CCI [redacted]

PEGCETACOPLAN (APL-2)

APL2-C3G-204

AN OPEN-LABEL, RANDOMIZED, CONTROLLED, PHASE 2 STUDY TO EVALUATE THE SAFETY AND EFFICACY OF PEGCETACOPLAN IN THE TREATMENT OF POST-TRANSPLANT RECURRENCE OF C3G OR IC-MPGN

Regulatory Agency Identifier Number(s)

PPD [redacted]

EudraCT: 2020-002637-15

SPONSOR'S APPROVAL

The protocol has been approved by Apellis Pharmaceuticals, Inc.

PPD [redacted]

04-Feb-2022 | 12:45 EST

03 February 2022

Amendment 3

Amendment Number

Apellis Pharmaceuticals, Inc
100 5th Avenue
Waltham, MA 02451

INVESTIGATOR'S AGREEMENT

I have received and read the investigator's brochure for pegcetacoplan (APL-2). I have read the APL2-C3G-204 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Approval date**
Amendment 3	03 February 2022
Amendment 2	01 March 2021
Amendment 1	27 May 2020
Original Protocol	29 May 2019

Protocol Amendment 3

Overall Rationale for the Amendment:

The protocol was amended to modify the eligibility criteria in order to improve subject recruitment and enrollment and to reduce the duration of the follow-up period, thus aligning with other nephrology clinical trials at Apellis.

Additional revisions were made to clarify study activities and procedures and to align with current company practices, and minor formatting and stylistic revisions were made to align with current templates and any identified typographical or other minor errors were corrected; these are not identified individually in the descriptions below.

Description of change	Section(s) affected by change
Removed eligibility requirement for proteinuria of at least 1 g/day in a 24-hour urine collection.	Synopsis, Section 6.2, Section 7.1.1
Reduced eGFR eligibility requirement from at least 30 mL/min/1.73 m^2 to at least 15 mL/min/1.73 m^2.	Synopsis, Section 6.2, Section 7.1.1
Reduced duration of follow-up period from 24 weeks to 8 weeks; because the effective half-life of subcutaneous pegectacoplan at the doses used in this study is approximately 8 to 10 days, this is sufficient to cover the washout period.	Synopsis, Section 6.1, Figure 1, Section 6.2, Schedule of Activities (Table 1, Table 2), Section 9.3, Section 9.4, Section 15.2.10 (Table 8, Table 9)
Changed secondary efficacy endpoint of the proportion of subjects with a 50% reduction in proteinuria and secondary efficacy endpoint of the proportion of subjects with normalization of proteinuria to exploratory endpoints; these endpoints will now be evaluated in subjects with baseline proteinuria above the upper limit of normal at both Week 12 and Week 52. Updated statistical analyses to align with this change.	Synopsis, Section 5.2.1, Section 12.3
Reorganized presentation of endpoints for improved clarity, including removal of discussion of exploratory endpoints from synopsis. Aligned presentation of statistical analyses with presentation of endpoints.	Synopsis, Section 5.2.1, Section 12
Added exploratory endpoints of C3G histologic index activity score and chronicity score.	Section 5.2.1.3
Reduced collection and analysis of samples for the measurement of C3 nephritic factor.	Schedule of Activities (Table 1), Section 15.1.1 (Table 7), Section 15.2.10 (Table 8, Table 9, Table 10)

Description of change	Section(s) affected by change
Reduced the frequency of collection of antidrug antibody samples in the long-term extension period (Part B of the study) as this will be sufficient to effectively monitor immunogenic responses.	Section 15.1.1 (Table 7), Section 15.2.10 (Table 10)
Added discussion of COVID-19 vaccination to COVID-19 risk mitigation section and COVID-19 appendix.	Section 4.4.1, Section 15.2.5
Added eligibility criterion excluding subjects with known or suspected hereditary fructose intolerance.	Synopsis, Section 7.1.2
Added wording describing shipping of investigational product and/or other study supplies directly to the subject to main body of protocol and removed from COVID continuity appendix.	Section 8.4, Section 15.2
Updated estimate of approximate blood volume to be collected during the study.	Section 10.18
Revised discussion of severity of adverse events to remove guidance on reporting changes in severity; this guidance will be provided in other study documentation.	Section 11.2.2

1. SYNOPSIS

Title of Study:	An Open-Label, Randomized, Controlled, Phase 2 Study to Evaluate the Safety and Efficacy of Pegcetacoplan in the Treatment of Post-Transplant Recurrence of C3G or IC-MPGN
Protocol Number:	APL2-C3G-204
Phase of Development:	Phase 2
Objectives:	**Primary:** To evaluate the efficacy of pegcetacoplan in improving the underlying pathophysiology of complement 3 glomerulopathy (C3G)/immune complex membranoproliferative glomerulonephritis (IC-MPGN) after 12 weeks of treatment. **Secondary:** • To evaluate the effect of pegcetacoplan on key clinical manifestations of the disease after 52 weeks of treatment. • To evaluate the safety of pegcetacoplan for up to 52 weeks in patients with recurrent C3G/IC-MPGN in a renal allograft.
Study Endpoints:	**Primary Efficacy Endpoint:** The primary efficacy endpoint is the proportion of subjects with reduction in C3c staining on renal biopsy after 12 weeks of treatment with pegcetacoplan. **Secondary Efficacy Endpoints:** The secondary efficacy endpoints are as follows: • The proportion of subjects with reduction in C3c staining on renal biopsy after 52 weeks of treatment • The proportion of subjects with stabilization or improvement in estimated glomerular filtration rate (eGFR), over time • The proportion of subjects with stabilization or improvement of serum creatinine concentration over time • Changes from baseline biopsy in C3c staining over time • Changes and percentage changes from baseline in eGFR and serum creatinine concentration over time **Safety Endpoints:** The safety endpoints are as follows: • The number and incidence of treatment-emergent adverse events (TEAEs) • The change from baseline in vital signs measurements and clinical laboratory test and ECG results
Study Design:	This Phase 2, multicenter, open-label, randomized, controlled study is designed to evaluate the safety and efficacy of pegcetacoplan in patients who have post-transplant recurrence of C3G or IC-MPGN. There will be up to 12 subjects enrolled in this study. There are 3 periods of this study: **Part A, Core Study:** • Screening period: up to an 8-week week screening period, during which a screening renal allograft biopsy will occur • Main period: a 52-week study period that contains 2 portions (Controlled and Noncontrolled) during which subjects will be randomized to either Group 1 or Group 2 at the Week 1 study visit:

	○ Controlled portion: Weeks 1-12 of the study ▪ Group 1: Up to 9 subjects will be randomized to this treatment group and will receive pegcetacoplan treatment throughout the entire study; biopsies will occur at Week 12. ▪ Group 2: Up to 3 subjects will be randomized to this treatment group and they will not receive pegcetacoplan treatment during the Controlled Portion; biopsies will occur at Week 12. ○ Noncontrolled portion: Weeks 13-52 of the study ▪ Group 1: Subjects will continue to receive pegcetacoplan treatment; biopsies will occur at Week 52. ▪ Group 2: Subjects will receive pegcetacoplan treatment following their Week 12 renal allograft biopsy; biopsies will occur at Week 52. • Follow-up period: an 8-week follow-up period **Part B, Long-Term Extension:** Any subject who, in the opinion of the investigator, is experiencing clinical benefit from pegcetacoplan administration may participate in Part B, a long-term extension, in order to continue to receive treatment with pegcetacoplan until it is commercially available for the disease under study. If invited to participate, the subject can enter Part B as soon as their 52-week treatment period has ended and does not need to participate in the 8-week follow-up period.
Selection of Subjects:	**Inclusion Criteria:** Individuals must meet all of the following criteria at screening visits to be included in the study: 1. At least 18 years of age at screening 2. Must have clinical and pathologic evidence of recurrent C3G or IC-MPGN, as evidenced by all of the following: a. A diagnosis of C3G or IC-MPGN, with at least 2+ staining for C3c in the renal allograft, confirmed by a central pathologist, based on the screening renal allograft biopsy b. C3G or IC-MPGN must be primary and not secondary to another condition (eg, infection, malignancy, monoclonal gammopathy, autoimmunity, chronic antibody-mediated rejection, chronic thrombotic microangiopathy, or a medication) 3. Stable (not improving) or worsening disease, in the opinion of the investigator, in the 2 months preceding the first dose of pegcetacoplan 4. eGFR ≥15 mL/min/1.73 m^2, calculated by the Chronic Kidney Disease–Epidemiology Collaboration (CKD-EPI) creatinine equation for adults 5. No more than 50% glomerulosclerosis or interstitial fibrosis on the screening renal allograft biopsy 6. Stable regimen for recurrent C3G/IC-MPGN for at least 4 weeks prior to the screening renal allograft biopsy and from the time of the screening renal allograft biopsy until randomization 7. Have received required vaccinations against *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* (type B) or agree to receive vaccinations if applicable vaccination records are not available.

	Vaccination is mandatory unless documented evidence exists that subjects are nonresponders to vaccination. 8. Women of childbearing potential, defined as any women who have experienced menarche and who are not permanently sterile or postmenopausal, must each have a negative blood pregnancy test at screening (and negative urine pregnancy at Visit 4) and must agree to use protocol-defined methods of contraception from screening through 12 weeks after receiving last dose of pegcetacoplan 9. Men must agree to use protocol-defined methods of contraception and agree to refrain from donating semen from screening through 12 weeks after receiving last dose of pegcetacoplan 10. Willing and able to provide written informed consent 11. Able to understand and willing to comply with all scheduled procedures and other requirements of the study in the opinion of the investigator 12. Willing and able to self-administer pegcetacoplan or have an identified caregiver who can perform the administration **Exclusion Criteria:** Individuals meeting any of the following criteria at screening or baseline are ineligible to participate in this study: 1. Absolute neutrophil count <1000 cells/mm^3 during screening (not including Day 1) 2. Previous treatment with pegcetacoplan 3. Evidence of rejection on the screening renal allograft biopsy that requires treatment 4. Diagnosis or history of HIV, hepatitis B, or hepatitis C infection or positive serology at screening indicative of infection with any of these viruses 5. Weight more than 100 kg at screening 6. Hypersensitivity to pegcetacoplan or any of the excipients 7. History of meningococcal disease 8. Malignancy, except for the following: a. Cured basal or squamous cell skin cancer b. Curatively treated in situ disease c. Malignancy free and off treatment for ≥5 years 9. Significant renal disease in the renal allograft secondary to another condition (eg, infection, malignancy, monoclonal gammopathy, rejection, or a medication) that would, in the opinion of the investigator, confound interpretation of the study results 10. Participation in any other investigational drug trial or exposure to other investigational agent, device, or procedure within 30 days or 5 half-lives from the last dose of the investigational agent (whichever is longer) prior to screening 11. Women who are pregnant, or who are currently breastfeeding 12. Inability to cooperate or any condition that, in the opinion of the investigator, could increase the subject's risk by participating in the study or confound the outcome of the study 13. Evidence of drug or alcohol abuse or dependence, in the opinion of the investigator 14. Known or suspected hereditary fructose intolerance.

Planned Sample Size:	Up to 12 subjects to be enrolled
Investigational Therapy:	Pegcetacoplan (APL-2) 1080 mg twice/week administered via subcutaneous infusion (20 mL)
Treatment Duration:	Part A: Each subject will have up to an 8-week screening period to be followed by a 52-week period, during which time Group 1 will have pegcetacoplan administration for all 52 weeks and Group 2 will receive pegcetacoplan administration only following the Week 12 biopsy through the remainder of the main period of the study. All subjects then enter the 8-week follow-up period or the long-term extension (Part B). Total duration of participation: up to 68 weeks (not including the long-term extension)
Statistical Methods and Planned Analyses:	Given the exploratory nature of the study, no formal statistical hypotheses testing will be performed, therefore the sample size is not based upon statistical power of the study. The following represent the analysis sets to be analyzed: screened, intent-to-treat (ITT), safety, pharmacokinetic, and pharmacodynamic. The specific assessments are outlined below.
Efficacy Assessments:	**Analysis of Primary Efficacy Endpoint:** The proportion of subjects with reduction in C3c staining on renal biopsy after 12 weeks on study will be tabulated. No formal statistical hypothesis testing will be performed. **Analysis of Secondary Efficacy Endpoints:** Changes from baseline biopsy in C3c staining over time will be summarized by treatment group. The proportion of subjects with reduction in C3c staining on renal biopsy after 52 weeks of treatment will be tabulated. Changes and percentage changes in eGFR and serum creatinine concentration over time will be summarized by treatment group. Estimated glomerular filtration rate and serum creatinine concentration will be measured at baseline and at each postrandomization assessment. The proportion of subjects with stabilization or improvement in each parameter will be tabulated. A stable or improved eGFR will be defined as no more than a 25% decrease in eGFR relative to baseline. A stable or improved serum creatinine concentration will be defined as no increase or an increase of no more than 25% from baseline.
Assessment of Safety:	The number and incidence of TEAEs (both serious and nonserious) as well as the number and incidence of discontinuations due to TEAEs will be tabulated. The adverse event summaries will be presented across all subjects. All adverse events will be listed by subject, along with information regarding onset, duration, severity, relationship to study drug, action taken with study drug, treatment of event, and outcome. In addition, the number and incidence of rejection episodes and graft loss in each group will be tabulated. Changes from baseline in clinical laboratory tests will be summarized using descriptive statistics by visit and nominal time postdose. Changes from baseline in vital signs will be summarized by visit using descriptive statistics. Changes from baseline in electrocardiogram parameters will be summarized by visit using descriptive statistics. Changes in physical examinations will be described in a data listing.

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

CCI

CCI

[redacted]

LIST OF TABLES

LIST OF FIGURES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation	Definition
ACIP	Advisory Committee on Immunization Practices
ADA	antidrug antibodies
AE	adverse event
AH50	50% alternative hemolytic complement pathway activity
ALT	alanine aminotransferase
AP	alternative pathway
AST	aspartate aminotransferase
C3G	complement 3 glomerulopathy
C3GN	C3 glomerulonephritis
CDC	Centers for Disease Control and Prevention
CH50	50% classical hemolytic complement pathway activity
CKD-EPI	Chronic Kidney Disease–Epidemiology Collaboration
COVID-19	coronavirus disease 2019
DDD	dense deposit disease
eCRF	electronic case report form
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	good clinical practice
GFR	glomerular filtration rate
IB	investigator's brochure
IC-MPGN	immune complex membranoproliferative glomerulonephritis
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IRB	institutional review board
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamic

Abbreviation	Definition
PEG	polyethylene glycol
PK	pharmacokinetic
PNH	paroxysmal nocturnal hemoglobinuria
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD-OCT	spectral domain optical coherence tomography
SMC	safety monitoring committee
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
uACR	urine albumin-to-creatinine ratio
ULN	upper limit of normal
uPCR	urine protein-to-creatinine ratio
WOCBP	women of childbearing potential

4. INTRODUCTION

Two similar diseases, complement component 3 glomerulopathy (C3G) and immune complex membranoproliferative glomerulonephritis (IC-MPGN), will be studied in this protocol. This protocol will study specifically primary C3G or IC-MPGN. Patients with C3G and IC-MPGN secondary to another underlying condition or situation (eg, infection, monoclonal gammopathy, malignancy, or medication) will be excluded from this study.

4.1. C3G and IC-MPGN and Unmet Medical Need

Component 3 glomerulopathy is a disease in which the complement system, specifically the alternative pathway (AP), is indiscriminately overactive, leading to excessive deposition of C3 breakdown products in the glomeruli of the kidney and damage to the renal parenchyma. The underlying AP hyperactivity can be due to various factors, most commonly, an acquired autoantibody which stabilizes the AP C3 or C5 convertase (C3 or C5 nephritic factor). This setting of AP hyperactivity leads to unbridled and uncontrolled C3 activation, and an excess of C3 breakdown products, which are deposited in the glomerular basement membrane and, along with the inflammatory response, disrupt the normal glomerular architecture and filtration barrier.

There are 2 subtypes of C3G: dense deposit disease (DDD) and C3 glomerulonephritis (C3GN), which are distinguishable only by renal biopsy. The clinical presentation, features, and disease course are similar between the 2 subtypes. Notable distinctions between the 2 subtypes are that DDD tends to present earlier in life than C3GN (median ages of diagnosis for DDD and C3GN are 12 and 26 years old, respectively), and that DDD is also associated with extrarenal manifestations, such as acquired partial lipodystrophy and macular degeneration. The incidence of C3GN is about 3-fold greater than that of DDD (Medjeral-Thomas et al. 2014; Servais et al. 2012; Lu et al. 2012).

Although IC-MPGN is typically considered a distinct pathologic entity from C3G, the underlying pathophysiology and clinical course of the 2 primary diseases are remarkably similar (Noris et al. 2019; Holle et al. 2018). As in C3G, patients with primary IC-MPGN often have evidence of AP hyperactivity, including the presence of genetic or acquired causes of AP dysregulation. In these patients, uncontrolled C3 activation and glomerular deposition of C3 breakdown products is also observed, similar to C3G. The only pathologic distinction from C3G is that the glomerular C3 deposition in IC-MPGN is accompanied by immunoglobulin deposition. The common clinical manifestations of primary IC-MPGN are the same as those of C3G and other glomerulonephritides—proteinuria, hematuria, hypertension, and reduced glomerular filtration rate. It is important to note that the term "immunoglobulin-associated membranoproliferative glomerulonephritis" may be a more appropriate term; however, in an effort to be consistent with the majority of the literature, the term IC-MPGN is used throughout this protocol.

Unfortunately, there are no approved or proven therapies to prevent or reverse disease progression in either C3G or IC-MPGN. Similar to other glomerular diseases, disease management includes nonspecific measures to manage proteinuria, hypertension, hyperlipidemia, edema, and other facets of glomerular and chronic kidney disease. Despite these various measures, the prognosis for both primary C3G and IC-MPGN is poor, with approximately 50% of patients progressing to end-stage renal disease (ESRD) within 5-10 years of diagnosis. While renal transplantation is an option for these patients, disease recurrence is not uncommon and can lead to graft loss. Indeed, up to 50% of

C3G patients lose their renal allografts due to disease recurrence (Medjeral-Thomas et al. 2014; Zhang et al. 2014; Pickering et al. 2013; Lu et al. 2012; Okpechi et al. 2014). Therefore, these are diseases with a high unmet medical need, especially for a therapy that targets the underlying pathophysiology of the disease and is able to prevent or reverse disease progression.

4.2. Study Rationale

There are no therapies approved to prevent or reverse disease progression in C3G or IC-MPGN. Similar to other glomerular diseases, disease management includes nonspecific measures to manage proteinuria, hypertension, hyperlipidemia, edema, and other facets of glomerular and chronic kidney disease. Despite these various measures, the prognosis of C3G and IC-MPGN is poor as patients can progress to ESRD (Medjeral-Thomas et al. 2014; Zhang et al. 2014; Pickering et al. 2013; Lu et al. 2012; Okpechi et al. 2014).

Renal transplantation is an option for patients who reach ESRD, but the incidence of disease recurrence is high, with up to 50% of patients losing their renal allografts due to disease recurrence (Medjeral-Thomas et al. 2014; Zhang et al. 2014; Pickering et al. 2013; Lu et al. 2012). Therefore, a therapy that can protect the kidneys, native or transplanted, from ongoing damage due to complement hyperactivity would be highly desirable.

As an inhibitor of C3 and its fragment, C3b, pegcetacoplan (APL-2) has the potential to address the underlying disease pathophysiology of complement hyperactivity in C3G and IC-MPGN. Specifically, by inhibiting C3, it is expected that pegcetacoplan will halt the inappropriate and excessive C3 activation that characterizes these diseases. Additionally, by inhibiting C3b, pegcetacoplan inhibits the activity of the AP C3 convertase (whether it is stabilized by nephritic factors or not) through a second complementary mechanism of action on top of the inhibition of C3 as a substrate in the complement cascade. These 2 complementary mechanisms will prevent further deposition of C3 breakdown products in the glomeruli, affording the opportunity for the kidney to recover by clearing existing deposits and resolving inflammation. This renal recovery would be expected, initially, to yield reductions in proteinuria, and ultimately, to result in prolonged renal survival. Therefore, pegcetacoplan is a potentially life-altering therapy for C3G and IC-MPGN.

An ongoing study, APL2-201, is studying pegcetacoplan in patients with C3G who have not undergone a renal transplant. Preliminary data from the APL2-201 study indicate that pegcetacoplan is able to target the complement hyperactivity of C3G. The sponsor now aims to study the safety and efficacy of pegcetacoplan in patients with recurrence of C3G or IC-MPGN in a renal allograft.

This study will explore the safety and biologic activity of pegcetacoplan in patients with C3G or IC-MPGN recurrence post-transplantation. Renal biopsies will be obtained at multiple time points to assess the ability of pegcetacoplan to reduce the amount of C3c glomerular deposition, one of the histologic hallmarks of these diseases. This finding, along with increases in intact serum C3, would provide strong evidence that pegcetacoplan is addressing the underlying pathophysiology of the disease by preventing excessive production of C3 breakdown products, and their subsequent deposition into the kidney.

4.2.1. Justification of Dose

The dosing regimen for adults will be 1080 mg SC twice weekly. This dosing regimen is intended to result in systemic exposures of pegcetacoplan similar to those seen in the ongoing

Phase 2 study in patients with complement-mediated glomerulopathies, Study APL2-201, and the ongoing Phase 3 study in patients with paroxysmal nocturnal hemoglobinuria (PNH), Study APL2-302, in which pegcetacoplan has been generally safe and well tolerated.

Modeling-based simulations were performed using an adult population pharmacokinetics (PK) model incorporating pegcetacoplan serum concentration-time data from 10 clinical studies (five Phase 1 studies in healthy volunteers, one special-population study in adults with severe renal impairment, three Phase 1b/2a studies in adult PNH patients, and one Phase 3 study [Study APL2-302; data up to Week 16]) in healthy adults and in patients with PNH. Modeling of exposure in high body weight subjects (>100 kg) results predicted exposures at least 15% lower than that for a reference 70-kg subject; subjects >100 kg will therefore be excluded from the study.

4.3. Summary of Clinical Experience With Pegcetacoplan

Pegcetacoplan is being studied in Study APL2-201, an ongoing Phase 2 study that includes patients with 1 of 4 glomerular diseases: C3G, immunoglobulin A nephropathy, primary membranous nephropathy, or lupus nephritis. Preliminary data from the first 3 C3G patients in this study indicate that pegcetacoplan is able to target the complement hyperactivity of C3G as well as reduce proteinuria in patients with C3G.

Clinical data is also available from 5 completed studies with pegcetacoplan in patients with PNH (Phase 1b: Studies APL-CP0514 and APL2-CP-PNH-204; Phase 2a: Study APL2-202; Phase 3: Studies APL2-302 and APL2-308). Results from these studies indicate that pegcetacoplan may be effective in providing broad control of intravascular and extravascular hemolysis, as evidenced by the following: increased and stable hemoglobin levels, improvement in Functional Assessment of Chronic Illness Therapy–Fatigue Scale score, normalization of lactate dehydrogenase, normalization of absolute reticulocyte count, normalization of total bilirubin levels, reduction in C3 fragment opsonization, and increased numbers of PNH red blood cells.

Pegcetacoplan at doses of 360 mg/day and 1080 mg twice weekly has been generally safe and well tolerated when administered via subcutaneous (SC) infusion, including to patients with C3G and other glomerular diseases. No expected serious adverse drug reactions have been identified, and no deaths have occurred that are considered related to treatment with pegcetacoplan.

Refer to the latest version of the pegcetacoplan investigator's brochure (IB) for the overall risk-benefit assessment and the most current information regarding the drug metabolism, PK, efficacy, and safety of pegcetacoplan.

4.4. Clinical Risks/Benefits of Pegcetacoplan

Pegcetacoplan has the potential to address the underlying disease pathophysiology of complement hyperactivity in C3G and IC-MPGN, and, therefore, to provide benefit in these diseases with a high unmet medical need.

The safety of subcutaneous pegcetacoplan administration has been studied in multiple Phase 2 and 3 studies for C3G and PNH, with an acceptable safety profile to date. Nonetheless, a number of safety monitoring practices are being employed by this protocol to ensure subject safety, including physical examination, vital signs monitoring, electrocardiograms (ECGs), hematology (including coagulation), serum chemistry, and urinalysis at specified intervals, as well as prompt reporting of adverse events (AEs).

Infusion site/pump safety will be assessed during clinical visits, and any significant finding from the assessment will be reported as an AE (see Section 10.10). The volume of blood planned for collection from each subject over the course of the study will be minimized in order to limit the impact on the overall health of these anemic subjects.

Systemic complement inhibition might predispose individuals to infections caused by encapsulated organisms, including *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*. Vaccinations against these organisms will be taken to minimize potential risk of infection. Use of prophylactic antibiotics is allowed, at the discretion of the investigator, and should take into consideration the level of immunosuppression, complement levels, and timing of vaccination relative to pegcetacoplan start, as well as local practices. Body temperature and vital signs will be monitored periodically, and relevant blood parameters monitored regularly throughout the study to assess for signs of infection. The subject will be counseled regarding this potential risk for infection and given a patient safety wallet card in the event of an emergency. The investigator should be contacted immediately in the event of a suspected infection for guidance on appropriate action to be taken.

Apellis is not currently aware of any evidence associating pegcetacoplan use with specific risks or complications of coronavirus disease 2019 (COVID-19). Apellis recognizes the need to consider the public health risks of the COVID-19 pandemic within the context of conducting a clinical trial. Because these risks may change as the pandemic evolves and may vary based on geographic location, Apellis will continue to evaluate the risks and benefits around study conduct on an ongoing and subject-by-subject basis.

4.4.1. COVID-19 Risk Mitigation Measures

Apellis is not currently aware of any evidence associating pegcetacoplan use with specific risks or complications of COVID-19. Apellis recognizes the need to consider the public health risks of the COVID-19 pandemic within the context of conducting a clinical trial. Because these risks may change as the pandemic evolves and may vary on the basis of geographic location, Apellis will continue to evaluate the risk/benefit around study conduct on an ongoing and subject-by-subject basis.

In the event that an investigative site is closed or subject is unable or unwilling to travel due to COVID-19 and if, in the opinion of the investigator, it is in the subject's best interest to continue in the study, the following mitigation measures may be implemented for the study and utilized if deemed necessary and authorized by the sponsor, including but not limited to:

- In locations where home nursing services may be utilized, a home nursing vendor may be set up to complete assessments at a subject's home.
- A minimized schedule of activities is presented in Table 8, Table 9, and Table 10 of Appendix 3.
- Any activities not performed because of COVID-19–related restrictions will be identified in the electronic data capture system.
- Any change in COVID-19 status (serology or antigen), if available, will be captured separately in the electronic data capture system.

- Where applicable, relevant study documentation will be updated and communicated to health authorities and/or institutional review boards (IRBs)/independent ethics committees (IECs) as required.

Apellis is currently not aware of any contraindications to vaccination (of any modality) and concurrent treatment with pegcetacoplan. In the absence of data, Apellis currently recommends that the decision to vaccinate study participants against COVID-19 should be made by the investigator and the subject, with consideration of local and national vaccination recommendations and a benefit-risk assessment. Vaccination against COVID-19 is not mandatory for continued study participation.

These measures are described in detail in Appendix 3.

5. STUDY OBJECTIVES AND ENDPOINTS

5.1. Study Objectives

5.1.1. Primary Objective

The primary objective of this study is to evaluate the efficacy of pegcetacoplan in improving the underlying pathophysiology of C3G/IC-MPGN after 12 weeks of treatment.

5.1.2. Secondary Objectives

The secondary objectives of the study are as follows:

- to evaluate the effect of pegcetacoplan on key clinical manifestations of the disease after 52 weeks of treatment
- to evaluate the safety of pegcetacoplan for up to 52 weeks in patients with recurrent C3G/IC-MPGN in a renal allograft

5.1.3. Exploratory Objectives

The exploratory objectives are to characterize the additional clinical, laboratory, and histologic findings of C3G/IC-MPGN in response to pegcetacoplan, including pegcetacoplan PK, pharmacodynamics (PD), and immunogenicity in patients with C3G/IC-MPGN.

5.2. Study Endpoints

5.2.1. Efficacy Endpoints

5.2.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with reduction in C3c staining on renal biopsy after 12 weeks of treatment with pegcetacoplan.

5.2.1.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- The proportion of subjects with reduction in C3c staining on renal biopsy after 52 weeks of treatment
- The proportion of subjects with stabilization or improvement in estimated glomerular filtration rate (eGFR) over time
- The proportion of subjects with stabilization or improvement of serum creatinine concentration over time
- Changes from baseline biopsy in C3c staining over time
- Changes and percentage changes from baseline in eGFR and serum creatinine concentration over time

5.2.1.3. Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are as follows:

- For subjects with baseline proteinuria above the upper limit of normal (ULN), the proportion of subjects achieving at least a 50% reduction in proteinuria over time
- For subjects with baseline proteinuria above the ULN, the proportion of subjects achieving complete clinical remission of proteinuria after 12 and 52 weeks of treatment, defined as normalization of proteinuria
- Changes and percentage changes in proteinuria over time
- Change over time in additional key biopsy features, including:
  - Glomerular myeloid cell infiltration
  - Glomerular macrophage infiltration (as measured by CD68 staining)
  - Glomerular crescents (in subjects with crescents)
  - Mesangial expansion and hypercellularity
  - Deposits by electron microscopy
  - Activity score (based on C3G histologic index)
  - Chronicity score (based on C3G histologic index)
- Ophthalmology endpoints:
  - Change in maximum drusen size at Week 52
  - Number of intermediate or large drusen at baseline and Week 52

5.2.2. Safety Endpoints

The safety endpoints are as follows:

- The number and incidence of treatment-emergent AEs
- The change from baseline in vital signs measurements and clinical laboratory test and ECG results

In addition, the following exploratory safety endpoints will be evaluated:

- The number and incidence of rejection episodes in each group
- The number and incidence of graft loss in each group

5.2.3. PK Endpoints

The PK endpoints are as follows:

- Pegcetacoplan serum concentrations over time

5.2.4. PD Endpoints

The PD endpoints are as follows:

- Change in complement biomarkers (50% classical hemolytic complement pathway activity [CH50] and 50% alternative hemolytic complement pathway activity [AH50]) over time

Additional complement components may be measured, as noted in Table 3 and Section 10.16, and evaluated as exploratory endpoints.

5.2.5. Immunogenicity Endpoints

The immunogenicity endpoints are as follows:

- The incidence of anti-pegcetacoplan antibodies and incidence of anti-PEG antibodies (including treatment-emergent and treatment-boosted responses) throughout the treatment and follow-up periods

6. INVESTIGATIONAL PLAN

6.1. Description of Overall Study Design and Plan

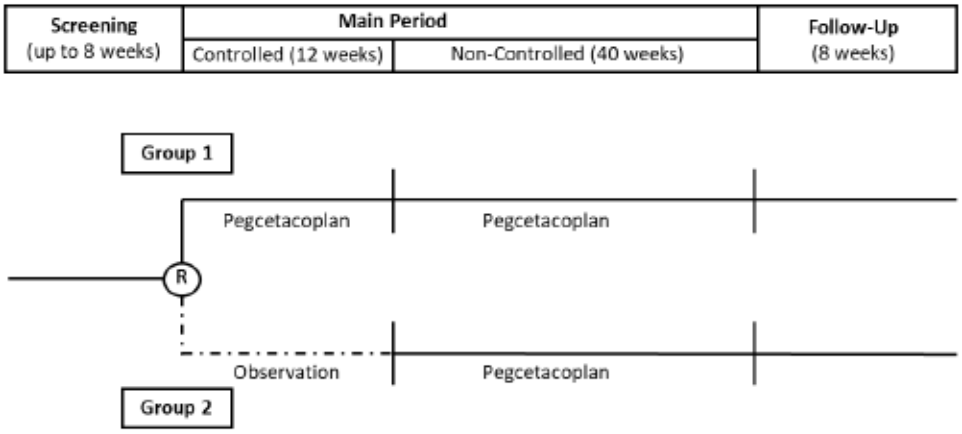
This Phase 2, multicenter, open-label, randomized, controlled clinical study is designed to evaluate the safety and efficacy of pegcetacoplan in patients who have post-transplant recurrence of C3G or IC-MPGN. There will be up to 12 subjects enrolled in this study. There are 3 main periods of this study for Part A, the core study.

- Screening period: an up to 8-week screening period, during which the screening renal allograft biopsy will occur
- Main period: a 52-week study period that contains 2 portions (controlled and noncontrolled) during which subjects will be randomized to either Group 1 or Group 2 at the Week 1 visit:
  - Controlled portion: Weeks 1-12 of the study
    - Group 1: Up to 9 subjects will be randomized to this treatment group and will receive pegcetacoplan treatment throughout the entire study; biopsies will occur at Week 12
    - Group 2: Up to 3 subjects will be randomized to this treatment group and will not receive pegcetacoplan treatment during the controlled portion; biopsies will occur at Week 12
  - Noncontrolled portion: Weeks 13-52 of the study
    - Group 1: Subjects will continue to receive pegcetacoplan treatment; biopsies will occur at Week 52
    - Group 2: Subjects will receive pegcetacoplan treatment following their Week 12 renal allograft biopsies; biopsies will occur at Week 52
- Follow-up period: an 8-week follow-up period

Any subject who, in the opinion of the investigator, is experiencing clinical benefit from pegcetacoplan administration may participate in Part B, a long-term extension, in order to continue to receive treatment with pegcetacoplan until it is commercially available for the disease under study. If invited to participate, the subject can enter Part B as soon as his/her 52-week treatment period has ended and does not need to participate in the 8-week follow-up period. See the appendices (Section 15) for details about Part B.

Figure 1 presents the study design.

Figure 1: Study Design



Abbreviation: R = randomization.

6.2. Study Design

This is an open-label, randomized, controlled, Phase 2 study consisting of a single cohort of up to 12 subjects with clinical and pathologic evidence of recurrent C3G or IC-MPGN in a renal allograft. Subjects will be randomized 3:1 to Group 1 (pegcetacoplan treatment throughout the main period) or Group 2 (no pegcetacoplan treatment for the first 12 weeks of the main period, followed by pegcetacoplan treatment), respectively. The visit schedule will be the same, regardless of randomization.

Pathologic evidence of disease recurrence requires a biopsy-based diagnosis of C3G or IC-MPGN in the renal allograft, confirmed by a study pathologist. The diagnosis need not be the same in the native kidney and the renal allograft; for example, a subject with C3G in the native kidney and IC-MPGN post transplant is still eligible for the study.

Subjects with either preexisting disease recurrence or upon initial identification of clinical and pathologic recurrence of disease will be invited to enter screening. Subjects must also have an eGFR of at least 15 mL/min/1.73 m^2 and no more than 50% fibrosis on renal biopsy.

The study will require a total of 3 renal allograft biopsies, during screening, Week 12, and Week 52. Flexibility has been built in for each biopsy as described below:

- Screening renal allograft biopsy: must occur within 4 weeks leading up to the day of randomization
  - A nonstudy biopsy may be used as the baseline biopsy provided it meets the following criteria:
    - it was performed no more than 12 weeks prior to Week 1
    - the subject has remained clinically stable since the biopsy with no changes in medication regimens that would be expected to significantly alter the baseline biopsy findings

  - the prior biopsy is available for central pathology review and includes all the required components of a study baseline biopsy (see Section 10.9 for more details)

- Week 12 renal allograft biopsy: must occur at a time point between Weeks 12 and 14, inclusive; Group 2 subjects cannot begin pegcetacoplan administration until after the biopsy occurs
- Week 52 renal allograft biopsy: must occur at a time point between Weeks 48 and 52, inclusive, but after completion of the 24-hour urine collection scheduled for Week 48.

In the event that a subject has a biopsy for clinical cause within the time frame allowed for a study biopsy, this clinical biopsy may be able to serve as one of the protocol biopsies, provided it includes all required components for this study. If it is not able to serve as a protocol biopsy, then information from that biopsy should still be collected within the study database, if possible.

After completion of the 52-week main period, any subject who, in the opinion of the investigator, is experiencing clinical benefit from pegcetacoplan administration will be invited to participate in Part B, the long-term extension, in order to continue to receive treatment with pegcetacoplan until it is commercially available for the disease under study (see Section 15). Those who do not continue on pegcetacoplan in the long-term extension protocol will enter a follow-up period of a minimum of 8 weeks.

6.2.1. Screening Period

The screening period will occur in 2 stages, such that all assessments described at Visit 1 must occur before those in Visit 2. This ensures that the more invasive procedures (vaccinations and biopsy of renal allograft) do not occur unless the subject is eligible by all other criteria. Vaccinations for *N. meningitidis*, *S. pneumoniae*, and *H. influenza* should be administered at least 2 weeks prior to randomization; however, in the event that an expeditious study start is warranted, the vaccination schedule may be adjusted. In general, administration of vaccinations immediately after the renal biopsy may be an efficient way to manage the assessments of Visit 2.

Subjects should be on stable doses of all medications relevant to their renal disease for at least 4 weeks prior to the screening renal allograft biopsy and from the time of the screening renal allograft biopsy until randomization. Changes to the baseline treatment regimen should be minimized to the greatest extent possible and made only when required for the well-being of the subject. See Section 8.8 (Concomitant Medications) for further guidance.

6.2.2. Main Period

All subjects who enter the main period will be randomized into either Group 1 or Group 2. The main period will be subdivided into the controlled (Weeks 1-12) and noncontrolled (Weeks 13-52) portions. Subjects in Group 1 will receive pegcetacoplan treatment during both the controlled and noncontrolled portions of the main period. Subjects in Group 2 will not receive pegcetacoplan treatment during the controlled portion, but following their Week 12 biopsy, they too will begin receiving pegcetacoplan treatment during the noncontrolled portion.

As with the screening period, changes to the baseline treatment regimen should be minimized to the greatest extent possible and made only when required for the well-being of the subject. See Section 8.8 (Concomitant Medications) for further guidance.

Pegcetacoplan treatment, the timing of which is indicated based on Group 1 or 2 randomization assignment, will consist of twice-weekly SC dosing of 1080 mg pegcetacoplan, self-administered at home, with the exception of scheduled clinic visits. For the first dose of pegcetacoplan only, the site staff will assist in administering pegcetacoplan. At subsequent clinic visits, subjects will self-administer pegcetacoplan in the presence of the site staff and undergo various safety and efficacy assessments by qualified site staff, as indicated in the Schedule of Activities (Table 1).

Use of prophylactic antibiotics is allowed, at the discretion of the investigator, and should take into consideration the level of immunosuppression, complement levels, and timing of vaccination relative to pegcetacoplan start, as well as local practices.

6.2.3. Part B: Long-Term Extension

At Visit 16 (Week 52), any subject who, in the opinion of the investigator, is experiencing clinical benefit from pegcetacoplan administration will be invited to participate in Part B, the long-term extension, in order to continue to receive treatment with pegcetacoplan until it is commercially available for the disease under study. Subjects who elect to enter the long-term extension should complete study procedures as outlined in the appendices (Section 15 and Table 7). If they enter Part B, they do not need to participate in the follow-up period.

6.2.4. Follow-up Period

After completion of the main period, if a subject does not enter Part B, the long-term extension, they will need to complete the 8-week follow-up period.

Additionally, for those subjects who discontinue the main period but are willing to remain in the study, they should continue in the study by beginning the follow-up period. Depending on the timing of pegcetacoplan discontinuation, some assessments planned for Visits 15 and 16 may also be necessary.

6.2.5. End of Study

A subject will have fulfilled the requirements for study completion if/when the subject has completed all study periods, including the 8-week follow-up period as indicated in the Schedule of Activities (Table 1).

The end of the study will be when the last subject has completed their last visit as indicated in the Schedule of Activities (Table 1) or the early termination and exit visits as indicated in the Part B Schedule of Activities (Table 7) or has withdrawn from the study as described in Section 7.2 or as requested by the sponsor.

7. STUDY POPULATION

This study aims to enroll patients with primary C3G or IC-MPGN who have had a post-transplant recurrence of their disease in their renal allograft. The inclusion and exclusion criteria below further identify the population to be studied. Additional information related to discontinuations and subjects lost to follow-up is presented in Section 7.2.

7.1. Selection of Study Population

7.1.1. Inclusion Criteria

Individuals must meet all of the following criteria at screening visits to be included in the study:

1. At least 18 years of age at screening
2. Must have clinical and pathologic evidence of recurrent C3G or IC-MPGN, as evidenced by all of the following:
   a. A diagnosis of C3G or IC-MPGN, with at least 2+ staining for C3c in the renal allograft, confirmed by a central pathologist, based on the screening renal allograft biopsy
   b. C3G or IC-MPGN must be primary and not secondary to another condition (eg, infection, malignancy, monoclonal gammopathy, autoimmunity, chronic antibody-mediated rejection, chronic thrombotic microangiopathy, or a medication)
3. Stable (not improving) or worsening disease, in the opinion of the investigator, in the 2 months preceding the first dose of pegcetacoplan
4. eGFR ≥15 mL/min/1.73 m^2, calculated by the Chronic Kidney Disease–Epidemiology Collaboration (CKD-EPI) creatinine equation for adults
5. No more than 50% glomerulosclerosis or interstitial fibrosis on the screening renal biopsy
6. Stable regimen for recurrent C3G/IC-MPGN for at least 4 weeks prior to the screening renal allograft biopsy and from the time of the screening renal allograft biopsy until randomization
7. Have received required vaccinations against *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* (type B) or agree to receive vaccinations if applicable vaccination records are not available. Vaccination is mandatory unless documented evidence exists that subjects are nonresponders to vaccination.
8. Women of childbearing potential (WOCBP), defined as any women who have experienced menarche and who are not permanently sterile or postmenopausal, must have a negative blood pregnancy test at screening (and negative urine pregnancy at Visit 4) and must agree to use protocol-defined methods of contraception from screening through 12 weeks after receiving last dose of pegcetacoplan
9. Men must agree to use protocol-defined methods of contraception and agree to refrain from donating semen from screening through 12 weeks after receiving last dose of pegcetacoplan
10. Willing and able to provide written informed consent
11. Able to understand and willing to comply with all scheduled procedures and other requirements of the study in the opinion of the investigator

12. Willing and able to self-administer pegcetacoplan or have an identified caregiver who can perform the administration

7.1.2. Exclusion Criteria

Individuals meeting any of the following criteria at screening or baseline are ineligible to participate in this study:

1. Absolute neutrophil count <1000 cells/mm^3 during screening (not including Day 1)
2. Previous treatment with pegcetacoplan
3. Evidence of rejection on the screening renal allograft biopsy that requires treatment
4. Diagnosis or history of HIV, hepatitis B, or hepatitis C infection or positive serology at screening indicative of infection with any of these viruses
5. Weight more than 100 kg at screening
6. Hypersensitivity to pegcetacoplan or to any of the excipients
7. History of meningococcal disease
8. Malignancy, except for the following:
    a. Cured basal or squamous cell skin cancer
    b. Curatively treated in situ disease
    c. Malignancy free and off treatment for ≥5 years
9. Significant renal disease in the renal allograft secondary to another condition (eg, infection, malignancy, monoclonal gammopathy, rejection, or a medication) that would, in the opinion of the investigator, confound interpretation of the study results
10. Participation in any other investigational drug trial or exposure to other investigational agent, device, or procedure within 30 days or 5 half-lives from the last dose of the investigational agent (whichever is longer) prior to screening period
11. Women who are pregnant or who are currently breastfeeding
12. Inability to cooperate or any condition that, in the opinion of the investigator, could increase the subject's risk by participating in the study or confound the outcome of the study
13. Evidence of drug or alcohol abuse or dependence, in the opinion of the investigator
14. Known or suspected hereditary fructose intolerance.

7.1.3. Approved Methods of Contraception

A woman is considered to be of childbearing potential following menarche and until becoming postmenopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Approved methods of contraception include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:

  - oral, intravaginal, or transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral, injectable, or implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner (*provided that the partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success*)
- Sexual abstinence (*defined as refraining from heterosexual intercourse during the entire period of risk associated with study treatments*)
- Male condom with or without spermicide (**for male study subjects with female partners of childbearing potential only**)

Note: Sexual abstinence is only accepted when it is the preferred and usual lifestyle of the subject.

Subjects must agree to use an approved method of contraception during the study and for 12 weeks after their last dose of study drug.

7.2. Discontinuations and Subjects Lost to Follow-up

7.2.1. Early Treatment Discontinuation and Study Withdrawal

A subject may withdraw from the study at any time, for any reason, without prejudice to his/her future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (eg, in the interest of the subject's safety). If a subject discontinues or is withdrawn from study treatment for any reason, the study site must immediately notify the medical monitor.

Once a subject is withdrawn from the study, the subject may not reenter the study.

Subjects who discontinue study treatment prior to the end of the main period should undergo all follow-up visits and procedures through the exit visit unless they are unwilling or unable or consent has been withdrawn. Subjects who wish to fully withdraw from the study before completion should be encouraged to complete the early termination visit as described in Section 9.5.

7.2.2. Reasons for Discontinuation

The date of and reason for treatment discontinuation must be determined by the investigator and recorded in the subject's medical record. If it is determined that there was more than one reason for the discontinuation, each reason should be documented in the source document, and the most clinically relevant reason, as determined by the investigator, should be identified. Treatment may be discontinued and/or a subject's participation in the study may be discontinued for any of the following reasons:

- Any serious adverse event (SAE), clinically significant AE, severe laboratory abnormality, intercurrent illness, other medical condition (including infections), or circumstance that indicates to the investigator that continued participation is not in the best interest of the subject
- Subject withdrawal of consent: At any time, a subject's participation in the study may be terminated at his/her request or on the basis of the investigator's clinical judgment. The reason for subject withdrawal will be noted in the subject's source document.
- Subject fails to adhere to the protocol requirements (eg, drug noncompliance, failure to return for defined number of visits)
- Subject is lost to follow-up: the subject stopped coming for visits, and study personnel were unable to contact the subject
- Termination of the study by the sponsor or regulatory authorities
- Liver toxicity (refer to Section 7.2.3 for further details)
- Pregnancy, as indicated in Section 11.3
- Failure to meet randomization criteria

Any subject who discontinues treatment early or is withdrawn from the study early due to a treatment-emergent adverse event (TEAE), whether serious or nonserious, will be followed until the TEAE resolves (returns to normal or baseline values) or stabilizes or until it is judged by the investigator to no longer be clinically significant.

If consent is withdrawn, no further study evaluations are to be performed and no attempts are to be made to collect additional data.

Additionally, the sponsor may stop the study at any time for safety, regulatory, legal, or other reasons aligned with good clinical practice (GCP). This study may be terminated at the discretion of the sponsor or any regulatory agency. An investigator may elect to discontinue or stop the study at his/her study site for any reason, including safety or low enrollment.

7.2.3. Liver Toxicity

Drug treatment continuation will be evaluated in case of any signs of possible drug-induced hepatic injury as follows:

Drug treatment will be discontinued immediately if either:

- alanine aminotransferase (ALT) or aspartate aminotransferase (AST) is >3× the ULN and (total bilirubin is >2× the ULN or international normalized ratio is >1.5)

or

- ALT or AST is >8× the ULN

Drug treatment will be withheld if either:

- ALT or AST is >5× the ULN

or

- ALT or AST is >3× the ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Drug treatment will be permanently discontinued and the subject withdrawn from the study if the condition persists for more than 2 weeks.

If the subject is not withdrawn from the study, drug treatment may be resumed when both ALT and AST are less than 1.5× ULN.

Any possible hepatic abnormalities will be monitored with repeat testing at a frequency of at least every 72 hours. Frequency of retesting will decrease to weekly or less once abnormalities stabilize. Repeat testing will discontinue once abnormalities are no longer detected.

Causes for the significant liver test abnormalities will be investigated (eg, acute viral hepatitis, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, toxoplasmosis, varicella, and parvovirus), and subjects will be followed up until all abnormalities return to normal or to the baseline state.

Workup will also include consideration of alcoholic and autoimmune hepatitis, hepatobiliary disorders (eg, gallstones), nonalcoholic steatohepatitis, cardiovascular causes (eg, right-sided heart failure), and concomitant medications or supplements.

7.2.4. Subjects Lost to Follow-up Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any subjects lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgment of receipt request) asking that the subject return to the site for final safety evaluations and to return any investigational product.

7.2.5. Replacement of Subjects

Subjects who discontinue treatment early or withdraw from the study early for reasons not related to the safety of pegcetacoplan may be replaced at the sponsor's discretion to ensure that the objectives of the study are met. Subjects assigned to treatment who discontinue or withdraw from the study may be replaced until 12 subjects complete Week 52 of the study.

8. TREATMENTS

8.1. Details of Study Treatments

The test product is pegcetacoplan, which will be provided as a sterile solution of pegcetacoplan 1080 mg/20 mL in acetate-buffered sorbitol, supplied in stoppered glass vials. Additional information is provided in the pegcetacoplan IB.

8.2. Dosage Selection

The dose of pegcetacoplan is 1080 mg twice per week via SC infusion (20 mL) during the main period of Part A (with dosing not beginning for Group 2 until Week 13) and during Part B. As noted in Section 4.2.1, this study uses the same 1080 mg twice weekly dosing schedule currently used in the Phase 3 studies in patients with PNH. This dose was also evaluated in Study APL2-201, a Phase 2 study that enrolled patients with C3G.

Group 1 subjects will receive their initial doses of pegcetacoplan at the scheduled clinic visit on Day 1 and will continue to receive their pegcetacoplan (1080 mg/20 mL twice a week) on Day 1 and Day 4 of each treatment week until Week 52 if they do not enter Part B; however, if they do enter Part B, the treatment schedule will continue as during Part A.

Group 2 subjects will receive their initial doses of pegcetacoplan after the Week 12 renal biopsy (see Schedule of Activities [Table 1]) and will continue to receive pegcetacoplan (1080 mg/20 mL twice a week) on Day 1 and Day 4 of each treatment week until Week 52 if they do not enter Part B; however, if they do enter Part B, the treatment schedule will continue as during Part A.

Dosing diaries will be utilized for pegcetacoplan and are to be completed for each dose administered at the clinic or outside regular clinic visits. Subjects should ideally maintain a consistent dosing schedule and should not delay or defer dosing. Missed doses will be handled on a case-by-case basis between the investigator and medical monitor, with the general approach being to administer a missed dose as soon as noticed, unless the next dose has already been administered.

8.3. Investigational Product Administration

Investigational product, pegcetacoplan, will be administered as a 20-mL SC infusion.

The preferred site of infusion will be the abdomen. If administration into the abdomen is not feasible, alternative appropriate sites are acceptable (see pharmacy manual for more details). Research nurses or other appropriately qualified research personnel will administer the SC infusions (as needed) and will qualify and supervise the self-administration (or caregiver administration). These qualified personnel will be made available for a minimum of 6 days on treatment (2 doses) to ensure the subject has been qualified to conduct self-administration; duration could be shortened if qualification happens sooner. During qualification, the subject (or caregiver) must demonstrate to the research personnel their ability to safely and effectively administer study drug using the infusion pump. Following self-administration qualification, subjects may self-administer the SC infusions without supervision. Once qualified, the subject will continue to self-administer infusions at the clinic on those days when a clinic visit occurs and at an off-site location convenient to the subject on all other days. Self-administration conducted at the clinic will be supervised to ensure that the subject continues to remain compliant with the administration guidelines.

NOTE: If the subject requires further training, the self-administration qualification period may be extended beyond 6 days on treatment (2 doses). Self-administration may also be conducted by a member of the subject's household or family member, etc, who will undergo the same qualification criteria by the in-home medical professional (qualification is not intended to be restricted to the subject). Please refer to the pharmacy manual for further details regarding self-administration qualification.

8.4. Labeling, Packaging, Infusion Supplies, and Storage and Handling

8.4.1. Labeling

Labels containing study information and pack identification are applied to the investigational product(s) container.

All investigational product is labeled with a minimum of the following: protocol number, dosage form (including product name and quantity in pack), route of administration, directions for use, storage conditions, batch number and/or packaging reference, the statements required per local regulations (eg, "For clinical trial use only"), and name and address of the sponsor.

Space is allocated on the label so that the site representative can record a unique subject identifier and date dispensed by the site to the subject.

Additional labels may, on a case-by-case basis, be applied to the investigational product in order to satisfy national, local, or institutional requirements but must not do any of the following: contradict the clinical study label, obscure the clinical study label, identify the study subject by name.

Additional labels may not be added without the sponsor's prior full agreement.

8.4.2. Packaging

Investigational product is supplied in 20-mL glass vials. Please refer to the pharmacy manual for details.

Changes to sponsor-supplied packaging prior to dosing may not occur without full agreement, in advance, by the sponsor.

8.4.3. Infusion Supplies

The sponsor will supply syringes, vial adapters, infusion sets, and ambulatory syringe infusion pumps, as required. Refer to the pharmacy manual for further details.

8.4.4. Storage and Handling

The investigational product should be stored refrigerated at 2-8 °C, both at home and in the clinic. Temperature monitoring is required at the investigator site (or documented storage location) to ensure that the investigational product is maintained within an established temperature range.

The investigator or appropriately qualified site staff will be responsible for the following:

- ensuring that the investigational product is stored in a secure, limited-access location at the site

  - limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented
- ensuring that the temperature is monitored throughout the duration of the study and that records are maintained

A pharmacist or appropriately qualified designated person will be responsible for the following:

- storing the investigational product appropriately
- dispensing the vials of investigational product to the subject
- entering the unique subject identifier on the investigational product bottle/carton labels as they are distributed

When the subject receives the investigational product from the site, it should be transported in a sponsor-approved bag or box containing previously temperature-conditioned cold plates to ensure that the storage temperature (2-8 °C) is maintained. Temperature monitoring will not be required during transport or at the subject's residence, but a log will be kept for every infusion to ensure that all investigational product was kept refrigerated.

With sponsor prior approval, investigational product and/or ancillary supplies may be shipped from the study site to a subject's designated location. Such shipments will only be implemented at sites where this activity is approved by the IRB/EC and health authority (if required). Subject consent will be required prior to any subject information being provided to a courier. The responsibility to return both empty vials and any unused investigational product shall remain unchanged.

8.5. Measures to Minimize Bias: Study Treatment Assignment

Randomization will occur through the interactive response technology system.

8.5.1. Method of Study Treatment Assignment

All subjects who meet all the inclusion criteria and none of the exclusion criteria will be enrolled in the study, until such time that up to 12 subjects have been enrolled in the study. Subjects will then be randomized through the interactive response technology system to either Group 1 (pegcetacoplan) or Group 2 (control). Following completion of the main period, all subjects will enter the follow-up period unless they enter the sponsor-planned long-term extension protocol.

8.6. Investigational Product Accountability

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained. The investigator is responsible for ensuring the retrieval of all returnable study supplies from subjects.

At the conclusion of the study, any unused investigational product will either be destroyed at the investigator site or be returned to the sponsor or designee for destruction, and destruction will be documented appropriately. If no supplies remain, this fact will be documented appropriately.

8.7. Subject Compliance

Subjects must be instructed to bring their empty/unused investigational product packaging to every visit. The pharmacist/nominated person will record details on the drug accountability form.

8.8. Prior and Concomitant Medications and Procedures

All medications administered and procedures performed within 12 weeks of screening will be collected as prior medications and procedures. Medications administered and procedures performed from the time of informed consent through the end-of-study visit are regarded as concomitant and will be documented. Use of rituximab, belimumab, eculizumab, and ravulizumab during the study (and/or within 24 weeks prior to the first dose of pegcetacoplan) must be discussed with the sponsor for consideration and approval.

Subjects should be on stable doses of all medications relevant to their renal disease for at least 4 weeks prior to the screening renal allograft biopsy until the end of the study. During the study, including the screening period, changes to the baseline treatment regimens (including medications, dietary restrictions, and lifestyle modifications) should be minimized to the extent possible and made only when required for the well-being of the subject. However, in the setting of an acute crescentic glomerulonephritis at the time of study entry, steroid treatment may be initiated along with, or around the same time as, pegcetacoplan treatment, if deemed necessary by the investigator.

If the subject is in a post-transplant time frame in which immunosuppression or other transplant-related medication adjustments are anticipated, these adjustments should still occur, adhering to the center's standard protocol for post-transplant care. For all subjects, the plan for post-transplant immunosuppression for the duration of the study should be documented prior to randomization. Any deviation during the study from the prespecified plan should be documented with a justification for the change. Subjects with evidence of rejection on the screening biopsy that requires treatment will need to undergo their antirejection treatment, and then can be reconsidered for pegcetacoplan dosing, but will need to meet all other study eligibility criteria, including a screening biopsy that is within the designated assessment window, to serve as the baseline (refer to Section 9.1.3 for further details). Subjects with evidence of subclinical rejection on the screening biopsy may proceed with pegcetacoplan treatment, at the discretion of the investigator, provided no treatment is initiated for the rejection.

8.8.1. Empiric Antibiotic Treatment for Possible Infection

Body temperature, vital signs, and relevant blood parameters will be monitored regularly throughout the study to assess for signs of infection. The investigator should be contacted immediately in the event of a suspected infection for guidance on appropriate action to be taken. Action to be taken may include empiric administration of a broad-spectrum antibiotic to cover possible serious infections, such as meningococcus.

9. STUDY PROCEDURES

Table 1 outlines the timing of procedures and assessments to be performed throughout Part A of the study, once written informed consent has been obtained from the subject. Section 10.13 specifies laboratory assessment samples to be obtained. The schedule of visit dates should be established, either prior to or at the time of screening to allow subjects an opportunity to assess whether there are likely to be significant conflicts with other activities or planned absences. To the extent possible, subjects will be expected to adhere to the visit schedule, and any rescheduling of visits must be agreed, in advance, with the investigator and sponsor.

The investigator may, at his/her discretion, arrange for a subject to have an unscheduled assessment, especially in the case of AEs that require follow-up or are considered by the investigator to be possibly related to the use of study drug. The unscheduled visit page in the eCRF must be completed.

Study discontinuation procedures are described in Section 7.2.1.

Details regarding participation in Part B, the long-term extension, are provided in the appendices (Section 15).

Table 1: Schedule of Activities for Part A

Study Period	Screening period (up to 8 weeks) All subjects[A]		Main period														Follow-up period (8 weeks) All subjects not entering Part B		
			Controlled portion					Noncontrolled portion											
Study Week	**–8 to –4**	**–2**	**1**	**2**	**4**	**8**	**12**	**14[B]**	**16**	**20**	**24**	**30**	**36**	**42**	**48**	**52**	**54**	**56**	**60 Exit**
Study Day	**–56 to –28**	**–14**	**1**	**14**	**28**	**56**	**84**	**98**	**112**	**140**	**168**	**210**	**252**	**294**	**336**	**364**	**378**	**392**	**420**
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Visit window (± days)	**N/A[C]**		**0**	**3**	**3**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**3**	**3**	**7**
Informed consent	X																		
Demographics	X																		
Medical history	X																		
Inclusion/exclusion[D]	X	X	X																
Vaccination[E]		X				X													
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[F]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Renal biopsy[G]	X						X								X				
Randomization			X																
Pegcetacoplan administration[B]			Group 1 only					All subjects											
Infusion site/pump safety assessment[H]			Group 1 only					All subjects											

Table 1: Schedule of Activities for Part A

Study Period	Screening period (up to 8 weeks) All subjects[A]		Main period														Follow-up period (8 weeks) All subjects not entering Part B		
			Controlled portion					Noncontrolled portion											
Study Week	**–8 to –4**	**–2**	**1**	**2**	**4**	**8**	**12**	**14[B]**	**16**	**20**	**24**	**30**	**36**	**42**	**48**	**52**	**54**	**56**	**60 Exit**
Study Day	**–56 to –28**	**–14**	**1**	**14**	**28**	**56**	**84**	**98**	**112**	**140**	**168**	**210**	**252**	**294**	**336**	**364**	**378**	**392**	**420**
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Visit window (± days)	**N/A[C]**		**0**	**3**	**3**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**3**	**3**	**7**
Vital sign measurements[I]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine samples (below)																			
24-hour urine collection[J]	X						X				X				X				X
Triplicate first-morning spot urine[K]		X	X[L]	See Table 2															
In-clinic (random) spot urine	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis (microscopic & dipstick)[M]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1: Schedule of Activities for Part A

Study Period	Screening period (up to 8 weeks) All subjects[A]		Main period														Follow-up period (8 weeks) All subjects not entering Part B		
			Controlled portion					Noncontrolled portion											
Study Week	**–8 to –4**	**–2**	**1**	**2**	**4**	**8**	**12**	**14[B]**	**16**	**20**	**24**	**30**	**36**	**42**	**48**	**52**	**54**	**56**	**60 Exit**
Study Day	**–56 to –28**	**–14**	**1**	**14**	**28**	**56**	**84**	**98**	**112**	**140**	**168**	**210**	**252**	**294**	**336**	**364**	**378**	**392**	**420**
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Visit window (± days)	**N/A[C]**		**0**	**3**	**3**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**3**	**3**	**7**
Blood samples (below)																			
Hematology[M] & chemistry[M]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK sample			X[N]	X[N]	X[N]	X[N]	X[N]	X	X	X	X	X	X	X	X	X	X	X	X
ADA assays[O]			X[N]	X[N]	X[N]	X[N]			X		X		X			X	X		X
Complement profile[M]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C3 nephritic factor	X		X																
eGFR[P,Q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy (β-HCG)	X															X			

Table 1: Schedule of Activities for Part A

Study Period	Screening period (up to 8 weeks) All subjects[A]		Main period														Follow-up period (8 weeks) All subjects not entering Part B		
			Controlled portion					Noncontrolled portion											
Study Week	**–8 to –4**	**–2**	**1**	**2**	**4**	**8**	**12**	**14[B]**	**16**	**20**	**24**	**30**	**36**	**42**	**48**	**52**	**54**	**56**	**60 Exit**
Study Day	**–56 to –28**	**–14**	**1**	**14**	**28**	**56**	**84**	**98**	**112**	**140**	**168**	**210**	**252**	**294**	**336**	**364**	**378**	**392**	**420**
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Visit window (± days)	**N/A[C]**		**0**	**3**	**3**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**3**	**3**	**7**
Urine pregnancy test		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FSH, HIV, HCV, HBsAg, HBcAb[R]	X																		
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Post-transplant immunosuppression plan documentation		X																	
Ophthalmologic evaluation (optional)[S]		X[S]												X[S]					

Abbreviations: ADA = antidrug antibodies; AE = adverse events; β-HCG = β–human chorionic gonadotropin; CDC = Centers for Disease Control and Prevention; CKD-EPI = Chronic Kidney Disease–Epidemiology Collaboration; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; FSH = follicle-stimulating hormone; GFR = glomerular filtration rate; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV = hepatitis C; N/A = not applicable; PK = pharmacokinetic(s); RBC = red blood cell; SC = subcutaneous; SD-OCT = spectral domain optical coherence tomography.

NOTE: When multiple assessments/procedures occur at the same time, order should be: vital signs, ECGs, blood collection/sampling, pegcetacoplan dosing.

A. Subjects who meet the medical history requirements will enter the screening period at Visit 1 and return for Visit 2, but all Visit 2 assessments need not occur in a single visit and Visit 2 can be split into multiple visits (eg, 2a, 2b).

B. Subjects will self-administer SC pegcetacoplan after receiving appropriate training and sign-off by a research nurse or other personnel in their first treatment week. During site visits subjects will self-administer pegcetacoplan at the site, with the exception of the very first dose. Group 2 subjects will be trained on self-administration of pegcetacoplan and receive their supply of pegcetacoplan at the next scheduled clinic visit (Visit 7 or 8) following their biopsies.
C. Visit 2 must occur at least 7 days after Visit 1 and at least 14 days prior to the Day 1 dosing date; the vaccinations and biopsy can occur any time after confirmation of eligibility based on Visit 1 data.
D. Specific inclusion/exclusion criteria will be measured during screening, and some of them require confirmation prior to any activities of Day 1. See the inclusion/exclusion criteria in Section 7 for further detail.
E. Vaccinations against *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* are mandatory, unless documented evidence exists that subjects have received all recommended vaccines or are nonresponders to vaccination. Any required vaccines should be administered during screening (Day –14), and any required boosters should be administered at Visit 6 (Day 56), unless an alternative vaccination schedule has been agreed with the medical monitor, as described in Section 9.1.4. Subjects who withdraw from the study prior to a scheduled vaccine booster, as recommended by the current Advisory Committee on Immunization Practices adult immunization schedule, will be offered the opportunity to return to the site to receive the booster. Vaccination serum samples (for antibody titer) will be collected prior to subject receiving vaccinations on that study visit.
F. Full physical examination will only be performed at Study Weeks –4, 1, and 52. Brief physical examinations will be conducted at all other clinic visits, as noted. A symptom-driven physical examination may be performed at other times, at the investigator's discretion. Body height (cm) will be measured during screening only and weight (kg) will be measured throughout study, during brief and full physical examinations. Edema should be assessed at every visit.
G. Week 12 biopsy must occur at a time point between Weeks 12 and 14, inclusive; Group 2 subjects cannot begin pegcetacoplan administration until after the biopsy occurs. Week 52 biopsy must occur at a time point between Weeks 48 and 52, inclusive, but after completion of the 24-hour urine collection scheduled for Week 48.
H. Between site visits, subjects will be instructed to report any infusion site reaction to the study staff. Pump use safety assessment will be performed by licensed health care professional (ie, investigator or nurse) within 30 minutes following study drug administration at all clinic visits and during at-home qualification. See Manual of Procedures for more details.
I. When pegcetacoplan is administered at the study site, vital signs will be measured within 2 hours prior to infusion, before venipuncture and ECG. Following the first infusion, vital signs will be measured again at 30 minutes (±5 minutes) after dosing. For subjects in Group 2, vital signs will be measured once at each visit during the controlled period. For all evaluations, blood pressure and heart rate should be evaluated after the subject has been resting in a seated, recumbent, or supine position for at least 5 minutes.
J. The 24-hour urine collection requires collection of 24 hours of urine in a pooling container following the first urinary output on that day (first urinary output is discarded). The screening 24-hour urine collection should be done following Visit 1. Courier arrangements will be made by site personnel to pick up urine containers from subject's home. This collection should be done prior to the renal biopsy.
K. Urine protein-to-creatinine ratio samples (first urinary output for the day) should be collected on 3 consecutive days, every 2 weeks, throughout the study. On weeks of scheduled clinic visits, samples will be brought with subject during the site visit. On weeks when no clinic visit is scheduled, courier service will be arranged for urine sample pickup and delivery to the site.
L. The Day 1 triplicate first-morning urine samples should be collected before the first dose of pegcetacoplan (eg, Day –2, Day –1, and Day 1) and are required for randomization.
M. See laboratory assessments (Table 3) for more details.
N. During the controlled period, PK and ADA samples will be collected from subjects in Group 1 only.
O. Subjects who discontinue dosing will need to have ADA samples collected at 6 and 12 weeks after the last treatment. Subjects who test positive for anti-pegcetacoplan peptide or anti-PEG antibodies at any time will be followed up with ADA samples being collected every 6 months until the antibody levels revert to baseline.

P. Measured GFR is an optional assessment which, if done, should performed at 2 time points: once on Day 1, or within 4 weeks before Day 1, and again at 1 time point between Week 48 and Week 52, inclusive. Measured GFR should only be done at sites where it is routinely performed, as per the site's standard protocol.
Q. CKD-EPI creatinine equation; the CKD-EPI creatinine-cystatin C equation (if confirmation required).
R. Serum FSH to be performed on women only (see laboratory manual for more details).
S. Ophthalmologic evaluations are optional and will be performed at selected sites. If these evaluations are performed, subjects should have a baseline evaluation, including a basic ophthalmologic examination, SD-OCT, and color fundus photography, at an approved ophthalmologic clinical site at any time during the screening period. For those subjects with drusen prior to pegcetacoplan administration, a follow-up ophthalmologic evaluation, including a basic ophthalmologic examination, SD-OCT, and color fundus photography, should occur at a convenient time point between Week 42 and Week 52 of the study.

Table 2: First-Morning Urine Collection Schedule

Screening and main period, Weeks –2 to 24														
Study Week	**–2**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**
Study Day	–14	1	14	28	42	56	70	84	98	112	126	140	154	168
Study Visit	2	3	4	5		6		7	8	9		10		11
Triplicate first-morning spot urine	X	X	X	X	X	X	X	X	X	X	X	X	X	X
uPCR containers to be dispensed	3	3	3	6		6		3	3	6		6		9
Main period, Weeks 26 to 52														
Study Week	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**
Study Day	182	196	210	224	238	252	266	280	294	308	322	336	350	364
Study Visit			12			13			14			15		16
Triplicate first-morning spot urine	X	X	X	X	X	X	X	X	X	X	X	X	X	X
uPCR containers to be dispensed			9			9			9			6		3
Follow-up period (Weeks 54 to 60)														
Study Week	**54**				**56**				**58**			**60**		
Study Day	378				392				406			420		
Study Visit	17				18							19		
Triplicate first-morning spot urine	X				X				X			X		
uPCR containers to be dispensed	3				6							n/a		

Abbreviations: n/a = not applicable; uPCR = urine protein-to-creatinine ratio.

Note: Shaded columns indicate samples to be collected at home and brought to the clinic during visit weeks; unshaded columns indicate samples to be collected at home and picked up by courier during nonvisit weeks.

9.1. Screening

Subjects with either preexisting disease recurrence or upon initial identification of clinical and pathologic recurrence of disease will be invited to enter screening. Subjects will be screened to confirm that the subject selection criteria for the study have been met. Informed consent will be obtained at screening prior to the conduct of any study-related procedures.

A screen failure is defined as a subject who has provided written informed consent, failed to meet at least one of the inclusion criteria and/or met at least one of the exclusion criteria, and not been randomized or administered investigational product(s).

A subject should not have a Visit 2 unless they meet the study criteria.

For all subjects, the plan for post-transplant immunosuppression for the duration of the study should be documented prior to randomization. Any deviation during the study from the prespecified plan should be documented with a justification for the change.

9.1.1. Rescreening

Individuals who consent to participate in the study but who do not initially meet all the requirements as outlined in the inclusion and exclusion criteria are not able to be enrolled; however, these individuals may be held in the screening period at the discretion of the investigator until such time that they are able to be enrolled. In this case, additional screening visits and/or repeat screening assessments may be conducted, as needed, to establish eligibility.

In the event that rescreening occurs, and the subject has not remained in the screening period, the individual is required to reconsent and must be assigned a new identification number.

9.1.2. Screening Procedures

9.1.2.1. Visit 1

The following assessments will be performed and information collected during Visit 1:

- Informed consent reviewed and signed, both for the study and for the biopsies
- Demographics
- Medical history
- Review of inclusion/exclusion criteria
- Review of concomitant medications
- Physical examination, full
- 12-lead ECG
- Dispense 24-hour urine collection container
- Dispense 3 urine protein-to-creatinine ratio (uPCR) containers for consecutive collection
- Arrange home uPCR courier pickup
- Urinalysis assessment

- Blood samples for laboratory assessments
- eGFR
- AE collection

9.1.2.2. Visit 2

The following assessments will be performed and information collected during Visit 2:

- Review of inclusion/exclusion criteria
- Vaccination
- Review of concomitant medications
- Physical examination, brief
- Collect 3 uPCR containers from previous visit
- Dispense 3 uPCR containers for consecutive collection
- Arrange home uPCR courier pickup
- Urinalysis assessment
- Blood samples for laboratory assessments
- eGFR
- Urine pregnancy test, if applicable
- AE collection
- Post-transplant immunosuppression plan for the duration of the study should be documented (prior to randomization)
- Renal biopsy (see Section 9.1.3 below for further details)

9.1.3. Renal Biopsy

The screening renal allograft biopsy should be conducted during the screening period and must occur within 4 weeks leading up to the day of randomization. However, a nonstudy biopsy may be used as the screening biopsy provided it meets all the following criteria:

- it was performed no more than 12 weeks prior to Week 1
- the subject has remained clinically stable since the biopsy with no changes in medication regimens that would be expected to significantly alter the screening renal allograft biopsy findings
- the prior biopsy is available for central pathology review and includes all the required components of a study screening renal allograft biopsy

9.1.4. Vaccinations

Subjects will be required to be vaccinated as follows on the basis of Advisory Committee on Immunization Practices (ACIP) recommendations for adults with complement deficiencies

and/or immunocompromising conditions (available at https://www.cdc.gov/vaccines/schedules/hcp/imz/adult-conditions.html).

- *N. meningitidis* types A, C, W, and Y: First dose at least 2 weeks prior to start of pegcetacoplan with second dose 2 months later, and then boosters every 5 years.
- *N. meningitidis* type B: First dose at least 2 weeks prior to start of pegcetacoplan with a second dose after at least 1 month. First booster dose 1 year later, and then additional booster doses every 2 to 3 years.
- *S. pneumoniae*: PCV13 and/or PPSV23 as per ACIP guidelines for adults with immunocompromising conditions.
- *H. influenzae* type B: Documentation of childhood vaccination or 1 dose at least 2 weeks prior to start of pegcetacoplan dosing.

Vaccination is mandatory unless documented evidence exists that subjects have received all recommended vaccines or are nonresponders to vaccination. For subjects who do not have this documented evidence, the required missing vaccination(s) will be administered as needed to bring the subjects up to date. The investigator should discuss with the medical monitor any individual subject circumstances relevant to the vaccination requirements or that would make the above schedule not possible or reasonable. On an ongoing basis, including upon entry into Part B, the long-term extension, subjects should be reevaluated for the need for any vaccinations based on ACIP recommendations.

Vaccination at least 2 weeks prior to the first dose of pegcetacoplan is preferred; however, the vaccination schedule may be adjusted with written approval from the medical monitor and vaccinations may occur up to 2 weeks after initiation of treatment with pegcetacoplan. Subjects vaccinated after initiation of treatment with pegcetacoplan must receive prophylactic antibiotics as described in Section 9.1.5.

Vaccination serum samples will be collected on the day of vaccination prior to receiving vaccinations on that study visit. These samples will be analyzed for antibody titer in the event that the subject has a positive infection for *S. pneumoniae*, *N. meningitidis*, or *H. influenzae*.

Subjects who withdraw from the study prior to a scheduled vaccine booster, as recommended by the current ACIP adult immunization schedule, will be offered the opportunity to return to the site to receive the booster.

9.1.5. Prophylactic Antibiotics

Subjects who receive their initial vaccinations after initiation of treatment with pegcetacoplan will be required to receive antibiotic prophylaxis until at least 14 days after vaccination. The choice of prophylactic antibiotic is at the discretion of the treating investigator and with approval from the medical monitor. Following this or for any subject who does not require vaccination, prophylactic antibiotic therapy is allowed at the discretion of the treating investigator. The use of prophylactic antibiotics should be in accordance with local treatment guidelines for subjects who are receiving treatment with a complement inhibitor and should take into consideration the level of immunosuppression and complement levels, as well as local practices.

9.2. Main Period

This 52-week main period is divided into a controlled portion (Weeks 1-12) and a noncontrolled portion (Weeks 13-52) and will be completed by all subjects. Those subjects who are randomized to Group 1 will receive pegcetacoplan administration throughout the entire main period. Those subjects who are randomized to Group 2 will not receive pegcetacoplan administration during the controlled portion but will begin pegcetacoplan treatment during the noncontrolled portion (following the Week 12 biopsy). During the designated period of pegcetacoplan administration (which differs based on randomization assignment), subjects will receive 1080 mg pegcetacoplan SC infusions (20 mL) twice weekly.

9.2.1. Randomization Visit

The following assessments will be performed and information collected at the randomization visit (Visit 3, Study Day 1), as outlined in the Schedule of Activities (Table 1).

Randomization must occur at the outset of this visit to determine treatment group. The only laboratory assessment that would prevent randomization is a positive pregnancy test.

Please note the few items that are specific to the treatment group to which the subject is randomized. Group 2 subjects do not receive pegcetacoplan administration during the controlled portion but will begin to receive pegcetacoplan administration during the noncontrolled portion, following the Week 12 biopsy.

9.2.1.1. Immediately Following Randomization, All Subjects

- Review inclusion/exclusion criteria, confirm eligibility
- Review of concomitant medications
- Physical examination, full
- 12-lead ECG
- Collect 3 uPCR containers from previous visit
- Arrange home uPCR courier pickup
- Urinalysis assessment
- Blood samples for laboratory assessments
- eGFR
- AE collection
- Vital sign measurements

9.2.1.2. Group 1 Subjects Only

- PK collection: collect after blood sample draws and before dosing
- Dispense investigational product and infusion materials
- Train subject to perform home infusion

- Administer pegcetacoplan to subjects
- Infusion site/pump safety assessment
- Additional vital sign measurement at 30 minutes (±5 minutes) after dosing

9.2.1.3. All Subjects

- Dispense 3 uPCR containers for consecutive collection

9.2.2. Primary Endpoint Biopsy at 12 Weeks

The Week 12 renal allograft biopsy must occur at a time point between Weeks 12 and 14, inclusive; Group 2 subjects cannot begin pegcetacoplan administration until after the biopsy occurs. It is important to note that the 24-hour urine collection should occur for all subjects prior to the renal biopsy and for Group 2, prior to the initiation of pegcetacoplan; given this, the Week 8 visit should include the sending home of a 24-hour urine collection container with all subjects.

9.2.3. Visit 7 or 8 (Week 12 or 14)

Depending on when the Group 2 subjects receive their Week 12 renal biopsies (see Section 9.2.2), the following will occur at either Visit 7 or 8 (Week 12 or 14). The following assessments will be performed and information collected as noted above, as outlined in the Schedule of Activities (Table 1). Please note the few items that are specific to treatment group; Group 1 will not have to do all the same assessments as Group 2.

9.2.3.1. Prior to Pegcetacoplan Administration

- Review of concomitant medications
- Physical examination, brief
- 12-lead ECG
- Collect 3 uPCR containers from previous visit
- Arrange home uPCR courier pickup
- Urinalysis assessment
- Blood samples for laboratory assessments
- eGFR
- β–human chorionic gonadotropin, if applicable
- AE collection
- Vital sign measurements
- PK collection (predose)
- Dispense investigational product and infusion materials
- Train subject to perform home infusion (Group 2 only)

9.2.3.2. Administration of Pegcetacoplan

- Administer pegcetacoplan to subjects (Group 2 only; Group 1 can self-administer)
- Infusion site/pump safety assessment

9.2.3.3. Group 2 Subjects Only

- Additional vital sign measurement at 30 minutes (±5 minutes) after dosing

9.2.3.4. All Subjects

- Dispense 3 uPCR containers for consecutive collection

9.2.4. Remaining Visits During Main Period

For all of the remaining visits of the main period, all subjects, regardless of randomization, will experience the same assessment activities, as outlined in the Schedule of Activities (Table 1). Any discrepancies/additions are noted with an asterisk (*).

9.2.4.1. Prior to Administration of Pegcetacoplan

- Vaccination* (Study Week 8 only)
- Review of concomitant medications
- Physical examination*
  - brief, except for Visit 16, which is full
- 12-lead ECG
- Collect 3 uPCR containers from previous visit
- Arrange home uPCR courier pickup
- Urinalysis assessment
- Blood samples for laboratory assessments
- eGFR
- Urine pregnancy test, if applicable*
  - β–human chorionic gonadotropin at Visit 16 only, if applicable
- AE collection
- Vital sign measurements
- PK collection (predose)
- Dispense 24-hour urine collection container (Week 20 for Week 24 collection and Week 42 for Week 48 collection)*
- Dispense investigational product and infusion materials

9.2.4.2. Administration of Pegcetacoplan

- Pegcetacoplan administration
- Infusion site/pump safety assessment

9.2.4.3. Following Administration of Pegcetacoplan

- Dispense 24-hour urine collection container* (Week 8 for Week 12 collection; Week 20 for Week 24 collection; Week 42 for Week 48 collection only)
- Dispense uPCR containers for consecutive collection every 2 weeks, per the following container dispersal schedule:
  - Dispense 3 containers (visits spaced every 2 weeks): Weeks 1, 2, 12, 14, 52
  - Dispense 6 containers (visits spaced every 4 weeks): Weeks 4, 8, 16, 20, 48
  - Dispense 9 containers (visits spaced every 6 weeks): Weeks 24, 30, 36, 42

9.2.5. Week 52 Renal Biopsy

The Week 52 biopsy must occur at a time point between Weeks 48 and 52, inclusive.

9.3. Follow-up Period

All subjects who complete study treatment and do not enter Part B, the long-term extension, will return to the investigator site for follow-up visits for 8 weeks, where assessments will be performed as per the Schedule of Activities (Table 1), and where the visit window allowances are also provided.

Subjects who discontinue treatment early and do not elect to continue their participation in the study will complete a follow-up visit 2 weeks after discontinuation of treatment and also the exit visit, 6 weeks thereafter.

The following assessments will be performed during this period, as outlined in the Schedule of Activities (Table 1):

- Procure 3 previously collected consecutive uPCR samples
  - Arrange courier pickup for all every 2-week triplicate uPCR samples during weeks without clinic visits
- Physical examination, brief
- Concomitant medications review
- Infusion site/pump safety assessment
- Blood samples for laboratory assessments
- Anti–pegcetacoplan peptide/anti-PEG circulating antibodies collection
- eGFR assessment
- Urinalysis collection

- Urine pregnancy test
- AE review
- Vital signs
- 12-lead ECG
- PK sample collection
- Dispense uPCR containers for consecutive collection every 2 weeks, per the following container dispersal schedule:
  - Dispense 3 containers (visits spaced every 2 weeks): Weeks 54, 56
  - Dispense 9 containers (visits spaced every 6 weeks): Weeks 58, 64, 70
- Dispense 24-hour urine collection container

9.4. Exit Visit

All subjects will return to the clinic facility for the exit visit, 8 weeks following the final dose of pegcetacoplan, on Day 420 (or sooner if the subject discontinues prior to Week 52).

Study participation for each subject will be concluded following completion of the exit visit. If a subject withdraws from the study prior to the scheduled exit visit, all exit visit assessments should be performed at the subject's final visit to the clinic, including collection of blood samples for PK and/or PD assessments, as well as a postdose antigenicity sample, if not yet collected.

The exit visit procedures are listed in the Schedule of Activities (Table 1):

- Arrange courier service to pick up 24-hour urine collection to deliver to site
- Procure 3 previously collected consecutive uPCR samples to site
- Blood samples for laboratory assessments (see Schedule of Activities [Table 1] for details)
- Concomitant medications
- AE review
- Anti–pegcetacoplan/anti-PEG circulating antibodies assay
- eGFR assessment
- Urinalysis (see Schedule of Activities [Table 1] for details)
- Vital signs
- 12-lead ECG
- PK sample

9.5. Early Termination and Exit Visit

Subjects who discontinue treatment early and do not elect to continue their participation in the study will complete an early termination visit. If the early termination visit is prior to Week 48, then all

assessments from Week 48, in addition to a renal biopsy, should be done, if possible. An additional exit visit should occur 6 weeks after the early termination visit. If the early termination is during the follow-up period, then all the assessments from the exit visit should be performed.

9.6. Unscheduled Follow-up Visits

All subjects will be asked to return to the clinical facility for additional follow-up visits, if considered necessary by the investigator.

Unscheduled follow-up visits may include, but are not limited to, any of the procedures listed in the Schedule of Activities (Table 1).

9.7. Part B, Long-Term Extension

The appendices (Section 15) provide the details regarding the Part B, the long-term extension.

9.8. Safety Monitoring Committee

A safety monitoring committee (SMC) will review cumulative safety/tolerability data (eg, physical examinations, ECGs, vital signs, clinical laboratory tests, and AEs). The SMC will have the responsibility to conduct a thorough safety assessment at regular predefined intervals during the treatment period of the study.

The first SMC meeting will be scheduled 4 months after the first subject is dosed with study drug and at further 4-monthly intervals until all subjects complete the main period. An ad hoc SMC data review may be recommended by the SMC or requested by the sponsor at any time during the study.

The remit, roles, and responsibilities of the SMC will be specified in a separate SMC charter.

10. ASSESSMENTS

Safety assessments are to be performed at protocol-specified visits, as specified in the Schedule of Activities (Table 1) for Part A; assessments specific to Part B, the long-term extension, are provided in the appendices (Section 15). If deemed necessary, additional safety measurements will be performed, at the discretion of the investigator.

10.1. Medical History

Medical history will be recorded at screening. Investigators should document the occurrence, signs, and symptoms of the subject's preexisting conditions, including all prior significant illnesses, up to and including 3 years before screening. Additional preexisting conditions present at the time when informed consent is given up to the time of first dosing are to be regarded as concomitant. Medical history will include alcohol consumption and smoking history, if applicable.

Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs in accordance with Section 11.

Additionally, demographic data will be collected for all subjects and will include date of birth or age, according to applicable regulations, sex, ethnicity, etc.

A detailed medical history with regard to disease indication (C3G or IC-MPGN) will be requested and will include prior surgeries, renal biopsies, hospitalizations, dialysis, transplantation, laboratory data, and extrarenal manifestations of the disease. This information will be recorded on a detailed disease-specific eCRF. Available disease medical history for the 3 years preceding screening will be requested. Submission of additional historical data is encouraged, when available.

10.2. Prior and Concomitant Medications

All prior and concomitant medications for at least 12 weeks prior to screening should be collected at the initial screening visit. All disease-specific therapy for the preceding 3 years should also be collected, and collection of additional disease-specific medication history is encouraged, when available. The plan for post-transplant immunosuppression for the duration of the study should be documented prior to randomization.

10.3. Vital Signs

Vital signs (body temperature, respiration rate, heart rate, and systolic and diastolic blood pressure measurements) will be evaluated at the visits indicated in the Schedule of Activities (Table 1). All vital signs will be measured after the subject has been resting in a sitting position for at least 5 minutes, except when they are supine or semireclined because of study procedures and/or AEs, or if deemed necessary by the investigator. Blood pressure measurements are to be taken in the same arm for the duration of the study. Body weight (without shoes) will be recorded whenever vital signs are recorded; height (without shoes) will be recorded at screening only.

Vital signs measurements will be repeated if clinically significant or if machine/equipment errors occur. Out-of-range blood pressure, respiratory rate, or heart rate measurements will be repeated, at the investigator's discretion. Any confirmed, clinically significant vital signs measurements must be recorded as AEs.

When pegcetacoplan is administered at the study site, vital signs will be measured within 2 hours prior to infusion, before venipuncture and ECG. Following the first infusion, vital signs will be measured again at 30 minutes (±5 minutes) after dosing. For subjects in Group 2, vital signs will be measured once at each visit during the controlled period.

10.4. Physical Examination

All full physical examinations, performed by the investigator or designee, will include, at a minimum, assessment of the following: general, head, ears, eyes, nose, throat, dentition, thyroid (endocrine), heart, chest, lungs, abdomen, skin, extremities, back/neck, musculoskeletal, and lymph nodes.

Brief physical examinations will include general appearance, heart, lungs, abdomen, extremities, and weight and are to be performed at all visits where a full physical examination does not occur. Edema will be assessed at each visit.

Additional symptom-driven physical examinations may be performed at any time, as deemed necessary by the investigator.

See the Schedule of Activities (Table 1) for the details regarding which type of physical examination should be given at each visit.

10.5. Electrocardiograms

All 12-lead ECGs will be measured once, prior to dosing, at the time points outlined in the Schedule of Activities (Table 1). The ECG will be taken when the subject has been resting in the supine position for 10 minutes in a quiet environment and prior to any blood sampling procedures, unless specified at time points after timed blood sampling procedures.

All ECGs will be recorded at the sites using the equipment provided by the vendor performing the centralized ECG analysis.

The ECGs will be classified as normal, having a not clinically significant abnormality, or having a clinically significant abnormality. In addition, ECG parameters of ventricular rate, PR interval, QRS duration, and QT interval (corrected using Fridericia's method and uncorrected) will be reviewed for eligibility and ongoing safety.

Please see the pharmacy manual for further details on ECG collection and reporting.

10.6. 24-Hour Urine Collection

A 24-hour urine collection is defined as collection of all urinary voids for a 24-hour period. The 24-hour urine collection should begin following the (discarded) first urinary output for the day. Subjects will be provided a container for 24-hour urine collection that will be undertaken at home.

There will be five 24-hour urine collections:

- Week 1 (screening): will be used to determine eligibility for study entry, as well as to assess changes in proteinuria over the course of the study, to be obtained prior to the renal biopsy but no more than 4 weeks before randomization
- Week 12 (prior to the renal biopsy)

- Week 24
- Week 48 (prior to the renal biopsy)
- Week 76 (for subjects who do not enter Part B)

If menses are occurring at the scheduled time of a 24-hour urine collection, then the collection should be delayed until completion of menses, with this information recorded in the subject's source document. Urine will need to be stored at 2-8 °C (ie, in refrigerator). Courier arrangements will be made by the site to pick up the collection container from the subjects and return it to the site. Total urine volume, total protein concentration, total albumin concentration, and total creatinine concentration of the 24-hour urine collection will be measured, with calculation of total protein excretion, total albumin excretion, total creatinine excretion, and uPCR and urine albumin-to-creatinine ratio (uACR) based on the 24-hour collection.

10.7. Triplicate First-Morning Spot Urine Collections

Triplicate first-morning spot urine collection is defined as a collection of first-morning urine on 3 consecutive mornings, with each morning collected into a separate container. Triplicate first-morning spot urine samples should be collected every 2 weeks throughout the main period of study, and, for subjects who do not enter Part B, the long-term extension, through the follow-up period. Triplicate first-morning spot urine samples should be collected every 6 weeks in the long-term extension.

At each scheduled clinic visit, the site will dispense the number of spot urine containers needed prior to the next scheduled visit (see Table 2). For collection weeks in which there is a scheduled clinic visit, subjects will return the triplicate spot urine collections at the visit. On weeks where no clinic visit is scheduled, a courier service will be arranged to pick up samples from the subject's home for delivery to the clinic.

It is important that each of these collections represent the first urinary output upon awakening, after an extended period of rest. In the event that a subject has an atypical sleep/wake schedule, the appropriate timing for these spot urine collections may not be morning. In this case, the timing of the collection should be adjusted to ensure collection of the first urinary output after an extended period of rest (eg, at least 6 hours), and the alternate timing should be recorded in the subject's source document. After collection, the urine samples must be stored at 2-8 °C (ie, in refrigerator). Urine protein, albumin, and creatinine concentrations should be measured on all spot urine samples, with calculation of uPCR and uACR values. If menses are repeatedly occurring at the scheduled times of a triplicate first morning urine collection, the collection dates should be adjusted to avoid collection during menses to the extent possible, with this information recorded in the subject's source document.

The schedule for the triplicate first-morning spot urine collections is as follows:

uPCR collection schedule:

- Dispense uPCR containers for consecutive collection every 2 weeks, per the following container dispersal schedule:
  - Dispense 3 containers (visits spaced every 2 weeks): Weeks 1, 2, 12, 14, 52, 54, 56

- Dispense 6 containers (visits spaced every 4 weeks): Weeks 4, 8, 16, 20, 48
- Dispense 9 containers (visits spaced every 6 weeks): Weeks 24, 30, 36, 42, 58, 64, 70

10.8. Random Spot Urine Collection

At each clinic visit, subjects will be asked to submit a urine sample. As this sample will not necessarily reflect a specific time of day, it is considered a "random" spot urine sample, so as to distinguish it from the first-morning spot collections. After collection, the urine samples must be stored at 2-8 °C (ie, in a refrigerator). Urine protein, albumin, and creatinine concentrations should be measured on all spot urine samples, with calculation of uPCR and uACR values.

10.9. Renal Biopsy

A percutaneous biopsy of the renal allograft will be obtained at the times indicated in the Schedule of Activities (Table 1). The procedure should be performed according to the local standard practices at the site, including use of anesthesia/sedation, preprocedure evaluation (eg, laboratory testing prior to renal biopsy), and postprocedure observation and monitoring. The renal biopsy must include adequate material for light microscopy (7 or more glomeruli), immunofluorescence microscopy (3 or more glomeruli), and electron microscopy (2 or more glomeruli). Renal biopsy samples should be handled and processed as per the pathology manual. All renal pathology will be reviewed by the central pathology laboratory, which will be blinded to treatment assignment.

As a reminder, if a coagulation panel is performed for any reason, including as a prebiopsy assessment, the use of silica reagents for this test should be avoided in subjects treated with pegcetacoplan.

10.10. Measured Glomerular Filtration Rate

Measured glomerular filtration rate (GFR) is an optional assessment that may be done by a site that routinely performs this assessment. In this case, the site should follow its standard procedure for measured GFR (and document the procedure within the subject's source document) at 1 time point prior to the first pegcetacoplan dose (but no more than 4 weeks prior to the first dose) and at 1 time point between Week 48 and Week 52, inclusive.

10.11. Ophthalmologic Evaluation

Ophthalmologic evaluation is an optional assessment and will be performed at selected sites. If these evaluations are performed, subjects should have a baseline evaluation, including a basic ophthalmologic examination, spectral domain optical coherence tomography (SD-OCT), and color fundus photography, at an approved ophthalmologic clinical site at any time during the screening period. For those subjects with drusen prior to pegcetacoplan administration, a follow-up ophthalmologic evaluation, including a basic ophthalmologic examination, SD-OCT, and color fundus photography, should occur at a convenient time point between Week 42 and Week 52 of the study. The SD-OCT and color fundus photography will be acquired using a standardized protocol, performed by reading center certified imagers on registered equipment, and will be transmitted to a central reading center for evaluation. The basic ophthalmologic

examination should include best-corrected visual acuity, intraocular pressure, and a dilated fundus exam with comment on presence or absence of pigment, drusen, hemorrhage, atrophy, or other evidence of macular degeneration.

10.12. Infusion Site/Pump Safety Assessment

On the days of clinical visits, pump use safety will be assessed within 30 minutes after study drug administration. This technique evaluation will be performed by a physician or other licensed health care provider (eg, study nurse), as delegated by the investigator. The subject will be asked about any issues related to pump use.

Subjects will be instructed to notify the investigator or other study personnel if an infusion site reaction occurs after self-administration of pegcetacoplan. All clinically significant findings related to infusion procedures will be recorded as AEs.

10.13. Laboratory Assessments

Laboratory assessment samples (Table 3) are to be obtained at designated visits as detailed in the Schedule of Activities (Table 1).

Table 3: Laboratory Assessments

Hematology	Serum chemistry	Urine studies
Hb Hematocrit Platelet count RBC count WBC count with differential	Albumin ALT ALP AST Bicarbonate Bilirubin (total, direct, and indirect) BUN C3 C4 Calcium Chloride Creatinine Creatine kinase Estimated glomerular filtration rate (using CKD-EPI formula) GGT Glucose HDL LDH LDL Phosphorus Potassium Sodium Triglycerides Total cholesterol Total protein Uric acid	Urinalysis • Blood • Bilirubin • Glucose • Ketones • Leukocyte esterase • Microscopic examination of urine sediment, including for presence of RBCs, WBCs, and casts, will be performed on all urinalyses • Nitrite • pH • Pregnancy, when applicable • Protein • Specific gravity • Urobilinogen Spot urines (first-morning and random) • ACR • PCR • Total albumin concentration • Total creatinine concentration • Total protein concentration 24-hour urine • ACR • PCR • Total albumin concentration • Total creatinine concentration • Total protein concentration • Total volume

Table 3: Laboratory Assessments

Hematology	Serum chemistry	Urine studies
aPTT Fibrinogen INR	FSH (postmenopausal women) HBsAg HbcAb HCV HIV Serum pregnancy test, when applicable Serum pegcetacoplan concentration Complement profile: (AH50, CH50, C3a, C3b/iC3b, C5a, and C5b-9) C3 nephritic factor Anti–pegcetacoplan peptide/anti–polyethylene glycol antibody	Serum samples will be collected for analysis of antibody titers to *Neisseria meningitidis* (types A, C, W, Y, and B), PCV13 or PPSV23, and the Hib vaccination.

Abbreviations: ACR = albumin-to-creatinine ratio; AH50 = 50% alternative hemolytic complement pathway activity; ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CH50 = 50% classical hemolytic complement pathway activity; CKD-EPI = Chronic Kidney Disease–Epidemiology Collaboration; FSH = follicle-stimulating hormone; GGT = γ-glutamyltransferase; Hb = hemoglobin; HbcAb = hepatitis B core antibody; HbsAg = hepatitis B surface antigen; HCV = hepatitis C; HDL = high-density lipoproteins; Hib = *Haemophilus influenzae* type B vaccine; HIV = human immunodeficiency virus; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low-density lipoproteins; PCR = protein-to-creatinine ratio; PCV13 = pneumococcal conjugate vaccine; PPSV23 = pneumococcal polysaccharide vaccine 23; RBC = red blood cell; WBC = white blood cell.

A. The use of silica reagents in coagulation panels should be avoided in subjects treated with pegcetacoplan.
B. Serum samples will only be analyzed in the event that the subject has a positive infection for *Streptococcus pneumoniae*, *Neisseria meningitidis*, or *Haemophilus influenzae*.

Blood and urine samples will be analyzed at a central laboratory facility. Urine samples will be analyzed by dipstick and a microscopic analysis. All laboratory reports must be reviewed, signed, and dated by the investigator. A legible copy of all reports must be filed with the subject's medical record (source document) for that visit. Any laboratory test result considered by the investigator to be clinically significant should be considered an AE (clinically significant AEs include those that require an intervention). Clinically significant abnormal values occurring during the study will be followed up until repeat test results return to normal, stabilize, or are no longer clinically significant.

10.14. Pharmacokinetics

10.14.1. Blood Samples

Blood samples for PK assessment of pegcetacoplan will be collected via direct venipuncture at the time points delineated in the Schedule of Activities (Table 1).

PK samples will be taken predose at all other visits.

Instructions for collection, handling, processing, storage, and shipping of samples will be provided in a separate laboratory reference manual prior to study initiation.

10.15. PK Analytical Methodology

The concentration of study drug will be determined from the serum samples using a validated analytical method. Details of the method validation and sample analysis will be included with the final clinical study report.

10.16. Pharmacodynamics

Blood sample for PD assessment of pegcetacoplan will be collected via direct venipuncture at the time points delineated in the Schedule of Activities (Table 1) to assess complement activation (C3, C4, AH50, CH50, C3a, C3b/iC3b, C5a, and sC5b-9).

Instructions for collection, handling, processing, storage, and shipping of samples will be provided in a separate laboratory reference manual prior to study initiation.

10.17. Antidrug Antibody Assessment

Antidrug antibodies (ADA) include both anti–pegcetacoplan peptide and anti-PEG antibodies. The proposed ADA sampling schedule was established to capture the ADA signal at baseline, along with any potential early onset and the dynamic profile (transient or persistent) of antibody formation.

Subjects who discontinue dosing will need to have ADA samples collected 6 and 12 weeks following their last treatment.

Samples that test positive will be characterized by assays that will determine antibody titer and measure neutralizing capacity. Any titer that is at least 4-fold greater than baseline is considered treatment boosted. Subjects who have a treatment-emergent or treatment-boosted antidrug antibody response at any time will be followed up with ADA samples being collected every 6 months until the antibody levels are considered to be negative. Antibody levels will be considered to be negative when they revert to baseline or any titer that is less than a 4-fold increase from the baseline titer.

10.18. Blood Volume for Study Assessments

Table 4 presents the approximate blood volume to be collected for this study. See the laboratory manual for additional details regarding the blood volume required throughout this study.

Table 4: Approximate Blood Volume Collected

Sample type	Approximate volume per visit (mL)	Collections during screening	Collections during main period	Collections during follow-up	Approximate volume over course of study (mL)
Screening laboratory safety tests (including hematology, serum chemistry, coagulation serology), FSH (for postmenopausal female subjects only)	25	1	0	0	25
On-study serum chemistry	11	1	14	3	198
On-study hematology	4	1	14	3	72
On-study coagulation	3	1	14	3	54
PK samples	4	0	14	3	68
Complement profile	10	0	14	3	170
C3 nephritic factor	2	1	0	0	2
Immunogenicity (antidrug antibodies)	5	0	8	2	50
Vaccination titer sample	7	1	1	0	14
Approximate blood volume per visit (mL):		**25-27**	**32-44**	**32--37**	
Total approximate blood volume for study (mL):					**653**

Abbreviations: FSH = follicle-stimulating hormone; PK = pharmacokinetics.
Note: Represents the standard collection volume planned over the duration of the study actual volume may vary. For subjects entering Part B, the long-term extension, the sample volumes noted above will continue to be collected as described in Table 7.

10.19. Pregnancy Tests

For WOCBP, a serum pregnancy test will be performed during screening, at Visit 1, and at the end of the treatment period (Visit 16). A urine pregnancy test will also be performed at each site visit (predose), if applicable. Subjects with a positive result will be excluded or discontinued from the study. Urine pregnancy tests will be performed at every visit throughout the follow-up period. Male subjects will be counseled to avoid donating semen during the time between the first screening and the final exit visit and for the 12 weeks after their last dose of study drug.

11. ADVERSE EVENTS

11.1. Definitions

11.1.1. Adverse Events

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered drug related. An AE can, therefore, be any unfavorable and unintended sign, including a clinically significant abnormal laboratory finding, symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product.

AEs can be spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation and will be recorded during the study at the investigational site. All identified AEs must be recorded and described in the subject's source document.

Fluctuating or nonsignificant changes in laboratory values do not necessarily qualify for AE reporting. If changes in laboratory values are assessed as clinically significant and/or lead to discontinuation of administration of investigational product, they should be reported as an AE. If these laboratory values are linked to a diagnosis, only the diagnosis should be reported as an AE.

11.1.2. Serious Adverse Events

An SAE is any AE or suspected adverse reaction that, in the view of the investigator, results death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect. Important medical events that may not result in death, be life threatening*, or require hospitalization may be considered serious when, according to appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of important medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

**Life threatening* is defined as an AE or suspected adverse reaction that, in the view of either the investigator or sponsor, placed the subject at immediate risk of death as it occurred. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

11.1.3. Unexpected Adverse Events

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the reference safety information section of the IB that is in effect at the time of event onset.

11.2. Recording and Reporting Adverse Events

AEs and SAEs will be collected from the signing of the informed consent form (ICF) until the exit/early termination visit.

All SAEs will be followed until satisfactory resolution, until baseline level is reached, or until the SAE is considered by the investigator to be chronic or the subject is stable, as appropriate.

All SAEs that are suspected of being related to study treatment must be reported immediately to the sponsor if the investigator becomes aware of them, regardless of the time since the completion of the clinical trial.

Any events that occur prior to the start of dosing will be categorized as pretreatment events; events occurring after the start of dosing will be recorded as TEAEs (the start date of dosing and, therefore, categorization of the event will be dependent on randomization assignment).

For each AE, the investigator will evaluate and report the onset date (and time, if applicable), resolution date (and time, if applicable), intensity, causality, action taken, seriousness criteria met (if applicable), and whether or not the subject discontinued the study as a result of the event.

If possible, the outcome of any AE resulting in permanent discontinuation or that was present at the end of the study should be reported. Subjects experiencing AEs that cause interruption or discontinuation of investigational product and those experiencing AEs that are present at the last visit or early termination visit should receive follow-up as appropriate.

All SAEs must be reported to the sponsor/Apellis Safety by completing the SAE form within 24 hours of the investigator or their representative becoming aware of the event, whether or not the event is deemed treatment related. Completed SAE forms should be emailed to Safety@Apellis.com.

AEs will be coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA). If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms.

11.2.1. Relationship to Study Drug

The investigator will review each event and assess its relationship to study drug treatment (not related, unlikely related, possibly related, or definitely related). The date and time of onset, time relationship to drug dosing, duration, severity, action taken, and outcome (recovered/resolved, recovered/resolved with sequelae, recovering/resolving, not recovered/not resolved, fatal, or unknown) of each event will be noted.

Table 5 should be considered when evaluating the relationship of AEs/SAEs to study treatment.

Table 5: Definitions of Adverse Event Relatedness

Classification	Definition
Definitely related	Strong evidence of a causal relationship; the influence of other factors is unlikely.
Possibly related	Some evidence of a causal relationship, but other factors may have caused or contributed to the event (eg, another illness or concomitant treatment)
Unlikely related	A causal relationship is not a reasonable possibility, but it cannot be completely ruled out with the available evidence.
Not related	No evidence of a causal relationship

11.2.2. Severity of Events

The investigator will review each event and assess its severity. Note that severity is a measure of intensity, whereas seriousness is defined by the criteria in Section 11.1.2. An AE can be of severe intensity but not be considered serious.

Table 6 presents the definitions that should be considered when evaluating the severity of AEs and SAEs.

Table 6: Severity of Events

Severity	Definition/Description
Mild	Event results in mild or transient discomfort, not requiring intervention or treatment; does not limit or interfere with daily activities (eg, insomnia, mild headache).
Moderate	Event is sufficiently discomforting, so as to limit or interfere with daily activities; may require interventional treatment (eg, febrile illness requiring oral medication).
Severe	Event results in significant symptoms that prevents normal daily activities; may require hospitalization or invasive intervention (eg, anemia resulting in blood transfusion).

11.2.3. Reporting Adverse Events to Health Authorities, Institutional Review Boards, and Ethics Committees

The sponsor has the responsibility to inform concerned health authorities, IRBs, IECs, and investigators about suspected unexpected serious adverse reactions in line with GCP guidance and applicable regulatory requirements.

If required, specific SAEs should be reported to the concerned IRB or IEC in compliance with local requirements.

11.3. Pregnancy

Although pregnancy is not an AE, all pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) occurring with a female subject or the female partner of a male subject must be followed to conclusion to determine their outcomes and are considered immediately reportable events.

Any pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Apellis Safety by completing the pregnancy report form within 24 hours of the investigator or their representative becoming aware of the event. The pregnancy report form must be completed, signed, and dated by the investigator and submitted via email to Safety@Apellis.com.

The investigator must follow up the subject until completion of the pregnancy and must report the outcome of the pregnancy (eg, delivery, termination, etc) and neonatal status up to 12 months after delivery. An abnormal outcome is defined as the birth of a child with persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies, or birth defects. In the event of an abnormal outcome, an SAE must be reported using the SAE report form, as described in Section 11.2.

11.4. Abuse, Misuse, Overdose, and Medication Errors

Occurrences of events of overdose, drug misuse, drug abuse, and medication error must be reported to Apellis Safety.

Abuse of a medicinal product: Persistent or sporadic, intentional, excessive use of medicinal products that is accompanied by harmful physical or psychological effects.

Misuse: Intentional and inappropriate use of a medicinal product not in accordance with the prescribed or authorized dose, route of administration, and/or intended indication(s) or not within the legal status of its supply.

Overdose: Any dose administered to or taken by a subject (accidentally or intentionally) that exceeds the highest daily dose or is at a higher frequency than that described in the protocol.

Medication Error: An error made in prescribing, dispensing, administration, and/or use of the study drug. Medication errors are reportable to the sponsor as defined below.

- The dispensing, administration, and/or use of unassigned study drug
- The administration and/or use of an expired study drug

All AEs or SAEs associated with drug abuse, misuse, overdose, or medication error must be reported as appropriate. The investigator, in consultation with the sponsor, will decide whether a dose is to be considered an overdose. In the event of an overdose, the actual dose administered must be recorded in the subject's source document.

12. STATISTICAL ANALYSIS

A formal statistical analysis plan (SAP) will be developed and finalized prior to locking the database. The full details of data presentations and analyses will be provided in the SAP. Additional statistical analyses other than those described in this section may be performed if deemed appropriate and included in the SAP. Any deviations from either the final SAP or the protocol will be discussed in the final study report.

Endpoints that are not biopsy related (eg, proteinuria, changes in serum C3 levels) will be summarized by visit. Endpoints that are biopsy related (eg, glomerular myeloid cell infiltration, glomerular crescents) will be summarized by scheduled renal biopsy assessment. Continuous data will be summarized using descriptive statistics (eg, mean and standard deviation), and categorical data will be summarized using frequency tables (counts and percentages).

12.1. Determination of Sample Size

Given the exploratory nature of the study, no formal statistical hypothesis testing will be performed; therefore, the sample size is not based upon statistical power of the study.

Up to 12 subjects will be enrolled in this study. Because these complement-mediated glomerulopathies are rare diseases, as are subjects who have received a renal transplant, it may be difficult to recruit subjects. The intention is to collect safety, PK, PD, and efficacy data to support the progress of pegcetacoplan into further clinical studies.

12.2. Analysis Set

12.2.1. Screened Set

The screened set will consist of all subjects who have signed informed consent.

12.2.2. Intent-to-Treat Set

The intent-to-treat (ITT) set consists of all subjects for whom a randomization number has been assigned.

12.2.3. Safety Set

The safety set will include all subjects who receive at least 1 dose of pegcetacoplan, and subjects who are randomized into Group 2.

12.2.4. PK Set

The PK set will include all subjects in the ITT set who receive pegcetacoplan and have at least 1 evaluable postdose PK measurement.

12.2.5. PD Set

The PD set will include all subjects in the ITT set who receive pegcetacoplan and have at least 1 evaluable postdose PD measurement.

12.2.6. Data Review for Analysis Set

After all the data have been verified/coded/entered into the database, a review will be performed to define the analysis sets. The review will also check the quality of the data, identify outliers, and make decisions regarding data issues (eg, missing values, withdrawals, protocol deviations). After the preanalysis review, resolution of all issues, and documentation of all decisions, the database will be locked.

12.3. Efficacy Analysis

No formal inferential statistics will be applied to data collected in the study.

12.3.1. Analysis of Primary Efficacy Endpoint

The proportion of subjects with reduction in C3c staining on renal biopsy after 12 weeks on study will be tabulated. No formal statistical hypothesis testing will be performed. The screening renal allograft biopsy will be taken as defined per Section 9.1.3.

12.3.2. Analysis of Secondary Efficacy Endpoints

Changes from baseline biopsy in C3c staining over time will be summarized by treatment group. The proportion of subjects with reduction in C3c staining on renal biopsy after 52 weeks of treatment will be tabulated.

Changes and percentage changes in eGFR and serum creatinine concentration over time will be summarized by treatment group. eGFR and serum creatinine concentration will be measured at baseline and at each postrandomization assessment. The proportion of subjects with stabilization or improvement in each parameter will be tabulated. The Chronic Kidney Disease–Epidemiology Collaboration (CKD-EPI) creatinine equation for adults will be used to calculate eGFR, and a stable or improved eGFR will be defined as no more than a 25% decrease in eGFR relative to baseline. A stable or improved serum creatinine concentration will be defined as no increase or an increase of no more than 25% from baseline.

12.3.3. Analysis of Exploratory Efficacy Endpoints

Changes and percentage changes in proteinuria over time in subjects with baseline proteinuria above the ULN will be summarized by treatment group. Proteinuria will be calculated using the mean of the 3 spot uPCR samples collected for baseline and the subsequent treatment visits. Changes and percentage changes in proteinuria will also be assessed on the basis of 24-hour urine collection. The proportion of subjects with baseline proteinuria above the ULN with at least a 50% reduction in proteinuria will be tabulated. The proportion of subjects with baseline proteinuria above the ULN achieving complete clinical remission of proteinuria after 12 and 52 weeks of treatment (defined as mean triplicate uPCR or 24-hour urine protein in the normal range) will be tabulated.

Changes in additional key biopsy features over time (such as glomerular myeloid cell infiltration) will be summarized for each biopsy assessment.

Baseline will be taken as the measurement closest to but before randomization.

Changes in ophthalmologic features over time (including changes in maximum drusen size and in the number of intermediate or large drusen) will be summarized for subjects who have both baseline and on-study ophthalmologic evaluations.

12.4. Safety Analysis

TEAEs are defined as those AEs that develop or worsen after the first dose of study medication (or after randomization in Group 2) and up to 8 weeks beyond the last dose of study medication. All reported AEs will be coded using MedDRA and summarized by System Organ Class and Preferred Term. The number and incidence of TEAEs (both serious and nonserious) as well as the number and incidence of discontinuations due to TEAEs will be tabulated.

The AE summaries will be presented across all subjects. All AEs will be listed by subject, along with information regarding onset, duration, severity, relationship to study drug, action taken with study drug, treatment of event, and outcome. In addition, the number and incidence of rejection episodes and graft loss will be tabulated.

Changes from baseline in clinical laboratory tests will be summarized using descriptive statistics by visit and nominal time postdose. Out-of-range values will be flagged in data listings.

Changes from baseline in vital signs will be summarized using descriptive statistics by visit.

Changes from baseline in ECG parameters will be summarized using descriptive statistics by visit. Values of potential clinical significance will be flagged by listings.

Changes in physical examinations will be described in a data listing.

12.5. PK Analysis

The PK concentrations will be evaluated using the PK set.

Concentrations will be summarized using descriptive statistics over time in the treatment group (pegcetacoplan group) and the control group, starting at Week 12.

Individual subject concentration-time data will be plotted against actual sampling time. Median profiles of the concentration-time data using nominal sampling times will also be presented. Both linear-linear and linear-log plots will be presented.

Population PK and exposure-response modeling of the safety and efficacy data will be described in a pegcetacoplan population PK/PD analysis plan. The methods will be based on the FDA guidance for both exposure-response and population PK (FDA Guidance for Industry Population Pharmacokinetics, FDA Guidance for Exposure-Response Relationships).

12.6. PD Analysis

The PD endpoints will be evaluated using the PD set.

Absolute values, changes from baseline, and percentage changes from baseline will be summarized using descriptive statistics over time.

Individual subject time profiles will be plotted against actual sampling time. Median profiles over time, using nominal sampling time, will also be presented.

12.7. Immunogenicity Analysis

The proportion of subjects with treatment-emergent or treatment-boosted anti-pegcetacoplan peptide or anti-PEG ADA responses will be tabulated. ADA results will be summarized by treatment group, using appropriate descriptive statistics.

12.8. Other Analyses

Demographics, baseline characteristics, concomitant medication, medical history, and study medication exposure will be summarized.

World Health Organization and MedDRA coding dictionaries will be used for the concomitant medications and medical histories, respectively.

12.9. Interim Analysis

No interim analyses are planned for the primary endpoint.

12.10. Safety Monitoring Committee

As described in Section 9.8, an SMC will review cumulative safety and tolerability data (eg, physical examinations, ECGs, vital signs, clinical laboratory tests, and AEs). The SMC will have the responsibility to conduct a thorough safety assessment at regular predefined intervals during the treatment period of the study.

The remit, roles, and responsibilities of the SMC will be specified in a separate SMC charter.

13. STUDY MANAGEMENT

13.1. Approval and Consent

13.1.1. Regulatory Guidelines

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant regulations, in compliance with International Council for Harmonisation (ICH) and GCP and according to the appropriate regulatory requirements in the countries where the study was conducted.

The final report of this study will be written according to the ICH E3 Guideline (Structure and Content of Clinical Study Reports) as per the ICH Harmonized Tripartite Guidance (Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use M4 and the ICH M2 Expert Working Group).

13.1.2. Institutional Review Board or Independent Ethics Committee Review

The study protocol, any amendments to the protocol, the ICF, the IB, and other study-specific information will be reviewed and approved by the IRB or IEC. The study will not be initiated until the IRB/IEC has approved the protocol or a modification thereof. All records pertaining to IRB/IEC submission and approval should be kept in the site's regulatory files and sponsor's trial master file.

The IRB/ERC must be constituted and operate in accordance with the principles and requirements described in ICH Guidance E6 and national and local regulations deemed appropriate.

13.1.3. Informed Consent

For each study subject, written informed consent will be obtained before any protocol-related activities. As part of this procedure, the investigator or designee must explain orally and in writing the nature of the study; its purpose, procedures, and expected duration; alternative therapy available; and the benefits and risks involved in study participation. The subject should be informed that he/she may withdraw from the study at any time, and the subject will receive all information that is required by local regulations and ICH guidelines. The investigator will provide the sponsor or its representative with a copy of the IEC/IRB-approved ICF before the start of the study. The investigator shall retain the original, signed ICF in the subject's medical record and shall provide the subject with a copy of the consent.

If required by local or institutional policy, a biopsy consent form may also be utilized for the study kidney biopsy procedures. The biopsy-specific ICF should be from the center performing the biopsy, and it should be reviewed and signed at the same time as the study-specific ICF, covering the subject's consent to all 3 study biopsies. This biopsy-specific ICF is to specifically include the risks of the biopsy procedure, the planned anesthesia for the biopsy, the planned preprocedure evaluation, and the planned observation period following the biopsy. Within approximately 1 week of each biopsy procedure, the subject should be counseled again regarding the biopsy risks, planned anesthesia, required preprocedure laboratory values or tests, and observation period.

If there are any amendments to the approved protocol that may directly affect the subject's decision to continue participation in the study, the ICF will be amended accordingly, and the subject must re-sign the revised IEC/IRB-approved ICF.

13.2. Data Handling

The investigator must maintain all documentation related to this study. All essential documents (as defined in ICH Guideline E6) and the data generated in connection with this study, with the original copy of the final report, will be retained for at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor.

It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

13.3. Source Documents

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. The investigator will provide direct access to source documents and/or source data in the facilitation of trial-related monitoring, audits, review by IECs/IRBs, and regulatory inspections.

The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, not obscure the original entry, and be explained, if necessary.

13.4. Record Retention

Study records and source documents must be preserved for at least 15 years after the completion or discontinuation of/withdrawal from the study, at least 2 years after the drug being studied has received its last approval for sale, or at least 2 years after the drug development has stopped, and in accordance with the applicable local privacy laws, whichever is the longer time period.

The investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of patient health information, including, but not limited to, the Standards for Privacy of Individually Identifiable Health Information; Title 45 of the US Code of Federal Regulations, Parts 160 and 164; and the Health Insurance Portability Accountability Act of 1996 Privacy Rule. The investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with the Health Insurance Portability Accountability Act of 1996 Privacy Rule and in a form satisfactory to the sponsor.

13.5. Monitoring

On-site monitoring will be performed by the sponsor's designee for the duration of the study. The monitor will ensure that the study is conducted, recorded, and reported, in accordance with the protocol, standard operating procedures (SOPs), GCP, and the applicable regulatory

requirements. The monitor will verify the accuracy and completeness of the eCRF entries, source documents, and other study-related records against each other. The investigator will provide direct access to source data/documents for study-related monitoring. It is important that the investigator and the staff are available at these visits. The monitor will record the date of each visit, with a summary of the status and progress of the study. Proposed actions will be documented in writing to the investigator.

13.6. Quality Control and Quality Assurance

The sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, security, and reliability of the study data presented to the sponsor lies with the investigator generating the data.

Quality control and quality assurance systems are implemented and maintained using written SOPs from the investigative site, the sponsor, and/or its designee to ensure that the study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s), national and local laws, rules, and regulations.

Quality control checks will be applied at each stage of data handling (eg, edit checks) to ensure that all data are reliable and have been processed correctly.

The sponsor will arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, SOPs, GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions. Quality assurance procedures will be performed at study sites and during data management to assure that safety and efficacy data are adequate and well documented.

13.7. Protocol Amendment and Protocol Deviation

13.7.1. Protocol Amendment

Amendments to the protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no effect on the safety of subjects or the conduct of the study will be classed as administrative amendments and will be submitted to the IEC/IRB for information only. The sponsor will ensure that acknowledgment is received and filed. Amendments that are classed as substantial amendments must be submitted to the appropriate regulatory authorities and the IECs/IRBs for approval and will not be implemented at sites until such approvals are received, other than in the case of an urgent safety measure.

13.7.2. Protocol Deviations

Should a protocol deviation occur, the sponsor must be informed as soon as possible. Protocol deviations and/or violations and the reasons they occurred will be included in the clinical study report. Reporting of protocol deviations to the IRB/IEC and in accordance with applicable regulatory authority mandates is an investigator or contract research organization responsibility.

13.8. Ethical Considerations

This study will be conducted in accordance with this protocol; the accepted version of the Declaration of Helsinki; all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the US Code of Federal Regulations and EU 536/2014, Annex 1, D, 17 (a); and in compliance with GCP guidelines.

Institutional ethics committees/IRBs will review and approve this protocol and the ICF. All subjects are required to give written informed consent before participation in the study.

13.9. Confidentiality

Confidentiality of subject's information must be maintained, in accordance with national and local privacy laws.

13.10. ClinicalTrials.gov

This study has been listed with ClinicalTrials.gov, as required.

13.11. Study Termination

The sponsor reserves the right to suspend or discontinue this study for administrative and/or safety reasons at any time. The investigator reserves the right to discontinue dosing subjects at any time for safety reasons.

13.12. Financing and Insurance

A clinical trial agreement between the investigator/institution and the sponsor will address all finance and insurance matters.

13.13. Publication Policy/Disclosure of Data

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the institution and the sponsor or its designee. With respect to such rights, the sponsor or its designee will solely own all rights and interests in any materials, data, and intellectual property rights developed by investigators and others performing the clinical study described in this protocol, subject to the terms of any such agreement. In order to facilitate such ownership, investigators will be required to assign all such inventions either to their institution or directly to the sponsor or its designee, as will be set forth in the clinical study agreement.

14. REFERENCES

Holle J, Berenberg-Goßler L, Wu K, et al. Outcome of membranoproliferative glomerulonephritis and C3-glomerulopathy in children and adolescents. *Pediatr Nephrol*. 2018;33(12):2289-2298.

Lu DF, Moon M, Lanning LD, McCarthy AM, Smith RJ. Clinical features and outcomes of 98 children and adults with dense deposit disease. *Pediatr Nephrol*. 2012;27(5):773-781.

Medjeral-Thomas NR, O'Shaughnessy MM, O'Regan JA, et al. C3 glomerulopathy: clinicopathologic features and predictors of outcome. *Clin J Am Soc Nephrol*. 2014;9(1):46-53.

Noris M, Donadelli R, Remuzzi G. Autoimmune abnormalities of the alternative complement pathway in membranoproliferative glomerulonephritis and C3 glomerulopathy. *Pediatr Nephrol*. 2019;34:1311-1323. Doi: 10.1007/s00467-018-3989-0.

Okpechi IG, Dlamini TA, Duffield M, Rayner BL, Moturi G, Swanepoel CR. Outcome of patients with primary immune-complex type mesangiocapillary glomerulonephritis (MCGN) in Cape Town South Africa. *PloS One*. 2014;9(11):e113302.

Pickering MC, D'Agati VD, Nester CM, et al. C3 glomerulopathy: consensus report. *Kidney Int*. 2013;84(6):1079-1089.

Servais A, Noël LH, Roumenina LT, et al. Acquired and genetic complement abnormalities play a critical role in dense deposit disease and other C3 glomerulopathies. *Kidney Int*. 2012;82(4):454-464.

Zhang Y, Nester C, Martin B, et al. Defining the complement biomarker profile of C3 glomerulopathy. *Clin J Am Soc Nephrol*. 2014;9(11):1876-1882.

15. APPENDICES

APPENDIX 1. LONG-TERM EXTENSION ACTIVITIES

15.1. Part B: Long-Term Extension

This appendix contains only information that is specific to the design and conduct of Part B, the long-term extension. Any processes, procedure, or information not described in this appendix is identical to that described through the body of the main protocol.

15.1.1. Part B Overview/Rationale

Following Week 52 and the completion of Part A (the core study), any subject who, in the opinion of the investigator, is experiencing clinical benefit from pegcetacoplan administration will be invited to participate in Part B, the long-term extension, in order to continue to receive treatment with pegcetacoplan until it is commercially available for the disease under study. Dosing will remain the same throughout Part A and Part B.

Table 7 contains the Schedule of Activities for visits that will be conducted during Part B, the long-term extension.

Table 7: Schedule of Activities for Part B, Long-Term Extension (Following Week 52)

Study period	Long-term extension: Week 64 and beyond		ET & exit[A]
Study Week	64	≥76[B]	
Study Day	448	532[B]	
Study Visit	17B	18B[B]	
Visit window (±days)	7	7	
Physical examination[C]	X	X	X
12-lead ECG[D]	X		X
Infusion site/pump safety assessment[E]	X	X	
Concomitant medications	X	X	X
Vital sign measurements[F]	X	X	X
Urinalysis	X	X	X
Triplicate first-morning spot urine[G] (Dispense uPCR collection containers/arrange for home courier pickup)	X	X	X
Blood[H]			
PK sample	X	X	X
ADA assays[I]	X	X[I]	X
Hematology and chemistry	X	X	X
Complement profile	X	X	X
eGFR[J]	X	X	X
Pregnancy (β-HCG and FSH)			X
Urine pregnancy test[K]	X	X	X
Adverse events	X	X	X
Drug dispensation for home administration	X	X	

Abbreviations: β-HCG = β–human chorionic gonadotropin; ADA = antidrug antibody; CDK-EPI = Chronic Kidney Disease–Epidemiology Collaboration; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ET = early termination; FSH = follicle-stimulating hormone; PK = pharmacokinetics; uPCR = urine protein-to-creatinine ratio.

A. Subjects who discontinue treatment early should complete an ET visit immediately following discontinuation (but no later than 6 weeks after discontinuation of treatment) and an exit visit 6 weeks after the ET visit.
B. Following Visit 18B (Week 76) subjects should continue to schedule visits at 12-week intervals (±7 days) indefinitely until the subject discontinues or the pegcetacoplan development program is terminated.
C. Brief physical examinations should be performed at each visit, but symptom-driven physical examinations may also be performed at various unscheduled time points, if deemed necessary by the primary investigator. Edema should be assessed at every visit.
D. ECGs are to be performed before dosing and before blood sampling procedures.
E. Between site visits, subjects will be instructed to report any injection site reaction to the study coordinator.
F. On clinic dosing days, vital signs will be measured within 2 hours prior to dosing, before venipuncture and ECG assessments.

G. Starting at Visit 16 and continuing through the long-term extension, uPCR samples (first urinary output for the day) should be collected on 3 consecutive days, every 6 weeks, until the subject exits the study. At every clinic visit, the subject should be distributed 6 collection containers. For collections that happen between visits a courier service will be arranged for urine sample pickup and delivery to the site.
H. Blood samples will be taken before dosing.
I. Following Visit 18B (Week 76), ADA samples will be collected every 6 months (ie, at alternate visits). For subjects with positive anti–pegcetacoplan peptide antibody in last dose samples, additional samples will be collected 6 and 12 months after the last dose for further assessments.
J. CKD-EPI creatinine equation (see https://www.niddk.nih.gov); the CKD-EPI creatinine-cystatin C equation (if confirmation required).
K. Urine pregnancy test should be completed for women of childbearing potential prior to dosing.

15.1.2. Part B Study Design and Procedures

Following Visit 16 (Week 52), subjects who elect to continue in Part B, the long-term extension, will return to the site at 12-week intervals until pegcetacoplan is commercially available for the disease under study. Specific assessments for Part B are listed in Table 7.

The vaccination history for each subject should be reviewed prior to entry into the long-term extension, as described in Section 9.1.4, and any additional required vaccinations should be administered according to the current ACIP guidelines.

Subjects who discontinue treatment early should complete an early termination visit immediately following discontinuation (but no later than 6 weeks after discontinuation of treatment) and 1 exit visit 6 weeks after the early termination visit, as outlined in Table 7.

15.1.3. Part B Dose Rationale

The long-term extension maintains the same dose for Part A, which is described in Section 8.2.

15.1.4. Part B Study Treatments

This section contains study treatment information for Part B, the long-term extension.

15.1.4.1. Part B Identity of Investigational Product

The test product is pegcetacoplan, which will be provided as a sterile solution of pegcetacoplan (54 mg/mL) in acetate-buffered sorbitol, supplied in stoppered glass vials. Additional information regarding the investigational product is provided in the pegcetacoplan IB.

15.1.4.2. Part B Pegcetacoplan Dosing

Dosing will remain the same as Part A: subjects will continue to receive SC infusions pegcetacoplan at a dosage of 1080 mg twice weekly.

Dosing diaries will be utilized for pegcetacoplan and are to be completed for each dose administered at the study site or outside of regular clinic visits. Subjects should ideally maintain a consistent dosing schedule and should not delay or defer dosing. Missed doses will be handled on a case-by-case basis between the investigator and medical monitor, with the general approach being to administer a missed dose as soon as noticed, unless the next dose has already been administered.

15.1.4.3. Part B Pegcetacoplan Administration

Pegcetacoplan will be administered as a 20-mL SC infusion. The preferred site of infusion will be the abdomen; however, if a subject does not tolerate administration to the abdomen, alternative sites may be considered.

Subjects may choose to continue to self-administer pegcetacoplan infusions at the study site on scheduled dosing days when a study visit coincides, although this is not required. Self-administration conducted at the study site will be supervised to ensure that the subject continues to remain compliant with the administration guidelines.

15.1.5. Part B Labeling, Packaging, Storage, and Handling

15.1.5.1. Part B Labeling

Labels containing study information and pack identification are applied to the investigational product(s) container.

All investigational product is labeled with a minimum of the following: protocol number, dosage form (including product name and quantity in pack), route of administration, directions for use, storage conditions, batch number, packaging reference, the statements, "For clinical trial use only," and/or "CAUTION: New Drug—Limited by Federal (or US) Law to Investigational Use," and name and address of the sponsor.

Space is allocated on the label so that the site representative can record a unique subject identifier and date dispensed by the site to the subject.

Additional labels may, on a case-by-case basis, be applied to the investigational product in order to satisfy national, local, or institutional requirements, but they must not:

- Contradict the clinical study label
- Obscure the clinical study label
- Identify the study subject by name

Additional labels may not be added without the sponsor's prior full agreement.

15.1.5.2. Part B Packaging

Investigational product is supplied in 20-mL glass vials. Please refer to the pharmacy manual for details.

Changes to sponsor-supplied packaging prior to dosing may not occur without full agreement, in advance, by the sponsor.

15.1.5.3. Part B Infusion Supplies

The sponsor will supply syringes, vial adapters, infusion sets, and ambulatory syringe infusion pumps, as required. Refer to the pharmacy manual for further details.

15.1.5.4. Part B Storage and Handling

The investigational product should be stored refrigerated at 2-8 °C, both at home and in the clinic. Temperature monitoring is required at the investigator site (or documented storage location) to ensure that the investigational product is maintained within an established temperature range.

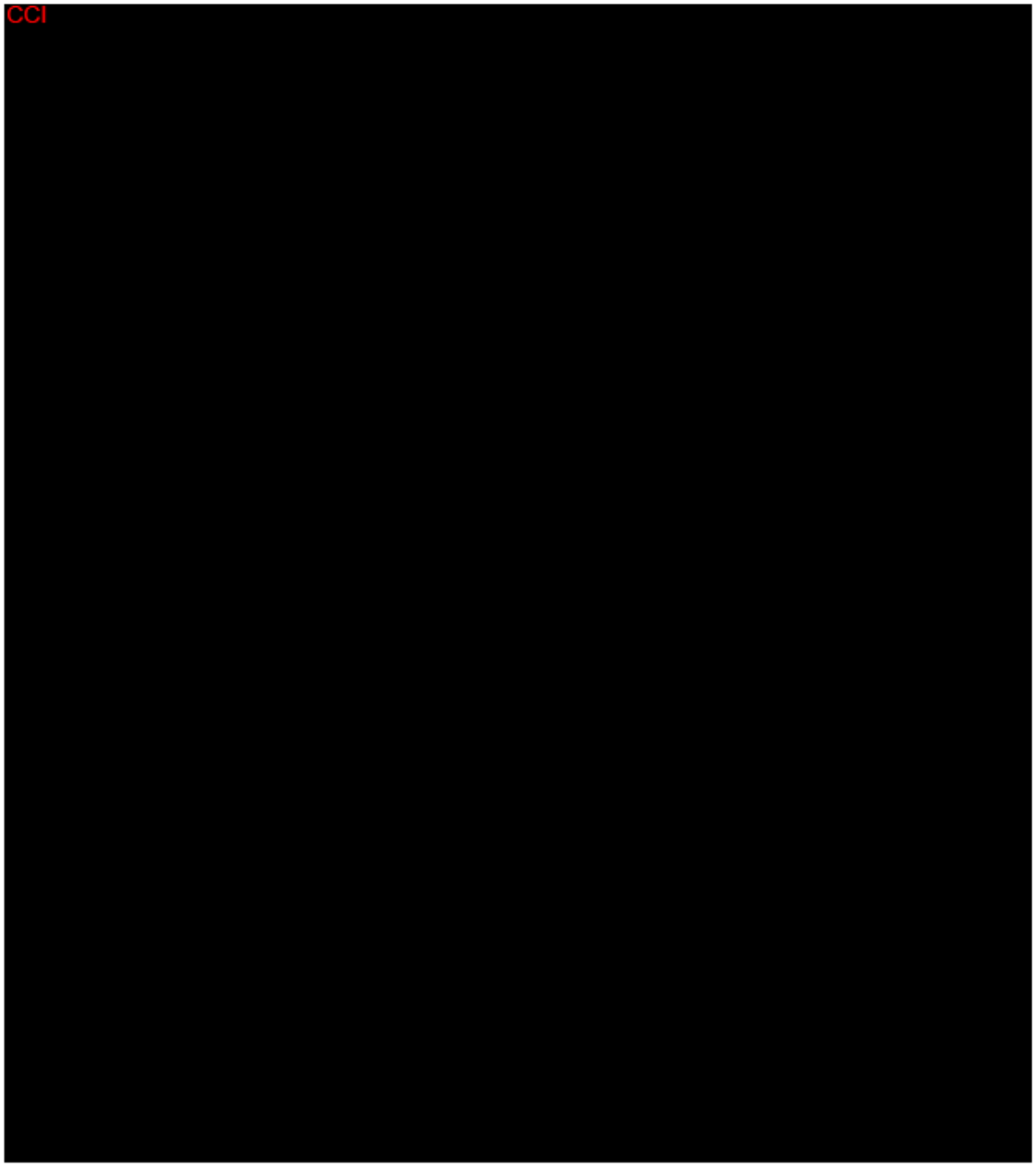
The investigator or appropriately qualified site staff will be responsible for the following:

- ensuring that the investigational product is stored in a secure, limited-access location at the site
  - limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented
- ensuring that the temperature is monitored throughout the duration of the study and that records are maintained

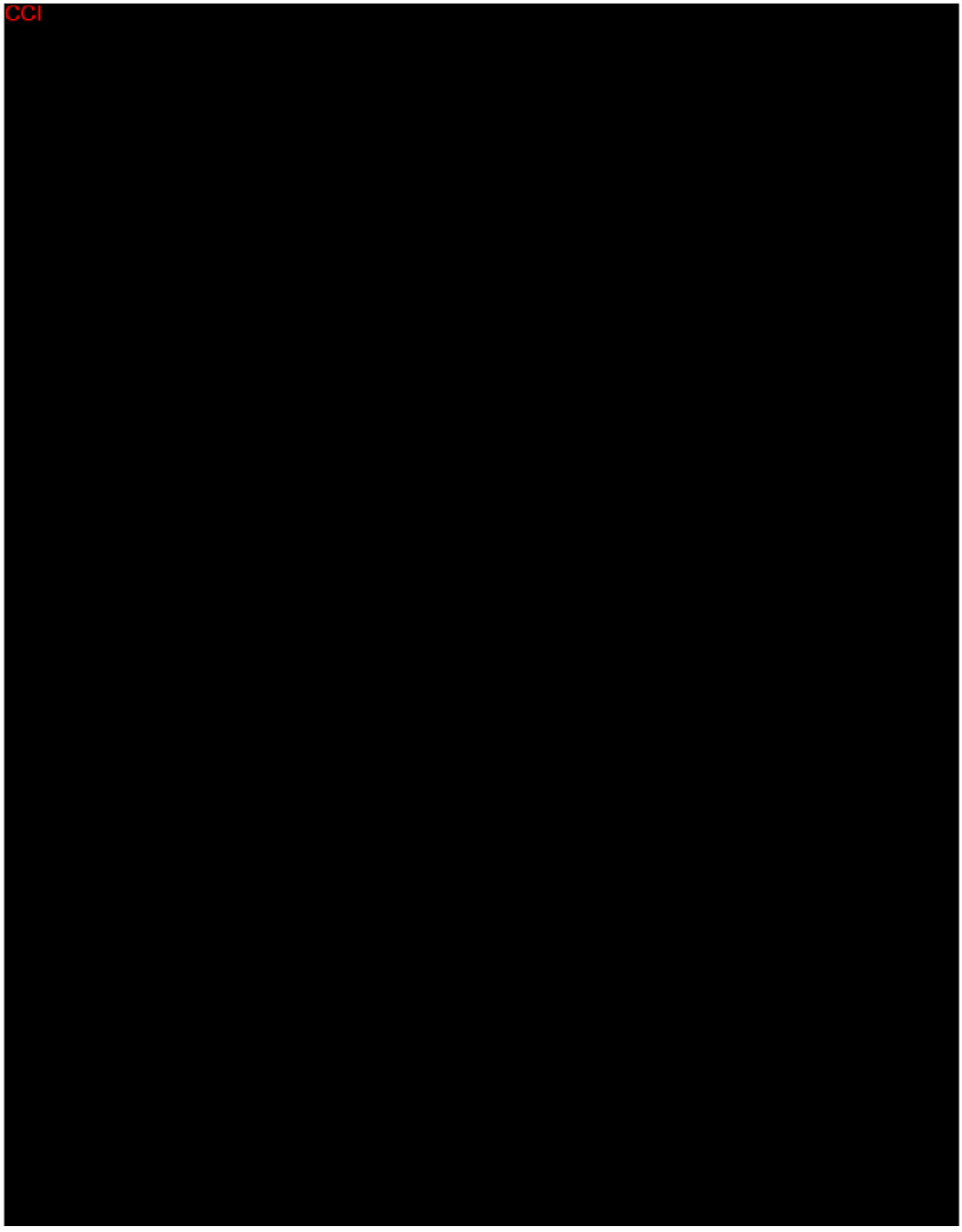
A pharmacist or appropriately qualified designated person will be responsible for the following:

- storing the investigational product appropriately
- dispensing the vials of investigational product to the subject
- entering the unique subject identifier on the investigational product bottle/carton labels as they are distributed

When the subject receives the investigational product from the site, it should be transported in a sponsor-approved bag or box, containing previously temperature-conditioned cold plates to ensure that the storage temperature (2-8 °C) is maintained. Temperature monitoring will not be required during transport or at the subject's residence, but a log will be kept for every infusion to ensure that all investigational product was kept refrigerated.


CCI

CCI

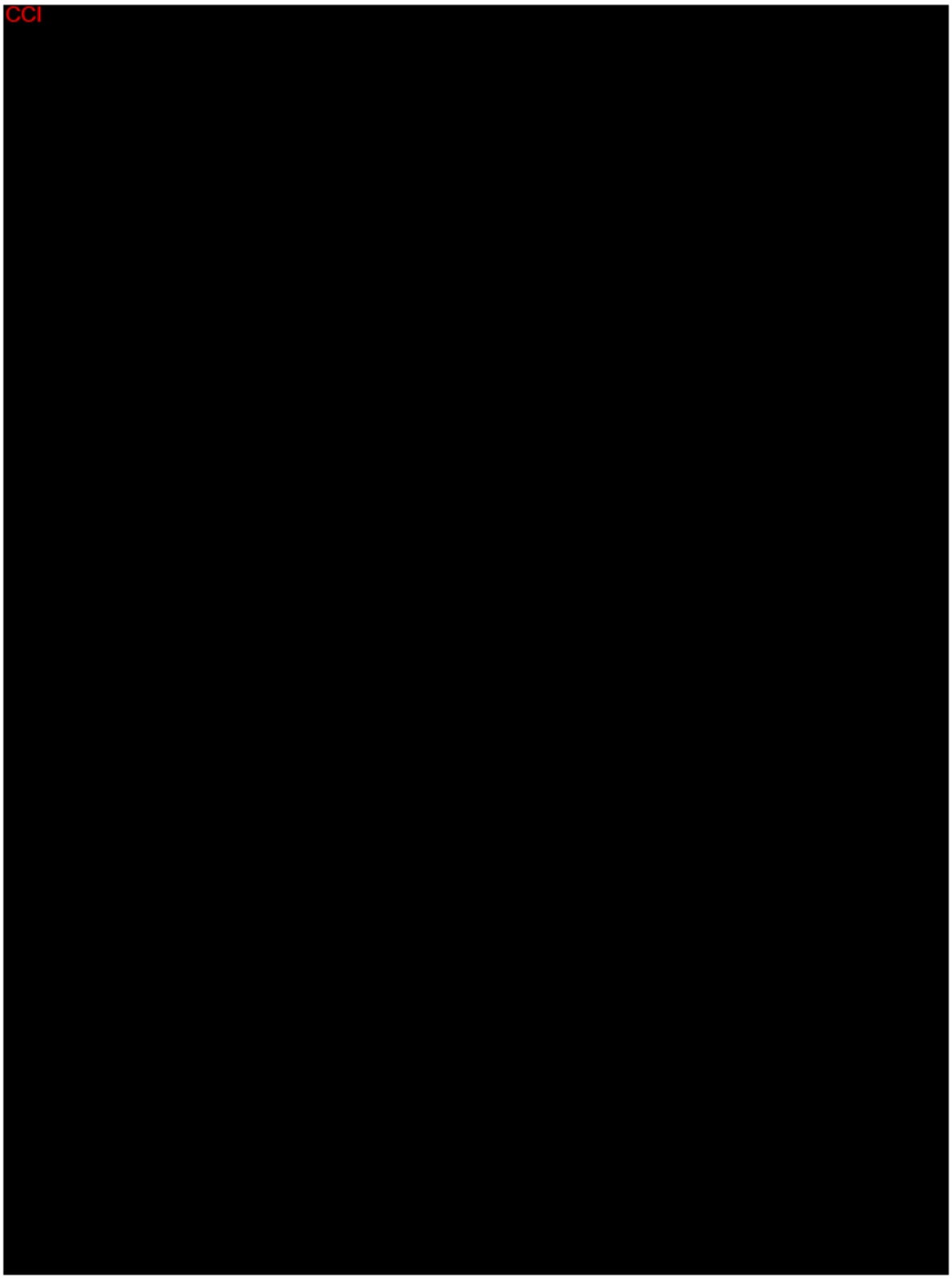


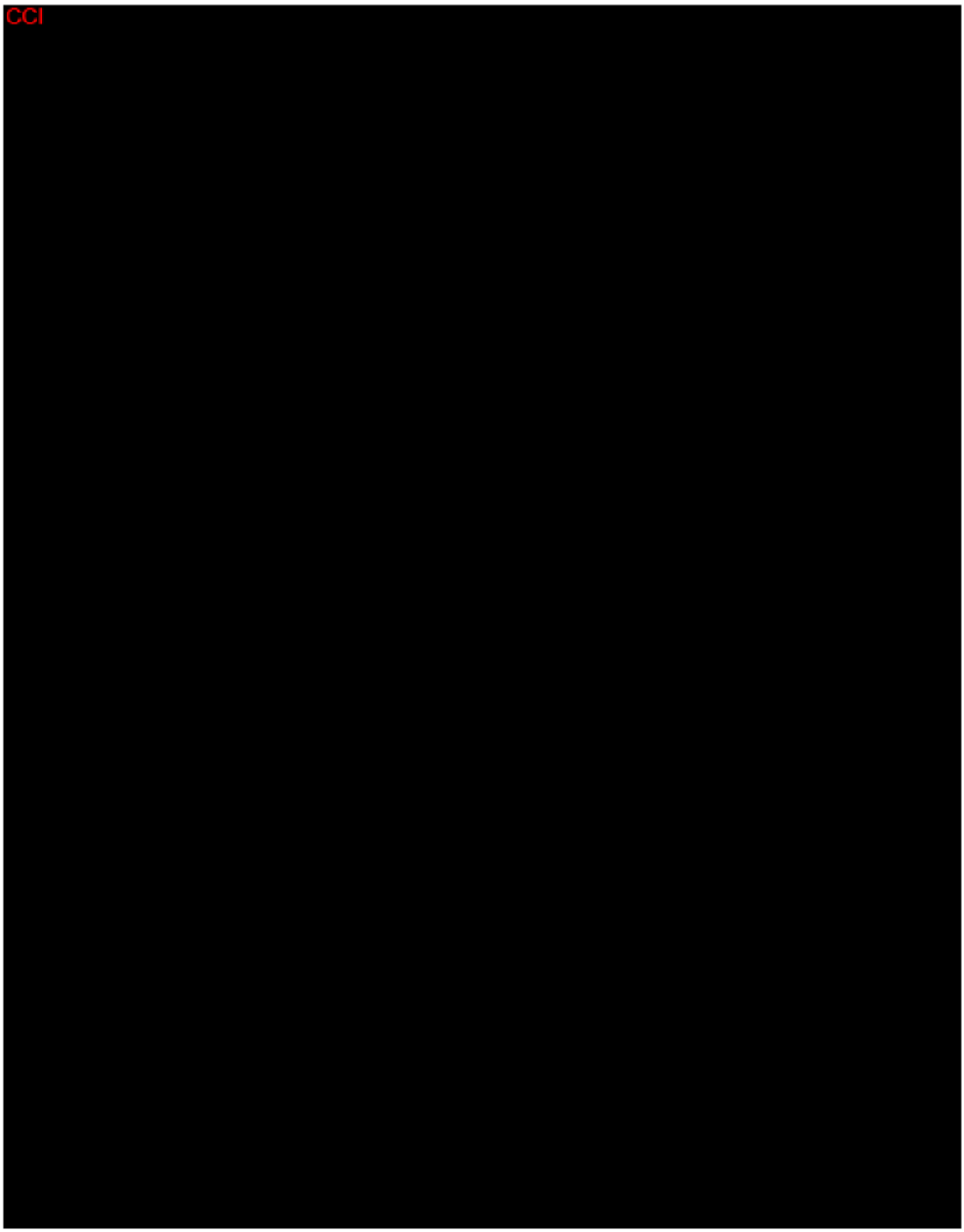
CCI

CCI

[redacted]

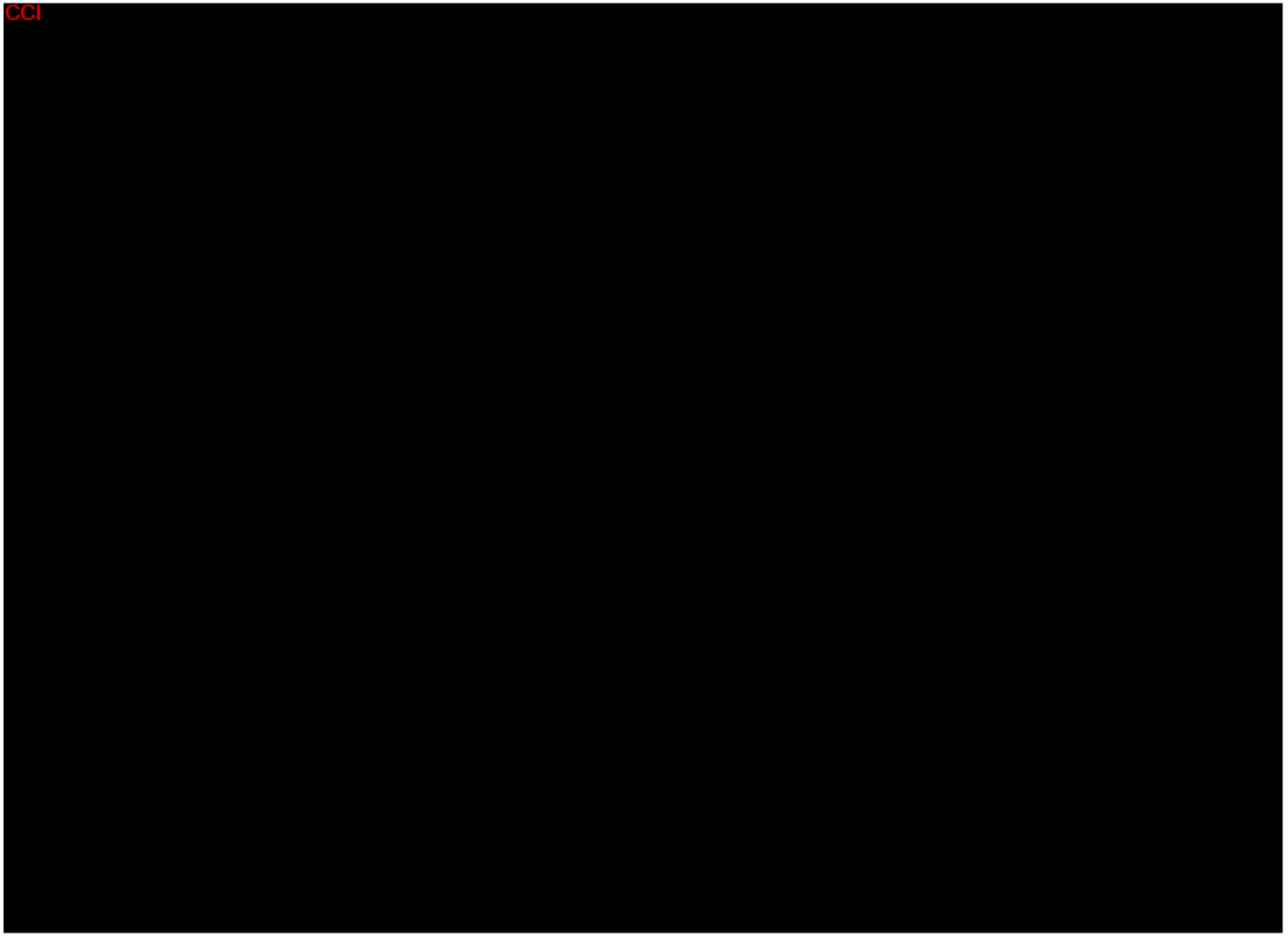
CCI

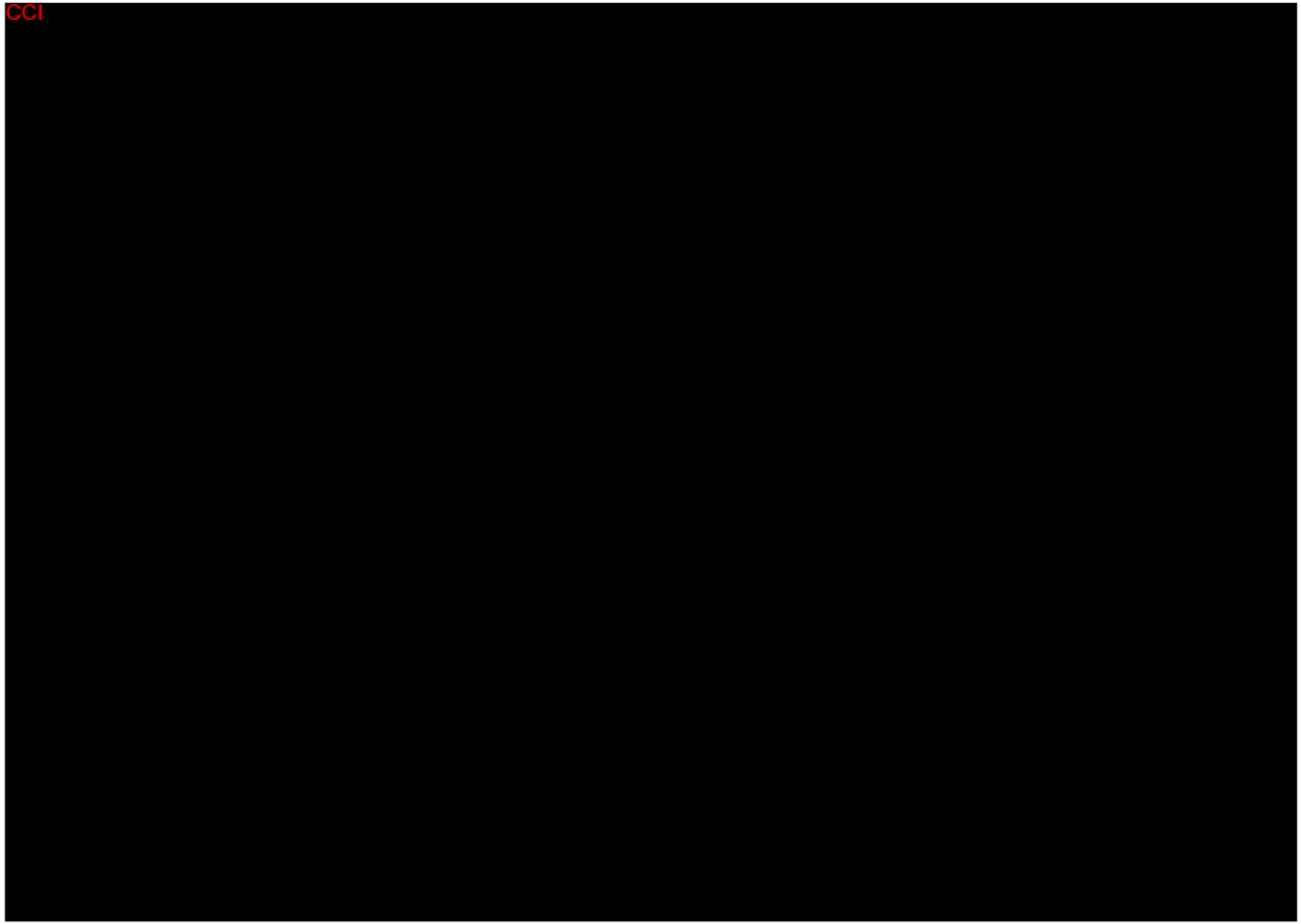



CCI

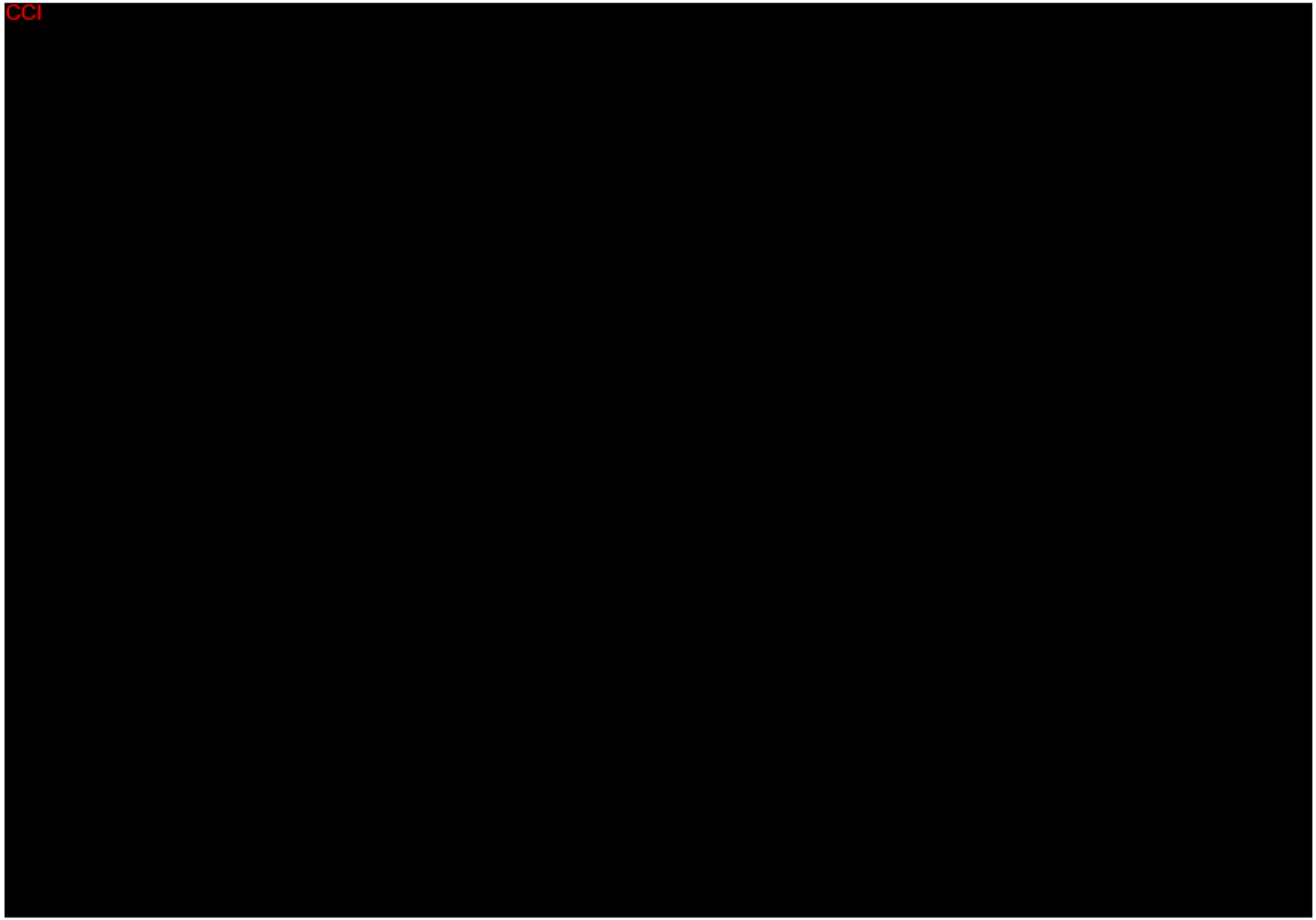
CCI


CCI


CCI


CCI

CCI



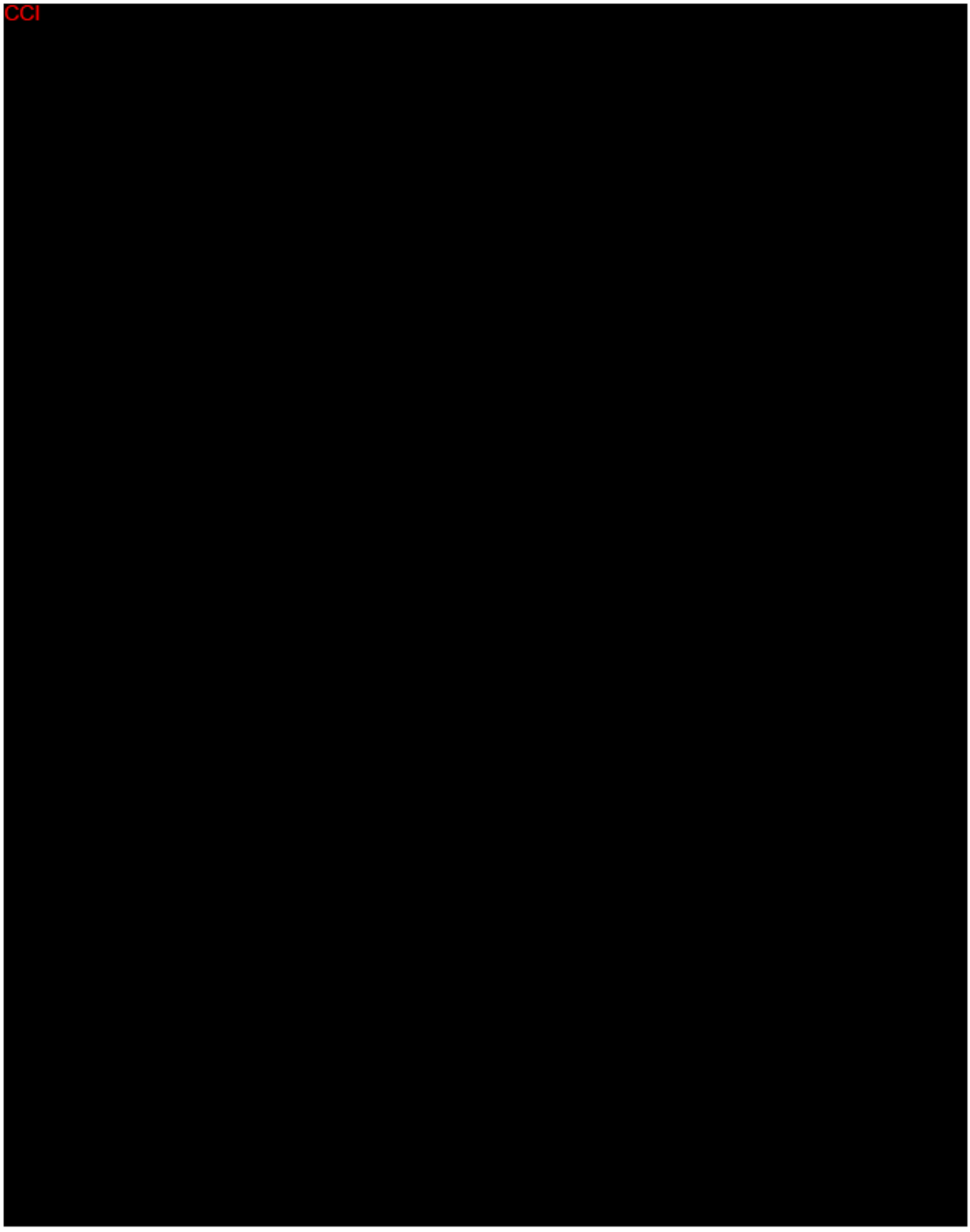

CCI

CCI

[redacted]


CCI

CCI



CCI

CCI