg albumin/g creatinine.

Urine MCP-1 will be measured by specific ELISA assay. Urine MCP-1 levels will be standardized to urine creatinine and expressed as pg MCP-1/mg creatinine.

Other inflammation and complement markers will be measured using validated assay methodology.

7.1.3. Estimated Glomerular Filtration Rate

For adults (aged 18 years or older), estimated glomerular filtration rate (eGFR) will be calculated from serum creatinine measurements at all applicable study visits using the Chronic Kidney Disease-Epidemiology Collaboration study (CKD-EPI) equation according to Table 3 (Levey et al., 2009).

Table 3: 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}

Source: Levey et al., 2009

The CKD-EPI equation is not optimal for evaluation of the eGFR in children (Selistre et al., 2016). The modified Schwartz equation has been developed to calculate the eGFR in children (Schwartz et al., 2009). The equation is as follows:

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

The revised Schwartz equation will be used to calculate eGFR in adolescents (12 to 17 years old) enrolled in this study.

Serum creatinine (and eGFR) measurements will be made according to the Time and Events Table. Change and percent change from baseline in eGFR will be calculated and will be assessed as a secondary endpoint in the study.

7.1.4. Health-Related Quality of Life Assessments

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

7.2. Safety Assessments

7.2.1. Physical Examinations, Vital Signs and 12-lead ECGs

A complete physical examination (including evaluation of general appearance/mental status, head, eyes, ears, nose, throat, and the following body systems: dermatologic, cardiovascular, respiratory, gastrointestinal, musculoskeletal and neurologic) will be performed at visits indicated in the Time and Events Table. Findings must be recorded in the source documents.

Any new or worsening findings upon physical examination need to be recorded as adverse events.

Body weight will be measured as part of the physical examinations. Height needs to be recorded at screening only, except for adolescents (12 to 17 years old) in whom height will also be included as part of all physical examinations. BMI will be calculated in the EDC from the body weight and height measurements.

Vital signs will be measured during screening and on each scheduled study day as indicated in the Time and Events Table. Sitting blood pressure, pulse rate, and body temperature will be measured. All vital signs assessments will be performed after the patient has rested for at least three minutes.

12-lead ECGs will be performed at visits indicated in the Time and Events Table. Findings must be recorded in the source documents. The ECG will be performed after the patient has rested for three minutes in a supine position. Abnormal and clinically significant changes in ECG per Investigator's assessment compared to baseline screening need to be recorded as adverse events.

7.2.2. Clinical Safety Laboratory Assessments

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

- Hematology: hemoglobin, hematocrit, RBC count, WBC count with differential, platelet count, mean cell hemoglobin, mean cell hemoglobin concentration, mean corpuscular volume;

- Serum Chemistry: liver panel (total and fractionated bilirubin, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase), 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: PT and INR if retest is performed because of ALT and/or AST >3x ULN;
- Urinalysis: at the central laboratory, nitrite, blood, and protein, will be tested. If positive, microscopy 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.

7.2.3. Complement Panel

The following panel will be measured in all patients 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 patient, 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.

7.2.4. Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event could therefore be any unfavorable and/or unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the use of the drug, whether or not considered related to the drug. This definition includes intercurrent illnesses or injuries, and exacerbation of pre-existing conditions.

An unexpected adverse event is an adverse event that is not identified in nature, severity, or frequency in the current Investigator's Brochure, or that is of greater severity than expected based on the information in the Reference Safety Information listing within the Investigator's Brochure.

All adverse events occurring in patients who have been randomized to treatment will be recorded in the EDC system and will be reported in accordance with regulatory requirements. Adverse events reported prior to commencement of administration of blinded study medication will be considered pre-treatment events and will also be captured.

All adverse events will be monitored until resolution or, if the adverse event is determined to be chronic, until a cause is identified. If an adverse event remains unresolved at the conclusion of the study, a clinical assessment will be made by the Investigator and the Sponsor's Medical Monitor to determine whether continued follow-up of the adverse event is warranted.

7.2.4.1. Adverse Event Severity Assessment

The severity of each adverse event will be determined by the Investigator using the following scale:

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

It is not necessary to utilize Common Terminology Criteria for Adverse Events (CTCAE) grading for clinical events. However, in terms of lab values, the lab CTCAE criteria may be used for severity assessment. If there is a clinical AE that is related to a lab abnormality, the AE should be reported as the clinical event, where possible.

7.2.4.2. Causality Assessment

The relationship of avacopan/placebo to an adverse event will be determined by the Investigator and Sponsor based on the following definitions:

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

7.2.4.3. Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening (i.e., the patient was, in the opinion of the Investigator, at immediate risk of death from the event as it occurred);
- Requires or prolongs hospitalization;

- Results in persistent or significant disability or incapacity;
- Is a congenital anomaly or birth defect;
- Is an important and significant medical event that, based on appropriate medical judgment, may jeopardize the patient and/or may require medical or surgical intervention to prevent one of the other outcomes defining serious.

Elective surgery already known during screening to occur in the course of the study, and elective hospitalizations for convenience of the patient which are clearly unrelated to any medical condition and agreed upon between the Investigator and the patient prior to randomization, will not have to be reported as SAEs.

7.2.4.4. Infections

For medically important infections, the organism(s) involved in the infection needs to be determined whenever possible. As a selective C5aR antagonist, avacopan does not appear to affect formation of the C5b-9 membrane attack complex, a defense mechanism against infection by encapsulated bacteria such as *Neisseria meningitidis*. Nevertheless, any such events need to be clearly documented in the EDC and all local and national vaccination recommendations should be followed.

7.2.4.5. SARs and SUSARs

A serious adverse reaction (SAR) is defined as an SAE for which there is at least a reasonable possibility that the study drug (avacopan or placebo) caused the event.

A suspected unexpected serious adverse reaction (SUSAR) is defined as an SAE for which there is at least a reasonable possibility that the study drug caused the event, and the SAE is ”unexpected”, i.e., not described in terms of nature, severity, or frequency in the Reference Safety Information within the current Investigator’s Brochure.

“Reasonable possibility” means that there is evidence to suggest a causal relationship between the study drug and the adverse event. Within the reporting requirements, the following examples illustrate the types of evidence that would suggest a causal relationship:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

Events related to the underlying disease, such as relapses or worsening of disease will not be considered as SUSARs, unless there is a reasonable possibility that avacopan use was associated with these events.

7.2.4.6. Laboratory Abnormalities

Safety laboratory tests are performed frequently over the course of the study. Laboratory reports with abnormal findings will be reviewed by the Investigator. The Medical Monitor will review notably abnormal laboratory results according to the Safety Monitoring Plan.

Please see Section 4.4 for guidance on laboratory abnormalities (white blood cell count, neutrophil count, lymphocyte count, AST or ALT and other lab abnormalities of impaired liver function or hepatic toxicity, CPK increase, creatinine or proteinuria increases) that would prompt pausing or permanently discontinuing study drug (avacopan or placebo).

7.2.4.7. Pregnancies

If a patient becomes pregnant during the study or within the safety follow up period defined in the protocol, the investigator is to stop dosing with study drug(s) (avacopan or placebo) immediately and the patient should be withdrawn from the study. Early termination procedures should be implemented at that time.

A pregnancy is not considered to be an AE or SAE; however, i must be reported to [redacted] Clinical Safety within 24 hours of knowledge of the event. [redacted] Clinical Safety wil then provide the investigator/site the Exposure In Utero (EIU) form for completion. The investigator/site must complete the EIU form and fax/email it back to [redacted] Clinical Safety.

If the female partner of a male patient becomes pregnant while the patient is receiving study drug or within the safety follow up period defined in the protocol, the investigator should notify [redacted] Clinical Safety as described above.

The pregnancy should be followed until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the EIU form should be complete follow-up form and faxed/emailed to [redacted] Clinical Safety. If the outcome of the pregnancy meets the criteria for immediate classifica on as an SAE, (i.e. postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly) the investigator should follow the procedures for reporting an SAE.

7.2.5. Special Situation Reporting

Special situation reports include reports of overdose, misuse and abuse of the IMP:

- Overdose: Refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol. Clinical judgment should always be applied. In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the patient has taken excess dose(s) or the Investigator has reason to suspect that the patient has taken additional dose(s).
- Misuse: Refers to situations where the medicinal product is intentionally and inappropriately used in a way that is not in accordance with the protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.

- Abuse: Is defined as persistent or sporadic, intentional excessive use of a medicinal product which is accompanied by harmful physical or psychological effects.
- Medication Error: Medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product by a healthcare professional, patient or consumer, respectively. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors, cases of patients missing doses of investigational product are not considered reportable as medication error.

All spec al situation reports must be reported on the special situations report form and forwarded to [redacted] Clinical Safety within 24 hours.

All adverse events (AEs) associated with these special situation reports should be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management and outcome will be reported, when available.

7.2.6. Serious Adverse Event Reporting

Any serious adverse event occurring from screening through the end of the follow-up period, whe her or not considered study related, will be reported immediately (within 24 hours) to the [redacted] Clinical Safety team. Patients who terminate early from the trial will have SAEs reco ded at follow-up visits or at least 30 days after last study drug (avacopan or placebo) administration. Reporting is done by completing the SAE form in the EDC system. If it is not possible to access the EDC system, the Investigator will send an email to the [redacted] clinical safety mailbox (see information below) or call their regional SAE hotline and fa he completed SAE report form within 24 hours of awareness. When access to the EDC system is resumed, the SAE information should be entered as soon as possible. Contact details are as follows:

[redacted]

[redacted] SAE hotline – USA:

Telephone: [redacted]

Facsimile: [redacted]

e-mail: [redacted]

[redacted] SAE hotline – Europe:

Telephone: [redacted]

Fax: [redacted]

e-mail: [redacted]

Any medication or other therapeutic measures used to treat the event, in addition to the outcome of the adverse event, will be recorded in the EDC system.

Follow-Up Reports

The Investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., patient discharge summary or autopsy reports) to [redacted] Clinical Safety via fax or e-mail. If it is not possible to access the EDC system, refer to th pr cedures outlined above for initial reporting of SAEs.

The Sponsor or its representatives will report all SUSARs to national health authorities and central ethics committees in an expedited manner in accordance with Clinical Trial Directive, Articles 16 and 17, ICH Guideline E2A and ENTR CT3 on the reporting of all SUSARs. Investigators will forward any safety communication as applicable to their local ethics committees.

7.3. Pharmacokinetic Assessments

Concentrations of avacopan (and its metabolite CCX168-M1) will be determined in plasma according to the schedule in the Time and Events Table, using a validated analytical method. The samples on Day 1 will be collected prior to the first dose of avacopan/placebo on that day. Only for patients 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 patients should be taken in the clinic, not at home. 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 open-label portion of the study) prior to the sample collections must be recorded in the EDC system.

On the day of the Week 52 visit, the patient should not take the dose, either at home or in the clinic. Two days before this visit, the patient should be reminded of such through a telephone call. The time of the last dose in the prior evening 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 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 AAV.

7.4. Pharmacodynamic Assessments

Blood samples will be collected according to the schedule in the Time and Events Table 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 schedule in the Time and Events Table for biomarker assessments including, for example, soluble CD163, complement fragments, and inflammatory cytokine and chemokine levels.

7.5. Study Completion and Withdrawal

The Week 60 visit will be the last Study Day for all patients. Procedures for this day will be completed per the Time and Events Table. Each patient's condition will be evaluated by the Investigator at the end of the clinical trial and appropriate standard of care medical treatment will be provided to all patients as needed. For early withdrawals from the study, the procedures for the Early Termination visit will be performed, when possible (see Section 6.23).

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

7.6. Data Monitoring Committee

In addition to continuous safety monitoring by the Medical Monitor and clinical staff, an external Data Monitoring Committee (DMC) will monitor the safety of patients over the course of the study. The DMC will consist of external physicians and a biostatistician. At least one of the DMC members will be a pediatric nephrologist. A DMC charter will be developed before start of the study and the DMC will function according to the charter.

It is anticipated that the DMC will have 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 will make recommendations about further conduct of the study.

8. STATISTICAL METHODS

Details of the statistical analysis will be provided in a separate statistical analysis plan (SAP), which will be written, finalized, and approved prior to database lock and will be included in the Clinical Study Report (CSR) for this protocol. The SAP will supersede the statistical analysis methods described in this clinical protocol. Any major deviations from the protocol will be documented and described in the final report. If changes to principal features stated in the protocol are required, these will be documented in a protocol amendment. The final SAP will take into account any amendment to the protocol. Data analysis and writing of a CSR for all study data will be performed by the designated CRO in accordance with its SOPs. Analysis of PK and PD data, and writing of PK and PD reports will be performed by designated PK and PD teams in accordance with their standard operating procedures.

8.1. Patient Populations

8.1.1. Intent-to-Treat Population

For the purposes of data analysis, the ITT Population will include all patients who have provided written Informed Consent/Assent and are randomized in the study.

8.1.2. Per Protocol Population

The Per Protocol (PP) population will consist of all randomized patients 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. Patients' inclusion/exclusion from the PP population will be determined and documented prior to the database lock and unblinding.

8.1.3. Safety Population

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

8.2. Target Patient Population

8.2.1. C5b-9 Elevated Stratum

This population includes all patients enrolled under the C5b-9 elevated stratum, and is the primary target population for analysis.

8.2.2. C5b-9 Non-Elevated Stratum

This population includes all patients enrolled under the C5b-9 non-elevated stratum. This is the secondary target population for analysis.

8.2.3. Exploratory Population

The two strata combined will be considered the exploratory population.

8.3. Efficacy Endpoints

8.3.1. Primary Endpoint

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

8.3.2. Secondary and Other Endpoints

Secondary efficacy endpoints include:

1. The proportion of patients 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 8.8 for basis of selection of 35% threshold);
2. The percent change from baseline in the C3G Histologic Index for disease chronicity over the placebo-controlled 26-week treatment period.

Other efficacy endpoints include:

1. The change and percent change from baseline in eGFR over the placebo-controlled 26-week treatment period;
2. The percent change from baseline in UPCR over the placebo-controlled 26-week treatment period;
3. The percent change from baseline in urinary MCP-1:creatinine ratio over the placebo-controlled 26-week treatment period;
4. 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.

8.4. Safety Endpoints

Safety endpoints include:

1. Patient incidence of treatment-emergent serious adverse events, adverse events, and withdrawals due to adverse events;
2. Change from baseline and shifts from baseline in all safety laboratory parameters;
3. Change from baseline in vital signs.

8.5. Pharmacokinetic Endpoints

Avacopan (and its metabolite CCX168-M1) plasma concentration results for both C5b-9 level strata combined will be used to calculate trough plasma concentrations (C_{min}) over the course of the clinical trial. When possible, the terminal elimination half-life will also be calculated.

The C_{max}, T_{max}, and $AUC_{0\text{-}6hr}$ will be determined for patients 12 to 17 years old based on avacopan and metabolite plasma concentration data on Day 1 and on Day 183 (Week 26).

8.6. Exploratory Pharmacodynamic Endpoints

The following PD endpoints may be assessed:

1. Change and percent change from baseline in plasma biomarkers such as inflammatory cytokine and chemokine levels;
2. Change and percent change from baseline in urine biomarkers such as urinary sCD163:creatinine ratio, inflammatory cytokine and chemokine levels;
3. Change from baseline in CBC count (especially WBCs, neutrophils, and lymphocytes) and lymphocyte subset counts including B cells, T cells, and natural killer cells;
4. The relationship between PK parameters and renal function based on eGFR will be evaluated. The data may also be used to evaluate the PK/PD relationship of avacopan treatment for both C5b-9 level strata separately as well as combined. To this end, the change and/or percent change from baseline in the C3G Histologic Index, UPCR, eGFR, urinary MCP-1:creatinine ratio, and other biomarkers may be used as PD markers.

8.7. Statistical Analysis Methodology

A statistical analysis plan (SAP).with specific details of all the planned analyses and sensitivity analyses will be generated and approved before unblinding the data for analysis.

All statistical testing will be two-sided, with the Type I error rate at $\alpha = 0.05$.

The efficacy analyses for the efficacy endpoints will be performed in the ITT and PP populations, with the ITT analysis being the primary analysis.

The earliest timepoint at which the primary analysis of the efficacy endpoints can be conducted is when all patients in the elevated stratum have completed at least the Week 26 study visit. Additionally, enrollment for the stratum with C5b-9 levels ≤244 ng/ml could terminate early, if patient enrollment in the other 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 – further details will be provided in the SAP.

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 non-elevated C5b-9 stratum with a two-sided $\alpha = 0.05$. If the test in the elevated stratum fails to reach statistical significance, then the test in the non-elevated C5b-9 stratum will not be performed and only 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.

Another analysis will be performed when all patients have completed the study after week 60. Individual patient group assignment will remain blinded to investigators and patients until after the analysis of the data from the second analysis in order to maintain study integrity.

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

8.7.1. Patient Disposition

The number of patients who were screened, who screen failed (by reason), who were randomized, who completed Week 26, Week 52, and Week 60 of the study, who withdrew early from the study, along with the reasons for withdrawal, will be presented by treatment group.

8.7.2. Demographics and Baseline Characteristics

All patient 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], eGFR, proteinuria [UPCR], complement marker levels, urinary MCP-1:creatinine ratio, physical examination abnormalities, medical history, previous [within 6 months of screening] and concomitant medications [including other treatments for C3G] at study entry) will be listed by study center and patient number, and will also be summarized.

8.7.3. Prior and Concomitant Medications

All medications will be coded using the World Health Organization Drug Dictionary (WHODD). All prior (within 12 months of screening for C3G medications, and within 6 months of screening for all other medications) and concomitant medications (including C3G medication) will be listed and summarized by WHODD Anatomic Therapeutic Chemistry (ATC) classification and preferred term.

8.7.4. Study Drug Exposure and Compliance

Patient drug exposure will be calculated comparing the study drug dispensing and return records, as well as avacopan plasma concentrations over the course of the study. The study drug exposure (duration, total dose, and average daily dose) and compliance will be summarized for the double-blind and active treatment periods separately. Individual patient data listing will also be provided.

8.7.5. Efficacy Analyses

Summary statistics will be calculated for each of the efficacy endpoints. For categorical endpoints, numbers and percentages, and 95% confidence intervals will be calculated. For continuous variables, numbers, means, medians, minimum, maximum, standard deviations, and standard error of means, and 95% confidence intervals will be calculated. Geometric means will be calculated for UPCR and urinary MCP-1:creatinine, and other data that are not normally distributed.

Results will be presented by treatment group. Results will be presented by stratum for C3GN vs. DDD and renal transplant vs. no renal transplant. Data will also be presented by geographic distribution (North America vs. Rest of World), sex, age group (including a separate analysis in 12-17 year old patients), race, and ethnicity for at least the primary endpoint.

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

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

- The null hypothesis (H_0) 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 (H_1) is that the avacopan group is superior to the placebo group when comparing the percent change from baseline to Week 26 in the C3G Histologic Index for disease activity.

Avacopan and placebo groups will be compared by ANCOVA with treatment group as factor and baseline C3G Histologic Index for disease activity as covariate. A point estimate and corresponding 95% confidence interval will be estimated for the treatment main effect. The heterogeneity of the treatment effect across disease diagnoses and renal transplant strata will be investigated through subgroup analyses. If data are not normally distributed, in addition to the ANCOVA for the percent change in C3G Histologic Index for disease activity and chronicity,

the Cochran-Mantel-Haenszel (CMH) test will be applied to the percent change results and ANCOVA will be applied to the change in C3G Histologic Index disease activity and chronicity scores.

The treatment effect based on the baseline complement profile of patients will also be investigated.

Data from patients who are treatment failures, i.e., requiring treatment rescue measures such as high dose glucocorticoids during the treatment period, will be excluded from efficacy analysis after the point of rescue treatment.

Since the placebo group will receive avacopan during the second 26 weeks of the study, the change from Week 26 to Week 52 in the C3G Histologic Index for activity in the placebo control group will be compared to the change from baseline to Week 26 in this 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).

The change from baseline to Week 52 in the C3G Histologic Index in the avacopan group will also be compared to the change from baseline to Week 26 in placebo control group using similar methodology as described for the primary efficacy endpoint.

Continuous variables, including eGFR, UPCR, urinary MCP-1:creatinine ratio, EQ-5D-5L, and SF-36 v2 will be analyzed using a mixed effects model for repeated measures (MMRM) with treatment group, visit, and treatment-by-visit interaction as factors, and baseline as covariate. Patients will be considered as repeated measure units over visits. The interaction term may be dropped if it is not significant at $\alpha = 0.25$ level. Point estimates and corresponding 95% confidence intervals will be estimated for the difference between the avacopan group and the control group at Week 26 using simple contrast from the model.

Similar to the primary endpoint, the second 26 weeks will be compared to the first 26 weeks for the placebo group. Changes in the efficacy parameters across 52 weeks will also be assessed.

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.

Change from baseline in individual components of the C3G Histologic Index activity and chronicity indices as well as glomerular leukocytes and leukocyte subsets based on immunohistochemistry will be summarized and, where appropriate, analyzed using similar methodologies as describe above.

The secondary endpoint of the proportion of patients who have a histologic response will be analyzed by the CMH chi-square test. Data from patients who are treatment failures, i.e., require rescue medication, will be summarized.

The primary efficacy analysis will be based on the intent-to-treat (ITT) population, defined as all patients who are randomized.

8.7.6. Handling of Missing Data

If data are missing after all efforts made to collect post-baseline C3G Histologic Index data, missing data will be imputed using the last observation carried forward (LOCF) method. This

method may impute Week 26 missing data with the baseline value if there are no unscheduled data from visits prior to the missing time point. Multiple-imputation using Markov Chain Monte Carlo (MCMC) or other statistical method may also be performed.

8.7.7. Covariates and Subgroups

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

- Randomization stratification variables, i.e. C3GN or DDD and Having received a renal transplant or not
- Sex
- BMI
- Age at diagnosis of C3G
- Age at study entry; a subgroup analysis will be performed in 12 to 17 year-old patients, if feasible.
- Duration of C3G
- Patient's age, 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)

8.7.8. Safety Analyses

All clinical safety and tolerability data will be listed by treatment group and by patients and will be summarized by treatment group.

All reported adverse events will be coded using MedDRA and listed by System Organ Class, preferred term, and verbatim term.

Treatment-emergent adverse events will be listed and summarized by System Organ Class and Preferred Term, by relatedness, by maximum severity and by treatment group.

Serious adverse events and adverse events leading to study withdrawal will be summarized by treatment group. This will include serious infections.

Individual vital signs and change from baseline in vital signs will be listed by treatment group, patient, and study visit, and summarized by treatment group.

Laboratory data (actual values and change from baseline) will be listed by treatment group, patient and study visit. Abnormal laboratory values will be flagged. Laboratory data will also be summarized by treatment group and study visit. Shift tables will be generated for shifts in laboratory parameters by study visit.

8.7.9. Pharmacokinetic and Exploratory 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.

8.8. Sample Size Justification

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.

8.9. Interim Analysis

Safety data from the study will be summarized for review by the DMC at various points over the course of the study (see Section 7.6). The DMC charter will include details of these reviews.

No Type I error adjustment will be made based on the DMC review of the data, since these reviews will focus on safety assessment.

The earliest timepoint at which the primary analysis can be performed is when all patients in the primary population have completed at least the Week 26 visit. Another analysis will be performed when all patients have completed the full study. 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.

8.10. Protocol Deviations

Significant protocol deviations will be listed and summarized by deviation category. The effect of significant protocol deviations on the safety and efficacy outcomes will be assessed by conducting sensitivity analyses excluding patients and/or study visits with significant protocol deviations. This will be determined and documented before unblinding the study.

The Sponsor will assess any protocol deviation and decide whether any of these should be reported to Competent Authorities (CAs) as a serious breach of GCP and the protocol. Protocol waivers are not acceptable.

9. STUDY COMPLETION AND TERMINATION

9.1. Study Completion

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

9.2. Study Termination

The end of study is defined as the last study visit of the last clinical trial patient.

The study will be terminated early if there is an insurmountable safety concern. This will be determined in conjunction with the DMC. In this case, the Investigators, CAs, and IRB/EC will be notified expeditiously and appropriate measures taken to safeguard the study patients.

10. REGULATORY AND ADMINISTRATIVE REQUIREMENTS

10.1. Investigator Responsibilities

Prior to trial initiation, the Investigator will provide the Sponsor with a fully executed and signed FDA Form 1572, a Financial Disclosure Form, and a curriculum vitae. Financial Disclosure Forms also will be completed for all Sub-Investigators listed on the Form 1572 who will be involved directly in the treatment or evaluation of research patients in this trial.

The study will be conducted in accordance with the Declaration of Helsinki (amended by the 59th World Medical Association General Assembly, October 2008) and Good Clinical Practices (GCP) according to International Conference on Harmonisation (ICH) guidelines. Specifically, the study is based on adequately performed laboratory and animal experimentation; the study will be conducted under a protocol reviewed by a properly constituted IRB/EC; the study will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the patients will be respected; and each patient or his/her legal guardian will give his/her written Informed Consent/Assent before any protocol-specific tests or evaluations are performed.

10.2. Institutional Review Board or Ethics Committee

Prior to initiating the study, the Investigator will obtain written confirmation from the IRB/EC that the IRB/EC was properly constituted and met the definition of all United States Code of Federal Regulations Title 21, Section 312.3(b) and Part 56, and/or the applicable local, regional or national Regulatory requirements. A copy of the confirmation will be provided to the Sponsor. The Principal Investigator will provide the IRB/EC with all appropriate materials, including the protocol and Informed Consent/Assent documents. The trial will not be initiated until IRB/EC approval of the protocol, the Informed Consent/Assent document, and all recruiting materials are obtained in writing by the Investigator and copies are received by the Sponsor. Appropriate reports on the progress of the study will be made to the IRB/EC and the Sponsor by the Principal Investigator in accordance with applicable governmental regulations and in agreement with the policy established by the Sponsor.

10.3. Informed Consent/Assent

A properly executed, written, and appropriately explained Informed Consent Form, or Assent Form (where relevant), in compliance with the Declaration of Helsinki, ICH GCP, and US Code of Federal Regulations for Protection of Human Patients (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 46, Subpart A), will be signed by each patient or his/her legal guardian prior to entering the trial. Either the Investigator or the Investigator's designee will obtain the consent of the study patient. The patient will be provided as much time as necessary to review the document, to inquire about details of the trial, and to decide whether or not to participate in the study. The Informed Consent/Assent will be signed and dated by the study patient/legal guardian and by the person who conducted the Informed Consent discussion. The Investigator will provide a copy of the signed Informed Consent/Assent Form to each patient and will maintain the original in the patient's record file.

10.4. Protocol Modifications

Only the Sponsor may modify the protocol. The only exception is when the Investigator considers that a patient's safety would be compromised without immediate action. In this circumstance, immediate approval of the chairperson of the IRB/EC must be sought, and the Investigator should inform the Sponsor's Medical Monitor and the full IRB/EC within five working days after the emergency occurred.

All other amendments that have an impact on patient risk or the study objectives, and/or that require revision of the Informed Consent/Assent Form, must receive approval from the IRB/EC

prior to their implementation, except when the changes involve only logistical or administrative aspects of the trial. The IRB/EC must be notified of changes that are made to study contact personnel, but IRB/EC review or approval of these changes is not required. If protocol amendments are substantial and are likely to have an impact on the safety of the trial patients or to change the interpretation of the scientific documents in support of the conduct of the trial, or if they are otherwise significant, the sponsor shall notify the FDA and other CAs concerned of the reasons for, and content of, these amendments according to the European Directive "Detailed guidance on the request to the CAs for authorization of a clinical trial on a medical products for human use, the notification of substantial amendments and the declaration of the end of trial (CT-1)(2010/C 82/01)" and other regulatory guidance. In case of a substantial amendment to the protocol, approval will be sought from CAs before implementation.

10.5. Regulatory Aspects

Before the study is conducted, the protocol will be submitted to the country-specific CA/regulatory agency for review and approval. The study will not commence until written approval has been obtained from the CA.

All regulatory documentation including regulatory submissions, 1572 forms, and correspondence regarding this study will be kept by the Sponsor. The CRO that will conduct the study on behalf of the Sponsor will maintain all study documentation according to their SOPs. Clinical trial related documents will be archived for the longest of:

1. 10 years according to national Swedish and EU regulations (LVFS 2003:3), or
2. For 2 years following the date a full marketing application is approved, or
3. For 2 years after the FDA is notified that the IND is discontinued if there is no marketing application.

10.6. Patient Identification Register

The Investigator agrees to complete a patient identification register, which will be used for the purpose of long term follow-up, if needed. This form will be treated as confidential, and will be filed by the Investigator in a secure locked place. Otherwise, all reports and communications relating to the study will identify participants by initials and/or assigned number only.

10.7. Record Retention

The Investigator must retain all study records required by the Sponsor and by the applicable regulations in a secure and safe facility. The Investigator must consult a Sponsor CRA before disposal of any study records, and must notify the Sponsor of any change in the location, disposition, or custody of the study files. Clinical trial related documents will be archived for the longest of:

1. 10 years according to national Swedish and EU regulations (LVFS 2003:3), or
2. For 2 years following the date a full marketing application is approved, or
3. For 2 years after the FDA is notified that the IND is discontinued if there is no marketing application.

10.8. Case Report Form Completion

Electronic Case Report Forms (CRFs) will be generated for each patient. The electronic data capture (EDC) system will comply with CFR 21 Part 11.

Participants will not be identified in the EDC by name or initials and birth date. Only the Investigator or his/her designated representative will enter data into the EDC. It is the policy of the Sponsor that study data must be verifiable to the source data, which necessitates access to all original recordings, laboratory reports, and patients' records. The Investigator must therefore agree to allow access to patients' records, and source data must be made available for all study data. Each patient (or their legal representative) must also allow access to their medical records; they will be informed of this requirement and will indicate their agreement when giving Informed Consent/Assent. Upon completion of the study, electronic copies of the CRFs will be provided to the Investigators and should be included as part of his/her study files and retained as per FDA or local regulations.

10.9. Monitoring

At intervals during the study, as well as after the completion of patient enrollment at the study center, the study center will be monitored by a CRA for compliance, which will include ensuring that accurate and complete data are promptly recorded in EDC, and reviewing source documentation and drug accountability records. The study will be conducted according to the principles of GCP as accepted in the United States and according to CPMP/ICH/135/95.

10.10. On-site Visits and Audits

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

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

10.11. Study Registration, Use of Information and Publication

The study will be registered in clinicaltrials.gov and other country-specific registries, as required, prior to initiation.

It is understood by the Investigator that the information generated in this study will be used by the Sponsor in connection with the development of the product and therefore may be disclosed to government agencies in various countries. To allow for the use of information derived from the study, it is understood that the Investigator is obliged to provide the Sponsor with complete test results, all study data, and access to all study records.

The Sponsor recognizes the importance of communicating study data and will disclose or publish the results in a suitable form regardless of outcome. The Sponsor will post the clinical trial

information on appropriate registries, e.g., clinicaltrials.gov prior to enrollment of the first patients, and publish the results of this study in scientific journals, at seminars or conferences, and/or in other manner(s) it so chooses. Results from this study shall not be made available to any third party by the investigating team without the express permission of the Sponsor.

11. REFERENCES

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12. APPENDICES

12.1. Statement of Obligations of Sponsor, Monitor, and Clinical Investigator

Sponsor and Monitor

If the Sponsor is not familiar with the study site, the Sponsor or its designated representative, will:

A. Conduct a pre-study visit to:

1. Establish the acceptability of the facility, the recruitment potential and the standard of patient care at this site, and record this in a written report.
2. Discuss the proposed clinical trial with the Investigator, review the CRF requirements, and supply the Investigator's Brochure and the draft protocol for review and approval.
3. Discuss with the Investigator FDA and other regulatory requirements with respect to Informed Consent/Assent, CA and IRB/EC approval of the trial, the protocol, protocol amendments, and Informed Consent/Assent changes.

B. Conduct periodic site visits to:

1. Assure adherence to the protocol.
2. Review CRFs and medical records for accuracy and completeness of information.
3. Examine pharmacy records for documentation of quantity and date of receipt of investigational supplies, dispensation and accountability data for administration to each patient, loss of materials, contamination, and unused supplies.
4. Record and report observations on the progress of the trial and continued acceptability of the facilities in a Site Visit Report.
5. Review Investigator files for required documents, e.g., protocols, protocol amendments, CA and EC approvals (protocols, amendments, Informed Consent/Assent, etc.), EC charter and membership, and communications between the EC and the Investigator.

Clinical Investigator

A. EC

The Investigator must assure the monitor that the EC:

1. Meets FDA regulations as defined in 21 CFR Part 56 and other applicable ICH and GCP requirements.
2. Has authority delegated by the parent institution and found in EC by-laws, operation guidelines, or charter to approve or disapprove clinical trials and protocols, including Informed Consent/Assent Forms and other documents (protocol amendments, information to be supplied to patients concerning Informed Consent/Assent, etc.).

3. Complies with proper personnel makeup of an EC and maintains an active up-to-date roster of all EC members participating in the meetings.
4. Convenes meetings using acceptable rules of order for making decisions, recording such decisions, and implementing them.
5. Files contain (a) documentation of its decisions such as are found in EC minutes and correspondence, (b) written guidelines or by-laws governing EC functions, (c) protocols, (d) protocol information to be supplied to the patient, (e) correspondence between the EC and the Investigator (Informed Consent/Assent Form changes, protocol amendments, etc.).

B. Informed Consent/Assent of Human Patients

The Principal Investigator must assure the monitor that the Informed Consent/Assent Form:

1. Meets FDA regulations as defined in 21 CFR Part 50 Informed Consent, and other applicable ICH and GCP requirements.
2. Has been approved by the EC, including, when required, information to be given to the patient regarding the trial in which s/he is enrolled.
    a. The Informed Consent/Assent Form includes the Basic Elements and any Additional Elements necessary.
    b. The patient and a study center representative sign the Informed Consent/Assent Form and the patient is given a copy.

C. Storage and Dispensing of Study Supplies

The Investigator (or pharmacist or pharmacy technician) must demonstrate to the Monitor that:

1. Adequate and accurate written records show receipt and disposition of all study supplies, including dates, serial or lot numbers, quantities received, and each quantity dispensed, administered, or used, with identification of each patient.
2. Purpose and reasons are given in written records for study material disposal, e.g., the amount contaminated, broken, or lost, and the quantity returned to the Sponsor.

D. Case Report Forms

The Investigator must assure the Monitor that:

1. Case report forms, when complete, accurately reflect the medical records on each patient.
2. Case report forms and medical records will be accessible to the Monitor or FDA and other regulatory inspectors during site visits.

E. Files and Records

The Investigator must assure the quality, integrity, and content of his or her files that will be inspected by the Monitor and regulatory inspectors. The files must contain, at a minimum:

1. Correspondence between the EC and the Investigator.

2. The following documents:
    a. EC-approved protocols.
    b. EC-approved protocol amendments.
    c. EC-approved Informed Consent/Assent Form and information supplied to the patient.
    d. EC charter, membership, and qualifications.
3. Clinical supplies:
    a. Record of receipt, date and quantity, and batch or lot number.
    b. Disposition dates and quantity administered to each patient.
    c. Inventory records.

Clinical trial related documents will be archived for the longest of:

1. 10 years according to national Swedish and EU regulations (LVFS 2003:3), or
2. For 2 years following the date a full marketing application is approved, or
3. For 2 years after the FDA is notified that the IND is discontinued if there is no marketing application.

12.2. Informed Consent/Assent Form

In seeking Informed Consent/Assent, the following information shall be provided to each patient/legal guardian, where relevant:

A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the patient's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

A description of any reasonably foreseeable risks or discomforts to the patient.

A description of any benefits to the patient or to others that may reasonably be expected from the research.

A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient.

A statement describing the extent, if any, to which confidentiality of records identifying the patient will be maintained and that notes the possibility that the Food and Drug Administration or other regulatory agency may inspect the records.

For research involving more than minimal risk, an explanation as to whether any compensation and as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

An explanation of who to contact for answers to pertinent questions about the research and research patients' rights, and who to contact in the event of a research related injury to the patient.

A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits to which the patient is otherwise entitled.

12.2.1. ADDITIONAL ELEMENTS OF INFORMED CONSENT

1. A statement that the particular treatment or procedure may involve risks to the patient (or to the embryo or fetus if the patient is or may become pregnant) which are currently unforeseeable.
2. Anticipated circumstances under which the patient's participation may be terminated by the Investigator without regard to the patient's consent.
3. Any additional costs to the patient that may result from participation in the research.
4. The consequences of a patient's decision to withdraw from the research and procedures for orderly termination of participation by the patient.
5. A statement that significant new findings developed during the course of the research which may relate to the patient's willingness to continue participation will be provided to the patient.
6. The approximate number of patients involved in the study.

12.3. Benefit-Risk Assessment

12.3.1. Nonclinical Evaluation

Single dose and repeat dose toxicology, safety pharmacology, and genotoxicity studies have been conducted with avacopan. General toxicity studies of up to 26-week duration in rats and 44-week duration in cynomolgus monkeys have been conducted at avacopan doses up to 200 and 45 mg/kg/day, respectively, significantly higher than the highest human daily dose of 30 mg twice daily (BID) being tested in patients with C3G and other indications.

Based on in vivo safety pharmacology studies, which included neuropharmacology, pulmonary, and renal safety studies in rats, and a cardiovascular safety study in conscious telemetered cynomolgus monkeys, there was no evidence of toxicity of avacopan. No evidence of electrocardiographic alterations was seen in the monkey 4-week, 20-week, or 44-week studies or in in vitro cardiovascular safety studies (IC_{50} values for hERG inhibition was determined to be >2.3 µM for avacopan and >3.0 µM for its metabolite avacopan-M1, the limit of solubility for both compounds). A safety margin for avacopan and its metabolite CCX168-M1 of at least 3,500-fold relative to expected steady state human unbound maximum plasma is projected.

Protein binding, red blood cell partitioning, hepatocyte metabolism, cytochrome P450 inhibition and induction, Caco-2 permeability and genotoxicity studies, including in vitro bacterial mutagenicity (Ames test) and in vitro mammalian cell mutagenicity (mouse lymphoma) studies, in vivo bone marrow rat micronucleus and in silico mutagenicity evaluation of starting materials, intermediates and chemical impurities utilized and formed during the synthesis of avacopan were also conducted; none of these studies identified any safety concerns or significant potential for drug-drug interactions. In an acute toxicology study, single doses of avacopan up to 100 mg/kg in rats produced no remarkable effects. No effects on IgG and IgM antibody production in rats or monkeys were noted following immunization with keyhole limpet hemocyanin antigen. Immunophenotypic analyses performed in the 44-week monkey study did not reveal any avacopan-related effects. No phototoxicity potential was observed for avacopan in the in vitro 3T3 assay.

Avacopan was well tolerated in studies up to 26 and 44 weeks in rats and cynomolgus monkeys, respectively, up to the highest doses tested (200 mg/kg/day in rats and 45 mg/kg/day in cynomolgus monkeys). These doses provide an exposure margin of ~19-fold and ~6-fold, respectively, compared to the avacopan 30 mg twice daily therapeutic dose in humans. There were no significant toxicological findings of concern in these chronic studies or the preceding sub-chronic studies. Metabolite CCX168-M1 (which has been identified in humans) was present in samples collected in the rat 13- and 26-week and the monkey 20- and 44-week studies at relatively high levels indicating that this metabolite has been qualified.

No avacopan-related effects were observed upon pregnancy or embryo-fetal development in studies at doses up to 1000 mg/kg and 200 mg/kg in hamsters and rabbits, respectively. No evidence of histopathological alterations to the male or female reproductive system was seen in rats or monkeys in toxicology studies.

In summary, no safety findings in toxicology studies in rats, cynomolgus monkeys, rabbits and hamsters have been observed that would preclude dosing to humans at the 30 mg twice daily dose in this clinical trial.

12.3.2. Clinical Evaluation

Five Phase 1 studies and four Phase 2 studies with avacopan have previously been completed. A Phase 3 study in patients with AAV previously completed enrollment but follow up is ongoing and the study remains blinded. A total of 182 healthy volunteers participated in the five Phase 1 studies; 153 of these patients received avacopan at doses ranging from 1 mg up to 100 mg (CL001_168, CL004_168, CL007_168, CL008_168, and Japanese Phase 1 study CCX1101). Avacopan was generally well tolerated in these studies.

The most frequently reported adverse events in patients receiving avacopan in Phase 1 clinical studies were headache (14.6% vs. 14.3% for placebo), diarrhea (6.7% vs. 7.1% for placebo), dizziness (4.5% vs. 0% for placebo), upper respiratory tract infection (4.5% vs. 0% for placebo), nausea (3.4% vs. 0% for placebo), oropharyngeal pain (3.4% vs. 7.1% for placebo), and decreased WBC count (3.4% vs. 0% for placebo). All other adverse events occurred at an incidence less than 3%.

In addition, two Phase 2 clinical trials (CL002_168 and CL003_168) have been conducted in 109 patients with AAV; 73 of these were randomized to receive avacopan in these trials. A total of 60 patients received 30 mg avacopan twice daily and 13 patients received 10 mg avacopan twice daily for 12 weeks.

No deaths were observed in the Phase 2 AAV studies. As anticipated, since all patients received rituximab or cyclophosphamide, and most also received glucocorticoids, serious infections were the most common serious adverse event. The incidence of serious infections was similar in patients receiving avacopan compared to the control group. Vasculitis or renal vasculitis (worsening) was also reported at a similar incidence in the two groups.

The most commonly reported treatment-emergent adverse events in patients with AAV receiving avacopan in studies CL002_168 and CL003_168 combined were hypertension (17.8% vs. 16.7% in the control group), nausea (17.8% vs. 19.4% in the control group), vomiting (13.7% vs. 0.0% in the control group), headache (11.0% vs. 11.1% in the control group), nasopharyngitis (11.0% vs. 8.3% in the control group), peripheral edema (9.6% vs. 11.1% in the control group),

arthralgia (8.2% vs. 2.8% in the control group), and diarrhea (8.2% vs. 2.8% in the control group). Grade 3 lymphopenia has been observed in more patients receiving avacopan plus cyclophosphamide or rituximab compared to cyclophosphamide or rituximab alone. This lymphopenia occurred within the first 2 weeks of treatment, and was not progressive with continued treatment.

Avacopan did not show evidence of pro-arrhythmic potential in an intensive ECG study (CL007_168).

Caution should be exercised when avacopan is given with potent CYP3A4 inhibitors such as itraconazole, since the avacopan plasma exposure may increase approximately two-fold.

Avacopan has shown evidence of efficacy in Phase 2 study CL002_168 based on BVAS, quality of life measurements, renal response, urinary albuminuria, and urinary MCP-1:creatinine results. This efficacy was demonstrated across a number of relevant immunological and clinical subgroups, i.e., patients with MPO ANCA-positive disease vs. PR3 ANCA-positive disease, newly diagnosed vs. relapsing patients, and in patients on cyclophosphamide vs. those on rituximab. Avacopan was able to safely replace the use of oral prednisone with the same or greater efficacy based on results from this study.

It is of note that avacopan as a selective C5aR blocker does not appear to affect the formation of C5b and the membrane attack complex (MAC) or terminal complement complex (TCC) which is needed to protect against *Neisseria* infections. Nevertheless, all local and national vaccination protocols should be followed and investigators should be vigilant in reporting all infections occurring during clinical trials and should attempt to identify the organisms involved in all infections.

In an ongoing Phase 3 study of avacopan and background therapy of cyclophosphamide followed by azathioprine, or in combination with rituximab in patients with AAV (ADVOCATE, CL010_168), review of safety data by the Data Monitoring Committee (DMC) for that study have commented on a potential risk of [redacted] and [redacted], and a potential risk of [redacted] after the [redacted] unblinded review of safety data from [redacted] enrolled patients. The Reference Safety Informa on section of the Investigator's Brochure has been updated to include the potential risk of [redacted], [redacted] and [redacted], and to state that general gastrointestinal adverse events (e g. nausea, diarrhea) as previousl observed in Phase 2 AAV studies have been observed in the ongoing Phase 3 CL010_168 study at approximately the same frequency and severity.

Based on DMC review of safety data from all completed and ongoing studies of avacopan, the frequency of monitoring of hematology has been increased to monthly and rules for pausing administration of blinded study drug have been modified. These changes to the protocol were based on observations of [redacted] in this blinded study in a patient with C3 glomerulopathy (CL011_168) and [redacted] in the ongoing and blinded Phase 3 study of avacopan in patients with AAV (ADVOCATE CL010_168). In all reported cases, patients were receiving multiple immunosuppressants (e.g., cyclophosphamide, rituximab, mycophenolate mofetil, others) in addition to study medication. Therefore a causal relationship with study medication is not clear**.**

12.3.3. Pediatric Testing

There is currently no approved therapy for C3G in adults or juveniles.

Avacopan appears to be generally well tolerated and safe in adults with ANCA-associated vasculitis who have been included in clinical trials. There are no data currently available on the efficacy and safety of avacopan in patients younger than 18 years of age. However, avacopan has been well tolerated at supra-therapeutic doses in young animals (rats and cynomolgus monkeys) in long term toxicology studies, and at doses up to 100 mg twice daily in adults. Therefore, it is reasonable to postulate that avacopan may be well tolerated in younger patients.

The current therapies that are used to treat C3G in children have significant safety concerns. Glucocorticoids increase the risk of infection, new onset diabetes and hypertension, acne and Cushingoid changes, psychiatric disorders, glaucoma, cataracts, and peptic ulceration. It may negatively impact growth, immunity, and adrenal function. Broad immunosuppressive drugs are associated with increased risk of infection.

Avacopan is a highly selective inhibitor of the terminal effector of the complement cascade, C5a, by blocking the binding of C5a to its receptor, C5aR. It does not block other parts of the complement pathway, e.g., formation of the terminal complement complex, C5b-9, C3a, C3b, or other parts of the immune system. It is not known at this time whether the efficacy and safety profile of avacopan would be different in children compared to adults. However, it is anticipated that the mechanism of action of avacopan would also apply to C3G in children. There is also no evidence from the animal toxicology studies in young growing animals that avacopan affects growth and organ maturation.

Avacopan is orally administered, which makes it convenient for use in children.

Avacopan has shown evidence of efficacy in adults in Phase 2 studies in adults with AAV (CL002_168 and CL003_168) based on the BVAS, quality of life, and other markers such as albuminuria.

The PK profile of avacopan in children is not known. However, since avacopan is cleared from the body primarily through hepatic metabolism mediated by CYP3A4, which is known to mature in children well before the age of 12 (Johnson et al., 2006), it can be scientifically justified to adjust the avacopan dose for 12 to 17 year old children based on body weight. This methodology is proposed in this clinical trial. In a recent study of 126 unique products with pediatric studies by FDA scientists (Momper et al., 2013), allometric scaling using body weight was found to predict adolescent drug clearance well, with an overall mean absolute percentage error of 17.0%. By taking this approach, a 40 kg adolescent would need a 2/3 dose relative to a 70 kg adult to produce similar drug exposure. In this study (CL011_168), a conservative approach will be followed with an adolescent <40 kg by beginning with a dose that is 1/3 of the adult dose (i.e., 10 mg instead of 30 mg avacopan twice daily); the dose may be adjusted based on the Day 1 avacopan plasma concentrations. Linear pharmacokinetics is assumed for this approach based on the approximate dose linearity in AUC observed between 10 mg and 30 mg in adult AAV patients in study CL003_168 (153 ± 86.7 and 525 ± 276 ng•hr/mL for 10 mg and 30 mg avacopan, respectively).

The level of discomfort and the risk threshold for adolescent participation in this study have been carefully considered, and measures taken to monitor patients closely during the study:

- Based on all available data, there is no evidence of a negative effect of avacopan on growth and maturation of all relevant organ systems.
- All patients will be monitored closely over the course of the study by the study center personnel, study monitors, as well as an external data monitoring committee for any untoward effects.
- The protocol provides stopping rules for significant laboratory abnormalities, such as hepatic enzyme elevations and WBC, neutrophil, and lymphocyte count decreases (Section 4.4).
- Patients will be seen frequently over the course of the study, with a particularly high frequency in the first 4 weeks of treatment.
- Adolescents will be kept for at least 6 hours at the clinic. During this time, patients will be monitored for any adverse effects, and plasma samples will be taken to measure the levels of avacopan, and to adjust the dose of avacopan if the plasma levels are too high or low (Section 3.3).

In summary, there are a number of potential benefits of testing avacopan in adolescent patients with C3G in this study. For example, there are no currently approved medications for C3G in juveniles and it has been demonstrated that complement biology is involved in C3G. Further, as avacopan is an orally administered selective inhibitor of C5aR it carries potential safety and efficacy advantages of avacopan compared to other non-oral and/or non-approved therapies such as glucocorticoids and other immunosuppressants that may be used. Given the favorable safety profile that has been demonstrated with avacopan to date in conjunction with a prudent dose adjustment for adolescents based on plasma drug exposure these benefits outweigh the potential risk and would justify the testing in adolescent patients.

12.3.4. Summary Benefit-Risk Statement

Based on the nonclinical and clinical study results, the potential benefits of testing avacopan in patients with C3G outweigh the potential risks.

Patients participating in clinical trials must be closely monitored for any adverse events, and laboratory, physical examination, or vital signs abnormalities. WBC and differential counts, and liver enzyme values must be monitored over the course of the studies.

As with all investigational compounds, the potential exists for unanticipated serious or life-threatening toxicities or adverse events not predicted by the animal toxicology or clinical studies conducted to date. Investigators should exercise vigilance in the monitoring of patients involved in this clinical trial with avacopan.