PEGCETACOPLAN (APL-2)

APL2-C3G-310

A PHASE 3, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLINDED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF PEGCETACOPLAN IN PATIENTS WITH C3 GLOMERULOPATHY OR IMMUNE-COMPLEX MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

Regulatory Agency Identifier Number(s) IND: 136409 EudraCT: 2020-003767-25	**Phase: 3**
	Version: Amendment 4
	Approval Date: 25 April 2024

SIGNATURE PAGE

Sponsor's Approval

The protocol has been approved by Apellis Pharmaceuticals, Inc.

Responsible Medical Director:

PPD

25-Apr-2024 | 14:12 EDT

Date

PPD

Medical Director, Nephrology
Apellis Pharmaceuticals, Inc
PPD

INVESTIGATOR'S AGREEMENT

I have read the Study APL2-C3G-310 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.

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Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Protocol Amendment 4

Overall Rationale for the Amendment:

The protocol was amended to revise the order of the key secondary endpoints in response to updated knowledge from the nephrology field. Intercurrent event (ICE) strategies for the statistical analysis of the endpoints were updated to align with comments from the FDA. The strategy for closing enrollment was clarified. Additional revisions were made to clarify study procedures and activities in response to feedback from investigators and/or to align with current company practices.

Minor formatting and stylistic revisions were made to align with current templates, and any identified typographical errors were corrected; these are not identified individually in the descriptions below.

Description of change	Section(s) affected	Rationale for change
Study endpoint changes		
Order of key secondary endpoints revised; change in eGFR at 26 weeks now the last key secondary endpoint	Synopsis Section 5.2.1 Section 12.3.2.1	Based on emerging data and recent expert discussions, histopathologic changes are expected to occur before improvements in eGFR are observed. The order of the key secondary endpoints was amended to prioritize the histopathologic endpoints over the eGFR endpoint.
Removed exploratory endpoint evaluating normalization of hematuria	Section 5.2.1	No post-baseline hematuria evaluations will be conducted.
Removed exploratory endpoint of evaluation of changes in drusen at 26 weeks	Section 5.2.1	If conducted, ophthalmologic evaluations are at baseline and between weeks 42 and 52 only.
Study assessment changes		
Revised description of the window for conducting the optional activities (ophthalmologic evaluations and measured GFR)	Schedule of Activities (Table 2), footnotes t and u Section 10.6 Section 10.7	Description revised to align with study visit schedule.
Safety reporting changes		
Moved definition of TEAEs and the period for recording and reporting TEAEs	Section 11.2.1.1 Section 11.2.2 Section 12.4	Moved so provided with other definitions related to safety reporting.
Statistical analysis changes		
Updated strategies for addressing ICEs	Section 12.3 and subsections	Updated to align with FDA comments.
Revised description of the data review for the analysis set	Section 12.2.7	Revised for clarity.

Description of change	Section(s) affected	Rationale for change
Clarified the analysis set for the evaluation of endpoints related to renal biopsy observations	Section 12.3.2	Revised for clarity.
Study conduct changes		
Added description of the activities at the closure of enrollment	Section 6.2	As the study was approaching target enrollment, the sponsor announced the planned closure of enrollment. Sites continued patient screening activities and all eligible participants were enrolled, resulting in a final enrollment of 124 participants. Added a description to clarify activities at the closure of enrollment.
Revised description of antidrug antibody assessments	Section 11.1.13	Revised to align with current Apellis practice.
Document organization changes		
Added an Appendix containing country-specific modifications to the protocol. Country-specific modifications are noted for Canada, Czech Republic, France, Germany, Netherlands, Israel, Japan, and Switzerland.	Appendix 2	Added to align with current Apellis practice.

1. SYNOPSIS

Name of Sponsor/Company:
Apellis Pharmaceuticals, Inc

Name of Active Substance:
Pegcetacoplan (APL-2)

Protocol Number: APL2-C3G-310

Title of Study:
A Phase 3, Randomized, Placebo-Controlled, Double-Blinded, Multicenter Study to Evaluate the Efficacy and Safety of Pegcetacoplan in Patients with C3 Glomerulopathy or Immune-Complex Membranoproliferative Glomerulonephritis

Objectives:

Primary:

To assess the efficacy of twice-weekly subcutaneous (SC) doses of pegcetacoplan compared with that of placebo in patients with primary C3 glomerulopathy (C3G) or immune-complex membranoproliferative glomerulonephritis (IC-MPGN) on the basis of a reduction in proteinuria.

Secondary:

- To assess the effect of pegcetacoplan on estimated glomerular filtration rate (eGFR)
- To assess the effect of pegcetacoplan on additional C3G/IC-MPGN disease–related parameters
- To evaluate the safety of pegcetacoplan over 52 weeks of treatment

Endpoints:

Primary:

The log-transformed ratio of uPCR at week 26 compared to baseline

Key Secondary Endpoints:

Key secondary endpoints (to be evaluated at week 26)

- The proportion of participants who meet the criteria for achieving a composite renal endpoint (a stable or improved eGFR compared to the baseline visit (≤15% reduction in eGFR), and a ≥50% reduction in uPCR compared to the baseline visit.)
- The proportion of participants with a reduction of at least 50% from baseline in uPCR
- For participants with evaluable renal biopsies, the change from baseline in the activity score of the C3G histologic index score
- The proportion of participants with evaluable renal biopsies showing decreases in C3c staining on renal biopsy from baseline
- Change from baseline in eGFR

Additional Secondary Endpoints (to be evaluated at week 26):

- The proportion of participants achieving proteinuria <1 g/day
- For participants with serum albumin levels below the lower limit of normal (LLN) at baseline, the proportion of participants with normalization of serum albumin levels
- For participants with serum C3 levels below the LLN at baseline, the proportion of participants with serum C3 levels above the LLN
- The change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue Scale score
- The change from baseline in Kidney Disease Quality of Life score

The primary, key secondary, and additional secondary endpoints will also be evaluated at week 52 as exploratory endpoints.

Safety Endpoints:

- Incidence and severity of treatment-emergent adverse events (TEAEs)
- Change from baseline in vital signs measurements, clinical laboratory tests, and electrocardiogram results
- Number and incidence of rejection episodes (posttransplant participants only)
- Number and incidence of graft loss (posttransplant participants only)
- Incidence of death, stratified by transplant history

Study Design:

Methodology:

This is a phase 3, randomized, placebo-controlled, double-blinded, multicenter study to evaluate the safety and efficacy of twice-weekly SC infusions of pegcetacoplan in patients diagnosed with primary C3G or IC-MPGN.

The planned duration of participation in the study for each participant is a maximum of approximately 70 weeks. The study will consist of 4 parts:

- Part 1: 10-week screening period
- Part 2: 26-week randomized controlled period (RCP)
- Part 3: 26-week open-label period
- Part 4: 8-week follow-up period (only for participants who do not roll into a long-term extension study)

Informed consent (and assent if applicable) will be obtained prior to the conduct of any study-related procedures.

<u>Part 1: Screening Period (10 Weeks)</u>

- Participants will be screened to confirm that eligibility criteria are met.
- One 24-hour urine sample and 3 sets of triplicate first-morning spot urine (FMU) samples (first-morning void collected on 3 consecutive days) will be collected to determine eligibility and establish a baseline uPCR.
- For adult participants, a renal biopsy will be performed to confirm diagnosis and eligibility and to serve as the baseline renal biopsy. A historic renal biopsy done within 28 weeks of randomization may be used for eligibility confirmation and serve as the baseline biopsy if it is confirmed as adequate by central pathology review. Biopsies will not be required for adolescent participants if they have an adequate previous renal biopsy to establish the diagnosis, even if the previous biopsy is more than 28 weeks prior to randomization.
- Retrospective data for a period of up to 3 years prior to study entry will be collected to calculate historical eGFR (using the Chronic Kidney Disease–Epidemiology Collaboration creatinine equation for adults and the Bedside Schwartz equation for adolescents).
- Vaccinations against *Streptococcus pneumoniae*, *Neisseria meningitidis* (types A, C, W, Y, and B), and *Haemophilus influenzae* (type B) are mandatory unless documented evidence exists that participants have received the recommended vaccinations or are nonresponders to vaccination. If required, vaccination series should be initiated at least 14 days prior to randomization.

<u>Part 2: Randomized Controlled Period (26 Weeks)</u>

Approximately 80 to 100 participants who meet all of the inclusion criteria and none of the exclusion criteria will be randomly assigned in a 1:1 ratio to either the pegcetacoplan treatment arm or the placebo treatment arm. To achieve balance between the arms, 2 stratification factors will be applied to the randomization. The first stratification factor examines participants with posttransplant recurrence versus nontransplant participants; the second stratification factor examines participants with baseline renal biopsies (either collected during screening or a historic biopsy collected within 28 weeks prior to randomization) versus participants without baseline renal biopsies.

- **Pegcetacoplan group:** Participants will receive SC pegcetacoplan twice weekly.
- **Placebo group**: Participants will receive SC placebo twice weekly.
- Every effort will be made to minimize changes to medications related to C3G/IC-MPGN disease.

- Triplicate first-morning spot urines will be collected at each visit, and an additional triplicate first-morning sample will be collected during week 25.
- Safety and efficacy will be assessed.
- At the end of the RCP, there will be a renal biopsy, which is required for adult participants to advance to the open-label period (Part 3). Participants younger than 18 years are not required to provide renal biopsies and may advance to the open-label period upon completion of all assessments for weeks 24 through 26 other than the renal biopsy.

Part 3: Open-Label Period (26 Weeks)

- All participants will be treated with pegcetacoplan twice weekly to assess durability of response and long-term safety and efficacy. Open-label dosing will begin at the first visit after the week 26 renal biopsy for adults and any adolescents providing renal biopsies. Open-label dosing for adolescents not providing renal biopsies should start at the week 26 visit.
- At the end of the open-label period, there will be an optional renal biopsy.

Part 4: Follow-up Period (8 Weeks)

- Participants who would benefit from continuing to receive pegcetacoplan, as per the investigator's opinion, may roll over into a long-term extension study after completion of the open-label period.
- Participants who do not enter a long-term extension study will discontinue pegcetacoplan treatment and complete the 8-week follow-up period.

Number of Participants (Planned) and Sample Size Justification:

Approximately 80 to 100 participants, including patients with disease in native kidney or post-transplant, will be randomized 1:1 to pegcetacoplan or placebo with 40 to 50 participants per arm.

Based on preliminary data from Study APL2-201, a reduction of 60% in uPCR in the pegcetacoplan group at week 26 is assumed vs a reduction of 20% in uPCR in the placebo arm, which corresponds to mean log ratio to baseline of −0.92 vs −0.22 respectively, and a standard deviation of 0.88 (on log-scale). Based on this assumption, a sample size of 70 participants in total provides at least 90% power at 1-sided significance level of 0.025. Considering a 10% attrition to account for potential missing assessments and impact by COVID-19, it is expected that at least 78 participants with native kidney disease should be enrolled.

A minimum of 63 participants with C3G in native kidneys will be enrolled, which is approximately 80% of the enrolled participants with native kidney disease.

Diagnosis:

Patients with a diagnosis of primary C3G or IC-MPGN, including those with posttransplant recurrence

Main Criteria for Inclusion:

Inclusion Criteria

1. Aged at least 18 years; where approved, adolescents (aged 12-17 years) weighing at least 30 kg may also be enrolled.
2. A diagnosis of primary C3G or IC-MPGN (with or without previous renal transplant).
3. Evidence of active renal disease, based on one or more of the following:
   a. In adults or adolescents with a baseline renal biopsy (either one collected during screening or a historic biopsy collected within 28 weeks prior to randomization), at least 2+ C3c staining on the baseline renal biopsy.
   b. In adolescents not providing a baseline renal biopsy, at least one of the following:
      – Plasma sC5b-9 level above the upper limit of normal during screening
      – Serum C3 below the LLN during screening
      – Presence of an active urine sediment during screening, as evidenced by hematuria with at least 5 red blood cells per high-power field and/or red blood cell casts on routine local or central microscopic analysis of urine
      – Presence of C3 nephritic factor within 6 months of screening, based on central laboratory results or medical history

4. No more than 50% global glomerulosclerosis or interstitial fibrosis on the baseline biopsy for adult participants or adolescent participants providing a baseline biopsy.
5. At least 1 g/day of proteinuria on a screening 24-hour urine collection and a uPCR of at least 1000 mg/g in at least 2 first-morning spot urine samples collected during screening.
6. eGFR ≥30 mL/min/1.73 m^2 calculated by the Chronic Kidney Disease–Epidemiology Collaboration creatinine equation for adults or the Bedside Schwartz equation for adolescents.
7. Stable regimen for C3G/IC-MPGN treatment, as described below:
    a. Angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, and/or sodium-glucose cotransporter-2 inhibitor therapy that is stable and optimized, in the opinion of the investigator, for at least 12 weeks prior to randomization
    b. Stable doses of other medications that can affect proteinuria (eg, steroids, mycophenolate mofetil, and/or other allowed immunosuppressants that the participant is receiving for treatment of C3G or IC-MPGN) for at least 12 weeks prior to randomization.
    c. If a participant is on prednisone (or other systemic corticosteroid) for C3G or IC-MPGN treatment, the dosage is stable and no higher than 20 mg/day (or equivalent dosage of a corticosteroid other than prednisone) for at least 12 weeks prior to randomization.
8. Have received vaccinations against *S pneumoniae*, *N meningitidis* (types A, C, W, Y, and B), and *H influenzae* (type B) as per ACIP recommendations for adults or children with complement deficiencies. Vaccination series should be initiated at least 14 days prior to randomization. Vaccination is mandatory unless documented evidence exists that participants are nonresponders to vaccination.
9. Female participants of childbearing potential, defined as any women who have experienced menarche and who are not permanently sterile or postmenopausal, must have negative blood pregnancy tests at screening (and negative urine pregnancy tests on day 1) and must agree to use protocol-defined methods of contraception from screening through at least 90 days after receiving the last dose of pegcetacoplan.
10. Male participants must agree to use protocol-defined methods of contraception and agree to refrain from donating semen from screening through at least 90 days after receiving the last dose of pegcetacoplan.
11. Participants above the legal age of consent, in accordance with local regulations, must be willing and able to provide informed consent. The legally authorized representative of participants under the legal age of consent must be willing and able to provide informed consent; where appropriate, participants under the legal age of consent must also give their assent to participation in the study.
12. Willing and able to self-administer pegcetacoplan or have an identified caregiver who can perform the administration.

Exclusion Criteria

1. Previous exposure to pegcetacoplan.
2. Evidence of improving renal disease in the 8 weeks prior to screening or during the screening period according to available data; improving renal disease is defined as >30% increase in eGFR or >50% decrease in proteinuria.
3. From a renal transplant participant, evidence of rejection that requires treatment in the baseline renal biopsy collected during screening.
4. C3G/IC-MPGN secondary to another condition (eg, infection, malignancy, monoclonal gammopathy, a systemic autoimmune disease such as systemic lupus erythematosus, chronic antibody-mediated rejection, or a medication), in the opinion of the investigator.
5. Current or prior diagnosis of HIV, hepatitis B, or hepatitis C infection or positive serology during screening that is indicative of infection with any of these viruses.
6. Body weight greater than 100 kg at screening.
7. Hypersensitivity to pegcetacoplan or to any of the excipients.
8. History of meningococcal disease.
9. 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

10. Severe infection (eg, requiring IV antibiotic therapy) within 14 days prior to the first dose of pegcetacoplan.
11. An absolute neutrophil count <1000 cells/mm^3 at screening.
12. Significant other renal disease that would, in the opinion of the investigator, confound interpretation of study results.
13. 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 investigational agent (whichever is longer) prior to screening period.
14. Use of rituximab, belimumab, or any approved or investigational anticomplement therapy other than pegcetacoplan within 5 half-lives of that product prior to the screening period.
15. Female participants who are pregnant or who are currently breastfeeding and are unwilling to discontinue for the duration of the study and for at least 90 days after the final dose of study drug.
16. Inability to cooperate or any condition that, in the opinion of the investigator, creates an undue risk for the participant by participating in the study or is likely to confound interpretation of the study results.
17. Evidence of ongoing drug or alcohol abuse or dependence, in the opinion of the investigator.
18. Presence or suspicion of severe infection during the screening period (including but not limited to recurrent or chronic infections) that, in the opinion of the investigator, may place the participant at unacceptable risk by study participation.
19. Known or suspected hereditary fructose intolerance.

Investigational Product, Dosage and Mode of Administration:

Pegcetacoplan will be provided as a sterile solution in single-use glass vials. Each vial contains an isotonic sterile solution of pegcetacoplan 1080 mg/20 mL (54 mg/mL) in 10 mM acetate buffer, pH 5.0, containing 4.1% sorbitol. Placebo will be provided as a sterile solution of 10 mM acetate buffer, pH 5.0, containing 4.1% sorbitol supplied in single-use glass vials.

All participants will receive SC infusions of pegcetacoplan or matching volumes of placebo twice weekly. All adult participants (regardless of weight), and adolescent participants who weigh at least 50 kg, will receive 20-mL SC infusions. Adolescent participants who weigh at least 35 kg but less than 50 kg will receive a reduced infusion volume (12 mL for the first infusion and 15 mL for each infusion thereafter). Adolescent participants who weigh at least 30 kg but less than 35 kg will receive a further reduced infusion volume (10 mL for the first 2 infusions and 12 mL twice weekly thereafter), as presented below. Study drug will be self-administered by the participant or administered by their caregiver, after receiving appropriate training and sign-off by a research nurse or other qualified personnel in their first treatment week.

Planned Dosing Regimens

Weight	First dose (infusion volume)	Second dose (infusion volume)	Maintenance dose (infusion volume)
All adult participants, adolescent participants ≥50 kg	1080 mg (20 mL)	1080 mg (20 mL)	1080 mg twice weekly (20 mL)
Adolescent participants 35 to <50 kg	648 mg (12 mL)	810 mg (15 mL)	810 mg twice weekly (15 mL)
Adolescent participants 30 to <35 kg	540 mg (10 mL)	540 mg (10 mL)	648 mg twice weekly (12 mL)

Duration of Participation:

Total participation will be 70 weeks (screening: 10 weeks; RCP: 26 weeks; open-label period: 26 weeks; follow-up: 8 weeks). Depending on treatment assignment, treatment with pegcetacoplan will be for a maximum of 52 weeks (RCP: 26 weeks; open-label period: 26 weeks).

Statistical Methodology:

Efficacy:

Primary Efficacy:

The targeted treatment regimen to be used for this study is pegcetacoplan or placebo plus stable regimen for C3G/IC-MPGN treatment. The primary estimand on the treatment effect of pegcetacoplan is for the participant population as defined through the study inclusion/exclusion criteria, with the primary endpoint based on the log-transformed ratio of uPCR (sampled from first-morning urine collections) at week 26 compared to baseline using an equal-weighted average over weeks 24, 25, and 26. Intercurrent events (ICEs) will be addressed as defined in Table 8.

The primary endpoint will be analyzed using a mixed effect model for repeated measures (MMRM). The model will include fixed categorical effects for treatment group, visit, stratification factors, disease type (C3G vs IC-MPGN), and the visit-by-treatment group interaction, as well as the continuous, fixed covariate of baseline log-transformed uPCR. Initially, an unstructured covariance matrix will be investigated. If this analysis fails to converge, other covariance structures will be used; details will be provided in the statistical analysis plan. The difference between treatment groups will be estimated with its 95% CI and corresponding *P* value.

Key Secondary Efficacy:

To preserve the overall type I error among the primary endpoint and key and additional secondary endpoints, a fixed-sequence testing strategy will be used; hence, statistical significance of the first secondary endpoint will be evaluated only if statistical significance is achieved with the primary analysis of the primary endpoint. The remaining secondary endpoints will also adhere to this testing strategy, and their order will match the order in which they are presented in Section 5.2.1.

- The numbers and proportion of participants who meet the criteria for achieving a composite renal endpoint at week 26 will be tabulated by treatment group and analyzed using a logistic regression model with treatment group as the independent variable and adjusted for baseline eGFR values, baseline log-transformed uPCR values, disease type, and stratification factors. The *P* value and odds ratio of being a responder for the pegcetacoplan group to being a responder for the placebo group and associated 95% CI will be provided.
- The numbers and proportion of participants who achieve uPCR response at week 26 (defined as a reduction from baseline in uPCR of at least 50% sampled from triplicate first-morning urine collections) will be tabulated by treatment group and compared using a logistic regression model similar to that for the composite renal endpoint. The odds ratio of being a responder for the pegcetacoplan group to being a responder for the placebo group with associated 95% CI and *P* value will be provided.
- For participants with evaluable renal biopsies, evaluation of the change from baseline to week 26 in the activity score in the C3G histologic index will use analysis of covariance (ANCOVA) model with treatment as a fixed effect, adjusted for baseline C3G histologic index activity score, disease type, and stratification factors. *P* value and least-square (LS) means will be presented for each treatment group, along with the between-treatment difference and 95% confidence interval.
- For participants with evaluable renal biopsies, the numbers and proportion of participants showing decreases in C3c staining on renal biopsy from baseline to week 26 will be tabulated by treatment group and compared using a logistic regression model similar to that for the composite renal endpoint. The odds ratio of being a responder for the pegcetacoplan group to being a responder for the placebo group and associated 95% CI and *P* value will be provided.
- Change from baseline in eGFR at week 26 will be analyzed using a MMRM model similar to that for the primary endpoint. The difference between treatment groups will be estimated with its 95% CI and corresponding *P* value.

Safety:

Adverse events (AEs) will be coded using the current version of the Medical Dictionary for Drug Regulatory Activities. TEAEs will be summarized by System Organ Class, Preferred Term, and treatment group for the number of participants and proportion reporting the event. A similar summary will be produced for serious adverse events, AEs leading to termination of study drug, severe AEs, and AEs related to the investigational product. The intensity of AEs and the relationship to investigational product will be summarized for each System Organ Class and Preferred Term by treatment group.

AEs leading to withdrawal will be summarized for each body system and Preferred Term by treatment group.

Laboratory assessments, antidrug antibody results, chest radiography, and electrocardiogram results will be summarized by treatment group using appropriate descriptive statistics.

Interim Analyses:

No interim analyses are planned.

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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
AP	alternative pathway
C3G	C3 glomerulopathy
C3GN	C3 glomerulonephritis
CH50	50% classical hemolytic complement pathway activity
CKD-EPI	Chronic Kidney Disease–Epidemiology Collaboration
CRF	case report form
DDD	dense deposit disease
DMC	data monitoring committee
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy–Fatigue
FDA	Food and Drug Administration
FMU	first-morning spot urine
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HHCP	home health care provider
HRQoL	health-related quality of life
IB	investigator's brochure
IC-MPGN	immune-complex membranoproliferative glomerulonephritis
ICE	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IND	Investigational New Drug
IRB	institutional review board
ITT	intent-to-treat
KDQOL	Kidney Disease Quality of Life

Abbreviation	Definition
LLN	lower limit of normal
MAR	missing at random
MMRM	mixed effect model for repeated measures
PD	pharmacodynamic
PEG	polyethylene glycol
PK	pharmacokinetic
PNH	paroxysmal nocturnal hemoglobinuria
PP	per-protocol
RCP	randomized controlled period
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD-OCT	spectral domain optical coherence tomography
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
uACR	urine albumin-to-creatinine ratio
uBCR	urinary β2-microglobulin–to-creatinine ratio
uPCR	urine protein-to-creatinine ratio
WOCBP	women of childbearing potential
WPAI	Work Productivity and Activity Impairment

4. INTRODUCTION

Two similar diseases, C3 glomerulopathy (C3G) and immune-complex membranoproliferative glomerulonephritis (IC-MPGN), will be studied in this protocol. This study will include patients with native kidney disease or with posttransplant disease recurrence and will exclude patients whose C3G or IC-MPGN is secondary to an underlying condition (eg, infection, monoclonal gammopathy, malignancy, or medication).

4.1. C3G and IC-MPGN and Unmet Medical Need

C3G 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). AP hyperactivity leads to uncontrolled C3 activation, resulting in an excess of C3 breakdown products that are deposited in the glomerular basement membrane and mesangium. This stimulates a brisk inflammatory response, disrupting the normal glomerular architecture.

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, but with some distinctions. 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 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.

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 steadily progress to end-stage renal disease (ESRD) (Smith et al. 2019; Regunathan-Shenk et al. 2019; 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 because of 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 is an unmet need.

As an inhibitor of C3 and its fragment, C3b, pegcetacoplan 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 in addition to the inhibition of C3 as a substrate in the complement cascade. These 2 complementary mechanisms are expected to 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 a reduction in proteinuria, and ultimately, to result in prolonged renal survival. Therefore, pegcetacoplan is a potentially life-altering therapy for C3G and IC-MPGN.

4.2.1. Justification of Study Population

Based on the mechanism of action of pegcetacoplan, Apellis aims to study patients with glomerular disease driven by complement over-activation and as such, will include patients with either C3G or IC-MPGN, as both are characterized by complement dysregulation leading to excessive deposition of C3 breakdown products in glomeruli (Iatropoulos et al. 2018; Cook 2018; Servais et al. 2012). Because the same underlying pathophysiology of complement dysregulation that leads to C3G/IC-MPGN in the native kidney also leads to disease recurrence posttransplant, and the clinical course for both is characterized by significant proteinuria and risk of progression to ESRD, the trial includes patients with posttransplant disease recurrence, in addition to nontransplant patients. Finally, the trial includes adolescents (ages 12–17), as the disease features in adolescents are similar to those of adults.

4.2.2. Justification of Study Design

A randomized, placebo-controlled, double-blinded trial design was selected in order to evaluate the treatment effect of pegcetacoplan on proteinuria and renal function in patients with C3G or IC-MPGN in a robust and minimally biased fashion. The placebo control enables identification of potential study effects that are not related to the study drug and provides data on the course of the disease in the absence of study treatment. Given that participants must have had stable or worsening disease for the preceding 3 months prior to study entry, a spontaneous disease remission is unlikely to occur during the study. However, participants may have improved (or worsened) compliance with nonstudy medications related to study participation. These types of study effects are expected to occur in the first 2 to 3 months of the study, so any placebo-related effect should be evident and stable by week 26.

To minimize unnecessary exposure for participants to placebo infusions, the study will include a 26-week placebo-controlled period, after which the placebo group will be transitioned to pegcetacoplan treatment. In this way, all participants will have the opportunity to receive pegcetacoplan in a reasonable time frame while still establishing the placebo response rate.

4.2.3. Justification of Dose

The dosing regimen for adults will be 1080 mg administered subcutaneously (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 phase 3 studies in patients with paroxysmal nocturnal hemoglobinuria (PNH), Study APL2-302 and Study APL2-308, in which pegcetacoplan has been generally safe and well tolerated.

The dosing regimens for adolescents are intended to yield similar exposures as 1080 mg twice weekly in adults. Modeling-based simulations were performed for adolescents on the basis of an adult population 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 adult PNH patients). The results of these model analyses were used to select the dosing regimens for adolescents, as summarized below:

- In adolescents aged 12 to 17 years with body weights of at least 50 kg, a dose regimen of 1080 mg twice weekly is expected to result in exposure similar to that seen in adults at the same dosage.
- In adolescents aged 12 to 17 years with body weights of 35 to 49 kg, a 648-mg initial dose followed by 810 mg twice weekly is anticipated to result in exposures at weeks 1, 2, and 16 (steady-state) that are similar to those of the adult dosage of 1080 mg twice weekly.
- In adolescents aged 12 to 17 years with body weights of 30 to 34 kg, the first 2 doses will be 540 mg, and following doses will be 648 mg twice weekly. This regimen is anticipated to result in exposures at weeks 1, 2, and 16 (steady-state) that are similar to those of the adult dosage of 1080 mg twice weekly.

Modeling of exposure in high body weight participants (those weighing >100 kg) results in predicted exposures at least 15% lower than those for a reference 70-kg participant; participants with body weights of >100 kg will therefore be excluded from the study.

4.3. Summary of Clinical Experience With Pegcetacoplan

Pegcetacoplan is being studied in APL2-201, an ongoing phase 2 study that includes patients with 1 of 4 glomerular diseases: C3G, immunoglobulin (Ig) A nephropathy, primary membranous nephropathy, or lupus nephritis. Preliminary data from the 8 C3G participants 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 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 is effective in providing broad control of intravascular and extravascular hemolysis, as evidenced by the following: increased and stable hemoglobin levels, normalization of lactate dehydrogenase levels, 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/d and 1080 mg twice weekly has been generally well tolerated when administered via SC infusion, including to patients with C3G and other glomerular diseases.

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, pharmacokinetic (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 SC pegcetacoplan administration has been studied in multiple phase 2 and 3 studies for C3G, PNH, and autoimmune hemolytic anemia, with an acceptable safety profile to date. Nonetheless, a number of safety monitoring practices are being employed by this protocol to ensure participant safety, including physical examination, vital signs monitoring, electrocardiograms (ECGs), hematology (including coagulation), serum chemistry, 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 recorded as an AE (see Section 11.2.2). The volume of blood planned for collection from each participant over the course of the study will be minimized to limit the impact on the overall health of these anemic participants.

Systemic complement inhibition might predispose individuals to infections caused by encapsulated organisms, including *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*. Vaccinations against these organisms according to the most current Advisory Committee on Immunization Practices (ACIP) recommendations for patients with complement deficiencies will be required to minimize potential risk of infection. Vaccinations will be initiated at least 14 days prior to receiving the first dose of pegcetacoplan; therefore, prophylactic antibiotic use is not required. Body temperature and vital signs will be monitored periodically, and relevant blood parameters monitored regularly throughout the study to assess for signs of infection. Participants will be counseled regarding this potential risk for infection and given a participant 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.

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 participant-by-participant basis.

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

- Collection of AEs or serious adverse events (SAEs) should be done over the phone and documented in the source documents.
- A minimized schedule of activities is presented in Table A1 of Appendix 3.
- Any activities not performed because of COVID-19–related restrictions will be identified in the participant source document.
- Any change in COVID-19 status (serology or antigen), if available, will be captured in the participant's source document.
- Where applicable, relevant study documentation will be updated and communicated to health authorities and/or institutional review boards (IRBs) or 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 participant, 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 more detail Appendix 3.

5. STUDY OBJECTIVES AND ENDPOINTS

5.1. Study Objectives

5.1.1. Primary Objective

The primary objective of this study is to assess the efficacy of twice-weekly SC doses of pegcetacoplan compared with that of placebo in patients with primary C3G or IC-MPGN on the basis of a reduction in proteinuria.

5.1.2. Secondary Objectives

The secondary objectives of the study are as follows:

- To assess the effect of pegcetacoplan on estimated glomerular filtration rate (eGFR)
- To assess the effect of pegcetacoplan on additional C3G/IC-MPGN disease–related parameters
- To evaluate the safety of pegcetacoplan over 52 weeks of treatment

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.

5.2. Study Endpoints

5.2.1. Efficacy Endpoints

Table 1 lists the efficacy endpoints and the time points at which they will be evaluated. The primary and secondary endpoints will be evaluated at week 26. The primary and secondary endpoints will also be evaluated at week 52 as exploratory endpoints. The table also lists additional exploratory endpoints which will be evaluated at both week 26 and week 52.

Table 1: Efficacy Endpoints

Study endpoints	Week 26	Week 52
Primary efficacy endpoint		
The log-transformed ratio of uPCR at week 26 compared to baseline	X	
Key secondary efficacy endpoints		
The proportion of participants who meet the criteria for achieving a composite renal endpoint (a stable or improved eGFR compared to the baseline visit (≤15% reduction in eGFR), and a ≥50% reduction in uPCR compared to the baseline visit.)	X	
The proportion of participants with a reduction of at least 50% from baseline in uPCR	X	
For participants with evaluable renal biopsies, the change from baseline in the activity score of the C3G histologic index score (Bomback et al. 2018)	X	
The proportion of participants with evaluable renal biopsies showing decreases in C3c staining on renal biopsy from baseline	X	
Change from baseline in eGFR	X	
Additional secondary efficacy endpoints		
The proportion of participants achieving proteinuria <1 g/day	X	
For participants with serum albumin levels below the LLN at baseline, the proportion of participants with normalization of serum albumin levels	X	
For participants with serum C3 levels below the LLN at baseline, the proportion of participants with serum C3 levels above the LLN	X	
The change from baseline in the FACIT-Fatigue Scale score	X	
The change from baseline in the KDQOL score	X	
Exploratory efficacy endpoints		
The log-transformed ratio of uPCR at week 52 compared to baseline		X
The proportion of participants who meet the criteria for achieving a composite renal endpoint		X
The proportion of participants with a reduction from baseline in uPCR of at least 50%		X
Change from baseline in eGFR		X
For participants with evaluable renal biopsies, the change from baseline in the activity score of the C3G histologic index (Bomback et al. 2018)		X
The proportion of participants with evaluable renal biopsies showing decreases in C3c staining on renal biopsy from baseline		X
The proportion of participants achieving proteinuria <1 g/day		X
For participants with serum albumin levels below the LLN at baseline, the proportion of participants with normalization of serum albumin levels		X
For participants with serum C3 levels below the LLN at baseline, the proportion of participants with serum C3 levels above the LLN		X
The change from baseline in the FACIT-Fatigue Scale score		X
The change from baseline in the KDQOL score		X
The change from baseline in uPCR using the 24-hour urine collections	X[1]	X[1]
The annual rate of change from up to 3 years prior to screening in eGFR	X	X

Table 1: Efficacy Endpoints

Study endpoints	Week 26	Week 52
The proportion of participants with reductions from baseline in proteinuria of at least 30%	X	X
The proportion of participants with normalization of proteinuria	X	X
The time to 50% reduction in uPCR with a stable or improved eGFR	n/a	n/a
The time to normalization for the following parameters for participants in whom the parameter is abnormal at baseline: • serum C3 • uPCR • serum albumin • blood pressure	n/a	n/a
The change in glomerular macrophage count, as determined by CD68 staining	X	X
The change from baseline in PGIC score	X	X
The change from baseline in EQ-5D-5L score	X	X
The change from baseline in WPAI score	X	X
Change in drusen from baseline: • change in maximum drusen size • change in number of intermediate or large drusen		X

Abbreviations: C3G = C3 glomerulopathy; eGFR = estimated glomerular filtration rate; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy–Fatigue; KDQOL = Kidney Disease Quality of Life; LLN = lower limit of normal; PEG = polyethylene glycol; PGIC = Patient Global Impression of Change; uPCR = urine protein-to-creatinine ratio; WPAI = Work Productivity and Activity Impairment.
1. 24-hour urine collections are at week 24 and week 48.

5.2.2. Safety Endpoints

The safety endpoints are as follows:

- The incidence and severity of treatment-emergent adverse events (TEAEs)
- The change from baseline in:
  - vital signs measurements
  - clinical laboratory tests
  - ECG results
- The number and incidence of rejection episodes (posttransplant participants only)
- The number and incidence of graft loss (posttransplant participants only)
- The incidence of death, stratified by transplant history

5.2.3. Pharmacokinetic, Pharmacodynamic, and Immunogenicity Endpoints

The PK endpoint is:

- Pegcetacoplan serum concentrations over time

The pharmacodynamic (PD) endpoints are:

- Changes from baseline in complement levels at week 26 and week 52:
  - CH50 (50% classical hemolytic complement pathway activity)
  - AH50 (50% alternative hemolytic complement pathway activity)
  - sC5b-9

Additional complement components may be measured, as noted in Table 4 and Section 11.1.11, and evaluated as exploratory endpoints.

The immunogenicity endpoint is:

- The incidence of antidrug antibodies (ie, antibodies against the peptide and polyethylene glycol [PEG] domains of pegcetacoplan)

6. INVESTIGATIONAL PLAN

This phase 3 randomized, placebo-controlled, double-blinded, multicenter clinical study is designed to evaluate the safety and efficacy of twice-weekly SC infusions of pegcetacoplan in patients with primary C3G or IC-MPGN. There will be approximately 80 to 100 participants enrolled in this study, at least 78 of whom will have native kidney disease and up to 22 of whom may have posttransplant recurrence of C3G or IC-MPGN. At least 63 participants with C3G in native kidney will be enrolled. The enrollment of participants with C3G or IC-MPGN will be monitored to ensure balance between the groups. At least 10 adolescent participants (aged 12-17 years) will be enrolled; adolescent participants may be either patients with native kidney disease or posttransplant disease recurrence. Participants initially screened as adolescents will follow adolescent procedures and requirements through the duration of their participation in study, even if they pass their 18th birthday while enrolled in the study.

The planned length of participation in the study for each participant is a maximum of approximately 70 weeks. This study will consist of 4 parts:

- Part 1: 10-week screening period
- Part 2: 26-week randomized controlled period (RCP)
- Part 3: 26-week open-label period
- Part 4: 8-week follow-up period (only for participants who do not roll into a long-term extension study)

Informed consent (and assent, when applicable) will be obtained prior to any study-related procedures being conducted. The screening period will start once informed consent has been obtained.

See Figure 1 for the study schematic, and Table 2 for the schedule of activities.

6.1. Overall Study Design

This is a placebo-controlled, double-blinded, phase 3 study in patients with clinical and pathologic evidence of primary C3G or IC-MPGN. Participants will be randomly assigned 1:1 to either the pegcetacoplan group (pegcetacoplan treatment throughout the RCP and open-label period) or the placebo group (placebo treatment during the RCP and pegcetacoplan treatment during the open-label period). The visit schedule will be the same, regardless of randomization.

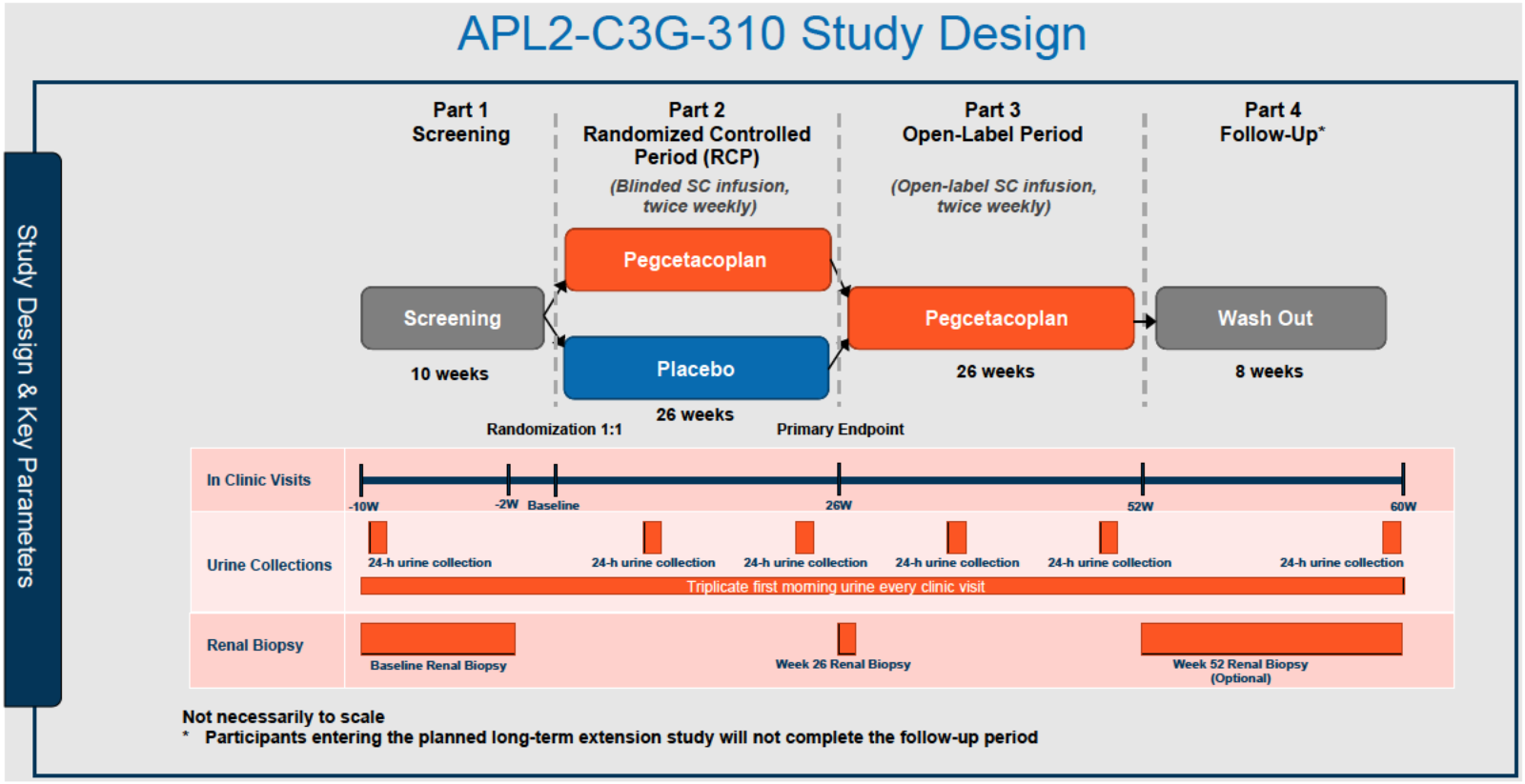
The study includes renal biopsies, one during screening and a second at the end of the RCP (week 26). An optional third biopsy may be collected at the end of the open-label period (week 52). The biopsy requirements are discussed in Section 10.5, including additional information on biopsies for participants under the age of 18.

After completion of the RCP and open-label period, any participant who, in the opinion of the investigator, is experiencing clinical benefit from pegcetacoplan administration will be invited to participate in a planned long-term extension study to continue to receive treatment with pegcetacoplan until it is commercially available for the treatment of C3G and/or IC-MPGN and accessible in their countries, or the development program for C3G and/or IC-MPGN is terminated, in compliance with all applicable national and local laws and regulations.

Participants who do not continue on pegcetacoplan in a planned long-term extension study will enter the 8-week follow-up period of this study.

See Figure 1 for the study schematic.

Figure 1: Study APL2-C3G-310 Design



Abbreviations: SC = subcutaneous; uPCR = urine protein-to-creatinine ratio; W = week.

6.1.1. Part 1: Screening Period (10 Weeks)

Participants will be screened to confirm that the selection criteria for the study have been met. The screening period will occur in 2 stages, and all assessments described in the schedule of activities (Table 2) at screening visit 1 should occur before those in screening visit 2. This ensures that the more invasive procedures (vaccinations and renal biopsy) do not occur unless the participants meet all other eligibility criteria.

- One 24-hour urine sample and 3 sets of triplicate first-morning spot urine (FMU) samples (first-morning void collected on 3 consecutive days) will be collected to determine eligibility and establish a baseline uPCR. Collection of urine samples is discussed in more detail in Section 10.2 and Section 10.3. Calculation of baseline uPCR is discussed in Section 12.3.1 and Section 12.3.2.
- For adult participants, a renal biopsy will be performed to confirm diagnosis and eligibility and to serve as the baseline renal biopsy. The baseline renal biopsy may be conducted at any time during screening once eligibility is confirmed by the assessments from screening visit 1. All biopsies will be evaluated by the central pathology laboratory. Renal biopsies are discussed in more detail in Section 10.5.
    - A historic renal biopsy done within 28 weeks of randomization may be used for eligibility confirmation and serve as the baseline biopsy if it is confirmed as adequate by the central pathology laboratory on the basis of review of the biopsy report as well as slides and/or images.
    - Participants under the age of 18 are not required to provide a biopsy if they have an adequate previous renal biopsy to establish the diagnosis, even if the previous biopsy is more than 28 weeks prior to randomization.
- Retrospective data for a period of up to 3 years prior to study entry will be collected to calculate historical eGFR using the Chronic Kidney Disease–Epidemiology Collaboration [CKD-EPI] creatinine equation for adults and the Bedside Schwartz equation (eGFR = 0.413 × [height (in centimeters)] / serum creatinine) for adolescents. Retrospective data for eGFR are discussed in more detail in Section 10.1.
- The participant's medical history and screening data will be reviewed by the investigator, in collaboration with the medical monitor, to confirm the diagnosis of primary C3G or IC-MPGN. The investigator and medical monitor will consider all available historical, laboratory, and pathology data. For an adolescent in whom a renal biopsy within 28 weeks of day 1 is not available, the investigator and medical monitor will consider alternative evidence for active renal disease as described in Section 7.1.
- Vaccinations against *S pneumoniae*, *N meningitidis* (types A, C, W, Y, and B), and *H influenzae* (type B) are mandatory unless documented evidence exists that participants are nonresponders to vaccination. If required, vaccination series should be initiated at least 14 days prior to randomization. Vaccinations are discussed in more detail in Section 8.2.

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 until such time that they meet inclusion requirements and are able to be enrolled. In this case, additional screening visits and/or repeat screening assessments may be conducted, as needed, to establish eligibility. The medical monitor will contact the investigator to identify screening activities related to the confirmation of participant eligibility that must be repeated.

6.1.1.1. Rescreening

In the event that rescreening occurs and the participant has not remained in the screening period (ie, is a screening failure), the individual is required to reconsent and must be assigned a new identification number. For rescreened participants, the historic biopsy (within 28 weeks before randomization), chest radiography, vaccination, ophthalmologic evaluations, and measured GFR in the previous screening period may be considered as validated testing for rescreening.

6.1.2. Part 2: Randomized Controlled Period (26 Weeks)

Approximately 80 to 100 participants who meet all of the inclusion criteria and none of the exclusion criteria will be randomly assigned in a 1:1 ratio to receive either pegcetacoplan or placebo. Randomization will be performed as described in Section 8.5.1.

- **Pegcetacoplan group**: Participants will receive SC pegcetacoplan twice weekly.
- **Placebo group**: Participants will receive SC placebo infusions twice weekly.
- Every effort will be made in both groups to minimize changes to medications related to C3G/IC-MPGN disease.
- Triplicate FMU samples will be collected at each visit, and an additional triplicate FMU uPCR sample will be collected during week 25.
- Safety and efficacy will be assessed.
- At the end of the RCP, there will be a renal biopsy, which is required for participants aged 18 years and older to advance to the open-label period (Part 3). Participants younger than 18 years are not required to provide renal biopsies and may advance to the open-label period upon completion of all assessments for weeks 24 through 26 other than the renal biopsy. Biopsy requirements are discussed in more detail in Section 10.5.

6.1.3. Part 3: Open-Label Period (26 Weeks)

At the end of the RCP, participants from both groups will proceed to the 26-week open-label period, in which all participants will be treated with pegcetacoplan twice weekly. Open-label dosing will begin at the first visit after the week 26 renal biopsy for adults and any adolescents providing renal biopsies. Open-label dosing for adolescents not providing renal biopsies should start at the week 26 visit. At the end of the open-label period, there will be an optional renal biopsy. Participants younger than 18 years who did not have a baseline biopsy within 28 weeks of day 1 will not have a biopsy at the end of the open-label period. Upon completion of the open-label period, participants will enter the follow-up period (Part 4) unless they enter a long-term extension study.

6.1.4. Part 4: Follow-up Period (8 Weeks)

After completion of the open-label period, participants who would benefit from continuing to receive pegcetacoplan, in the investigator's opinion, may roll over into a long-term extension study. Participants who do not enter a long-term extension study will discontinue pegcetacoplan treatment and complete the 8-week follow-up period. In addition, any participant who discontinues study drug during the RCP or open-label period should complete follow-up activities, as described in Section 7.3.1.

Table 2: Schedule of Activities

Study period	Screening period[a]		Randomized controlled period								Open-label period						Follow-up period		
Study week	**–10 to –4**	**–2**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**42**	**48**	**52**	**54**	**56**	**60 Exit**
Study day	**–70**	**–14**	**1**	**28**	**56**	**84**	**112**	**140**	**168**	**182**	**196**	**224**	**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[b]**		**0**	**3**	**7**	**7**	**7**	**7**	**3**	**3**	**3**	**7**	**7**	**7**	**7**	**7**	**3**	**3**	**7**
Assessments																			
Informed consent	X																		
Demographics	X																		
Medical history	X																		
Post-transplant immunosuppression plan documentation[c]		X																	
Inclusion/exclusion	X	X	X																
Vaccination[d]		X[b]				X													
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination (full)[e]	X		X							X[e]						X			
Physical examination (brief)[e]		X		X	X	X	X	X	X		X[e]	X	X	X	X		X	X	X
12-lead ECG	X		X		X		X		X	X	X		X		X	X	X		X
Chest radiography		X[b]								X						X			
Renal biopsy[f]	X[b]									X[g]						X[h]			
Randomization			X																
Study drug administration[i]			X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Infusion site/pump safety assessment[j]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Vital sign measurements[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HRQoL[l]		X								X						X			

Table 2: Schedule of Activities

Study period	Screening period[a]		Randomized controlled period								Open-label period						Follow-up period		
Study week	**–10 to –4**	**–2**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**42**	**48**	**52**	**54**	**56**	**60 Exit**
Study day	**–70**	**–14**	**1**	**28**	**56**	**84**	**112**	**140**	**168**	**182**	**196**	**224**	**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[b]**		**0**	**3**	**7**	**7**	**7**	**7**	**3**	**3**	**3**	**7**	**7**	**7**	**7**	**7**	**3**	**3**	**7**
Urine																			
24-hour urine collection[m]	X					X			X				X		X				X
Triplicate FMU uPCR[n]	X	X	X[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
In-clinic (random) uPCR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis (dipstick & microscopic)[p]	X																		
Urine pregnancy test		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood																			
Hematology[p] & chemistry[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK sample collection			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ADA assays[q]			X	X			X		X				X			X	X		X
Serum complement profile[p]	X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X
Plasma complement profile[p]	X		X		X		X		X	X	X		X		X	X	X		X
eGFR[r]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy (β-HCG)	X																		
Screening assays[s]	X																		
Optional assessments																			
Ophthalmologic evaluations[t]		X[t]												X[t]					
Measured GFR[u]			X[u]							X[u]				X[u]					

Table 2: Schedule of Activities

Abbreviations: Ab = antibodies; ADA = antidrug antibodies; AE = adverse events; AH50 = 50% alternative hemolytic complement pathway activity; ANA = antinuclear antibodies; ANCA = antineutrophil cytoplasmic antibodies; β-HCG = beta human chorionic gonadotropin; CH50 = 50% classical hemolytic complement pathway activity; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EQ-5D-5L = 5-Level EuroQol-5 Dimension; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy–Fatigue Scale; FMU = first-morning spot urine; FSH = follicle-stimulating hormone; GFR = glomerular filtration rate; HIV = human immunodeficiency virus; HRQoL = health-related quality of life; KDQOL = Kidney Disease Quality of Life; N/A = not applicable; PGIC = Patient Global Impression of Change; PK = pharmacokinetic; SC = subcutaneous; SD-OCT = spectral domain optical coherence tomography; SPEP = serum protein electrophoresis; uPCR = urine protein-to-creatinine ratio; WPAI = Work Productivity and Activity Impairment.

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

a. All visit 2 assessments need not occur in a single visit and visit 2 can be split into multiple visits (eg, visit 2a, visit 2b).
b. Vaccinations, baseline renal biopsy, and screening chest radiography can occur any time during screening after confirmation of eligibility based on visit 1 data.
c. For transplant participants only. Must be documented prior to assignment to study treatment.
d. Vaccine series should be initiated at least 14 days prior to randomization; additional vaccines may be required at visit 6. Please see Section 8.2 for more details on vaccination requirements. Vaccination serum samples will be collected on the day of vaccination before receiving vaccinations on that visit. These samples will be analyzed to evaluate response to vaccinations in the event that the participant has a positive infection for *Streptococcus pneumoniae*, *Neisseria meningitidis*, or *Haemophilus influenzae*.
e. A full physical examination is required at visits 1, 3 (week 1), 10 (week 26), and 16 (week 52). A full physical examination should also be conducted on the first day of open-label dosing, if that is not at the week 26 visit. Brief physical examinations, including weight (kg) and assessment of edema, will be conducted at all other visits noted. A symptom-driven physical examination may be performed at any time, at the investigator's discretion. Body height (cm) will be measured only during screening for adults but will be measured at screening and every 12 weeks throughout the study for adolescents; weight (kg) will be measured throughout study, during brief and full physical examinations for all participants. Both body weight and height will be assessed without shoes on; height will be measured using a calibrated stadiometer. Edema should be assessed at every visit.
f. Renal biopsies will not be required for participants younger than 18 years provided that they have adequate previous renal biopsies to establish the diagnosis as per the central pathology laboratory.
g. The week 26 renal biopsy need not occur on the same day as all other assessments for that visit. However, the week 26 triplicate FMU uPCR collections must occur before the renal biopsy. In addition, the week 26 biopsy must occur before the first visit of the open-label period at week 28. Participants younger than 18 years are not required to provide renal biopsies and may advance to the open-label period upon completion of all assessments for weeks 24 through 26 other than the renal biopsy.
h. The week 52 renal biopsy is optional for all participants. If performed it should be after collection of the week 48 24-hour urine and FMU samples, and not more than 8 weeks after the week 52 visit. In the event that a participant has a renal biopsy as part of their clinical management within this window, it may serve as the week 52 biopsy provided that it includes the required components for this study.
i. Study drug will be self-administered by the participant or administered by their caregiver, after receiving appropriate training and sign-off by a research nurse (or other qualified personnel) in their first treatment week, as described in Section 9.5. Once qualified, the participant or caregiver should administer study drug at site visits (as done at home) on those days when a clinic visit occurs on a dosing day. If a home nurse is administering study drug on nonvisit days, the site staff may administer study drug on days of site visits.
j. Between site visits, participants will be instructed to report any infusion site reactions to the study staff. Pump use safety will be reviewed by licensed health care professionals (eg, investigator or nurse) for each study drug administration at clinic visits and during at-home qualification.
k. Vital signs should be measured a maximum of 2 hours before study drug infusion. On day 1 and on the first day of open-label dosing (week 26 or week 28, depending on whether a week 26 renal biopsy is required and when it is performed), vital signs should also be measured approximately 30 minutes to 1 hour after the first infusion of study drug dosing, timed from the completion of the study drug administration. Blood pressure and heart rate should be evaluated after the participant has been resting in a seated 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.
l. FACIT-Fatigue, EQ-5D-5L, KDQOL, PGIC, and WPAI.
m. The screening 24-hour urine collection may be done any time between screening visit 1 and screening visit 2. After week 1, collections should be within ±1 week of the visit (except for the week 24 collection, which cannot be earlier than week 24). Courier arrangements can be made to pick up the collection container from the participant, or the participant may return the container directly to the site.

Table 2: Schedule of Activities

n. Triplicate FMU samples will be collected by the participant at home on 3 consecutive days throughout the duration of the study. These should be the first urinary output of the day. An additional triplicate FMU uPCR sample will be collected at week 25. Samples should be collected within ±1 week of the clinic visit (except for weeks 24 through 26, when sample collection should be within ±3 days of the clinic visit). Courier arrangements can be made to pick up the collection containers from the participants, or the participant may return the containers directly to the site. At every visit, enough uPCR collection containers should be dispensed to the participant to enable all at-home uPCR collections until the next clinic visit.

o. The day 1 triplicate FMU uPCR samples should be collected before the first dose of study drug (eg, day –2, day –1, and before dosing on day 1).

p. Serum complement profile includes AH50, CH50, and C3NeF; C3NeF will only be assayed in samples collected at the baseline (screening) visits. Plasma complement profile includes C3a, C3b/iC3b, C5a, and sC5b-9. See laboratory assessments (Table 4) for more details.

q. The day 1 samples should be collected before dosing with study drug. Participants who discontinue dosing will have ADA samples collected at 2 and 8 weeks after the last treatment. Participants who have a treatment-emergent or treatment-boosted ADA response at any time will have ADA samples collected approximately every 6 months until the antibody levels revert to baseline.

r. eGFR will be calculated using the Chronic Kidney Disease–Epidemiology Collaboration creatinine equation for adults or the Bedside Schwartz equation for adolescents. For each participant, eGFR will be calculated using the same formula for the duration of the study; the choice of formula will be determined by the participant's age at study entry.

s. Serum FSH (to be measured in female participants only), hepatitis B panel, hepatitis C panel, HIV antibodies, SPEP (adult participants only), ANA, and ANCA (see Table 4 and laboratory manual for more details).

t. Ophthalmologic evaluations are optional and will be performed at selected sites. If evaluations are performed, each participant should have a baseline ophthalmologic 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 participants who have drusen before pegcetacoplan administration, a follow-up ophthalmologic evaluation, including an SD-OCT and color fundus photography, should occur at a convenient time between weeks 42 and 52.

u. Measured GFR is an optional assessment that, if performed, should occur at 3 time points: once on day 1 or within 10 weeks before day 1, again at week 26, and a third time between week 42 and week 52, inclusive. Measured GFR should only be done at sites where it is routinely performed, as per the site's standard protocol.

6.2. Number of Participants

Approximately 80 to 100 patients with clinical and pathologic evidence of C3G or IC-MPGN will be randomized into this study, at least 78 of whom will have native kidney disease and up to 22 of whom may have posttransplant recurrence of C3G or IC-MPGN. At least 63 participants with C3G in native kidneys will be enrolled. At least 10 adolescent participants (aged 12-17 years) will be enrolled; adolescent participants may be patients with either native kidney disease or posttransplant disease recurrence. When the study is approaching the target enrollment, the sponsor will notify sites and investigators of the anticipated enrollment closure. Potentially eligible participants who have started screening may complete screening activities and enroll in the study if they meet eligibility criteria, even if this results in enrollment of more than the planned maximum of 100 participants.

6.3. Treatment Assignment

All participants who meet all the inclusion criteria and none of the exclusion criteria will be enrolled in the study, until such time that the intended enrollment has been met. After confirmation of study eligibility, participants will be randomized in a ratio of 1:1 to receive pegcetacoplan or placebo as described in Section 8.5.1.

Following completion of the RCP, all participants will receive pegcetacoplan starting on the first visit of the open-label period, after which they will enter the follow-up period, unless they enroll in a long-term extension study.

6.4. End of Study

Participants will be considered to have completed the study when they have completed the exit visit activities described in the schedule of activities (Table 2), when they have enrolled in a subsequent study of pegcetacoplan, or when they have discontinued study treatment and completed the activities described in Section 7.3.1.

The end of the study will be the last participant's last visit or the last participant's last scheduled visit/assessment as indicated in the schedule of activities (Table 2) or as requested by the sponsor.

7. SELECTION AND WITHDRAWAL OF PARTICIPANTS

7.1. Inclusion Criteria

1. Aged at least 18 years; where approved, adolescents (aged 12-17 years) weighing at least 30 kg may also be enrolled.
2. A diagnosis of primary C3G or IC-MPGN (with or without previous renal transplant).
3. Evidence of active renal disease, based on one or more of the following:
   a. In adults or adolescents with a baseline renal biopsy (either one collected during screening or a historic biopsy collected within 28 weeks prior to randomization), at least 2+ C3c staining on the baseline renal biopsy
   b. In adolescents not providing a baseline renal biopsy, at least one of the following:
      – Plasma sC5b-9 level above the upper limit of normal during screening
      – Serum C3 below the lower limit of normal (LLN) during screening
      – Presence of an active urine sediment during screening, as evidenced by hematuria with at least 5 red blood cells per high-power field and/or red blood cell casts on routine local or central microscopic analysis of urine
      – Presence of C3 nephritic factor within 6 months of screening, based on central laboratory results or medical history
4. No more than 50% global glomerulosclerosis or interstitial fibrosis on the baseline biopsy for adult participants or adolescent participants providing a baseline biopsy.
5. At least 1 g/day of proteinuria on a screening 24-hour urine collection and a uPCR of at least 1000 mg/g in at least 2 FMU samples collected during screening.
6. eGFR ≥30 mL/min/1.73 m^2 calculated by the CKD-EPI creatinine equation for adults or the Bedside Schwartz equation for adolescents.
7. Stable regimen for C3G/IC-MPGN treatment, as described below:
   a. Angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, and/or sodium-glucose cotransporter-2 inhibitor therapy that is stable and optimized, in the opinion of the investigator, for at least 12 weeks prior to randomization
   b. Stable doses of other medications that can affect proteinuria (eg, steroids, mycophenolate mofetil, and/or other allowed immunosuppressants that the participant is receiving for treatment of C3G or IC-MPGN) for at least 12 weeks prior to randomization.
   c. If a participant is on prednisone (or other systemic corticosteroid) for C3G or IC-MPGN treatment, the dosage is stable and no higher than 20 mg/day (or equivalent dosage of a corticosteroid other than prednisone) for at least 12 weeks prior to randomization.
8. Have received vaccinations against *S pneumoniae*, *N meningitidis* (types A, C, W, Y, and B), and *H influenzae* (type B) as per ACIP recommendations for adults or children with complement deficiencies. Vaccination series should be initiated at least 14 days prior to randomization. Vaccination is mandatory unless documented evidence exists that participants are nonresponders to vaccination.

9. Female participants of childbearing potential, defined as any women who have experienced menarche and who are not permanently sterile or postmenopausal, must have negative blood pregnancy tests at screening (and negative urine pregnancy tests on day 1) and must agree to use protocol-defined methods of contraception from screening through at least 90 days after receiving the last dose of pegcetacoplan.
10. Male participants must agree to use protocol-defined methods of contraception and agree to refrain from donating semen from screening through at least 90 days after receiving the last dose of pegcetacoplan.
11. Participants above the legal age of consent, in accordance with local regulations, must be willing and able to provide informed consent. The legally authorized representative of participants under the legal age of consent must be willing and able to provide informed consent; where appropriate, participants under the legal age of consent must also give their assent to participation in the study.
12. Willing and able to self-administer pegcetacoplan or have an identified caregiver who can perform the administration.

7.1.1. Acceptable Methods of Contraception

Women of childbearing potential (WOCBP) and male participants with female partners of childbearing potential will be instructed to practice an acceptable method of birth control throughout the duration of the study and for 90 days following the end of study drug administration.

A woman is considered to be of childbearing potential following menarche and until becoming postmenopausal, unless she is 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 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 participants with female partners of childbearing potential only)

Not all methods of contraception may be available in all of the countries in which this study is being conducted.

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

7.2. Exclusion Criteria

1. Previous exposure to pegcetacoplan.
2. Evidence of improving renal disease in the 8 weeks prior to screening or during the screening period according to available data; improving renal disease is defined as >30% increase in eGFR or >50% decrease in proteinuria.
3. From a renal transplant participant, evidence of rejection that requires treatment in the baseline renal biopsy collected during screening.
4. C3G/IC-MPGN secondary to another condition (eg, infection, malignancy, monoclonal gammopathy, a systemic autoimmune disease such as systemic lupus erythematosus, chronic antibody-mediated rejection, or a medication), in the opinion of the investigator.
5. Current or prior diagnosis of HIV, hepatitis B, or hepatitis C infection or positive serology during screening that is indicative of infection with any of these viruses.
6. Body weight greater than 100 kg at screening.
7. Hypersensitivity to pegcetacoplan or to any of the excipients.
8. History of meningococcal disease.
9. 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
10. Severe infection (eg, requiring IV antibiotic therapy) within 14 days prior to the first dose of pegcetacoplan.
11. An absolute neutrophil count <1000 cells/mm^3 at screening.
12. Significant other renal disease that would, in the opinion of the investigator, confound interpretation of study results.
13. 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 investigational agent (whichever is longer) prior to screening period.
14. Use of rituximab, belimumab, or any approved or investigational anticomplement therapy other than pegcetacoplan within 5 half-lives of that product prior to the screening period.
15. Female participants who are pregnant or who are currently breastfeeding and are unwilling to discontinue for the duration of the study and for at least 90 days after the final dose of study drug.

16. Inability to cooperate or any condition that, in the opinion of the investigator, creates an undue risk for the participant by participating in the study or is likely to confound interpretation of the study results.
17. Evidence of ongoing drug or alcohol abuse or dependence, in the opinion of the investigator.
18. Presence or suspicion of severe infection during the screening period (including but not limited to recurrent or chronic infections) that, in the opinion of the investigator, may place the participant at unacceptable risk by study participation.
19. Known or suspected hereditary fructose intolerance.

7.3. Discontinuations and Participants Lost to Follow-up

7.3.1. Early Treatment Discontinuation and Study Withdrawal

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

Once withdrawn from the study, the participant may not reenter the study.

Participants who discontinue study treatment prior to the end of the RCP should be encouraged to complete the remaining visits for the RCP. If discontinuing study treatment after week 18, participants should also complete the activities described for the exit visit in the schedule of activities (Table 2) approximately 8 weeks after their last dose of study drug. If the participant is unwilling or unable to complete the exit visit activities, they should be encouraged to complete the other follow-up visits and procedures described in the schedule of activities (Table 2).

Participants who discontinue study treatment during the open-label period should enter the follow-up period of the study, including all follow-up visits and procedures through study completion, unless unwilling, unable, or consent has been withdrawn. Participants who wish to fully withdraw from the study during the open-label period but prior to the week 52 visit and are unwilling or unable to complete the follow-up visits and procedures should complete the activities described for the exit visit in the schedule of activities (Table 2) at their last visit.

7.3.2. Reasons for Discontinuation of Treatment or Withdrawal From the Study

The date of and reason for treatment discontinuation must be determined by the investigator and recorded in the participant's medical record. If it is determined that there was more than one reason for the discontinuation, each reason should be recorded in the source document and the most clinically relevant reason, as determined by the investigator, should be noted. Treatment will be discontinued if any of the following occur:

- Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition (including infections) or circumstance that indicates to the investigator that continued participation is not in the best interest of the participant.

- Participant withdrawal of consent: at any time, a participant's participation in the study may be terminated at his or her request or on the basis of the investigator's clinical judgment. The reason for participant withdrawal will be noted in the participant's source document.
- Participant fails to adhere to the protocol requirements (eg, drug noncompliance, failure to return for defined number of visits, failure to meet randomization criteria), such that continued participation in the study is not in the best interest of the participant (in the opinion of the investigator) or compromises the ability of the sponsor to appropriately analyze the data from the study.
- Participant is lost to follow-up: the participant stopped coming for visits, and study personnel were unable to contact the participant.
- Termination of the study by the sponsor or regulatory authorities.
- Pregnancy, as indicated in Section 11.2.4.

Any participant who discontinues treatment early, or is withdrawn from the study early, because of a 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.

Participants for whom study treatment is discontinued should be encouraged to complete additional activities as described in Section 7.3.1, unless unwilling, unable, or consent has been withdrawn. 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.

7.3.3. Lost to Follow-up Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any participants lost to follow-up at any time 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 participant's last known address via courier or mail (with an acknowledgment of receipt request) asking that he/she return to the site for final safety evaluations and to return any study drug.

Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

7.3.4. Replacement of Participants

Participants who discontinue the study will not be replaced.

8. TREATMENT OF PARTICIPANTS

8.1. Study Interventions

All participants will receive SC infusions of pegcetacoplan or matching volumes of placebo twice weekly. The planned dosing regimens for pegcetacoplan and the matching volume of placebo are presented in Table 3. All adult participants (regardless of weight), and adolescent participants who weigh at least 50 kg, will receive 20-mL SC infusions. Adolescent participants who weigh at least 35 kg but less than 50 kg will receive a reduced infusion volume (12 mL for the first infusion and 15 mL for each infusion thereafter). Adolescent participants who weigh at least 30 kg but less than 35 kg will receive a further reduced infusion volume (10 mL for the first 2 infusions and 12 mL twice weekly thereafter). As described in Section 11.1.3, participant weight will be assessed at each visit; if an adolescent participant's weight has changed, the dose and infusion volume should be adjusted accordingly.

Table 3: Planned Dosing Regimens (Pegcetacoplan and Placebo)

Weight	First dose (infusion volume)	Second dose (infusion volume)	Maintenance dosing regimen (infusion volume)
All adult participants, adolescent participants ≥50 kg	1080 mg (20 mL)	1080 mg (20 mL)	1080 mg twice weekly (20 mL)
Adolescent participants 35 to <50 kg	648 mg (12 mL)	810 mg (15 mL)	810 mg twice weekly (15 mL)
Adolescent participants 30 to <35 kg	540 mg (10 mL)	540 mg (10 mL)	648 mg twice weekly (12 mL)

Participants and/or their caregivers will be trained to administer the infusions, as described in Section 9.5.

If a participant misses any regularly scheduled doses for any reason, all efforts should be made to restart dosing as soon as possible to reach and maintain therapeutic steady-state concentrations of pegcetacoplan. A single missed dose should be administered as soon as possible, regardless of whether the missed dose is administered on a regularly scheduled dosing day. Dosing should then continue twice weekly at the prescribed dose level (see Table 3 above) according to the original dosing schedule, even if this results in an interval of less than 3 days between 2 doses. If multiple doses are missed, dosing should resume as soon as possible at the prescribed dose level (see Table 3 above) according to the original dosing schedule. The medical monitor should be notified of any gaps in dosing.

8.2. Vaccinations

To receive study drug, participants will be required to be vaccinated as follows on the basis of ACIP recommendations for adults or children with complement deficiencies (available at https://www.cdc.gov/vaccines/schedules/hcp/index.html) or other similar local guidelines.

- *N meningitidis* types A, C, W, and Y: First dose at least 14 days prior to randomization with a second dose 2 months later, and then boosters every 5 years.

- *N meningitidis* type B: First dose at least 14 days prior to randomization 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*: pneumococcal conjugate vaccine (PCV13, PCV15, or PCV20, depending on participant age and vaccine availability) and/or pneumococcal polysaccharide vaccine 23 (PPSV23). Adults who have not previously received any pneumococcal vaccine may receive PCV20, if the site is able to procure it, and a subsequent dose of PPSV23 would not be required. Multiple scenarios exist depending on previous vaccination history and investigators should consult ACIP guidelines for adults or children with complement deficiencies or other similar local guidelines.
- *H influenzae* type B: Documentation of childhood vaccination or one dose at least 14 days prior to randomization.

Vaccination is mandatory, unless documented evidence exists that participants have received the recommended vaccinations or are nonresponders to vaccination. For participants who do not have this documented evidence, the required missing vaccination(s) will be administered as needed to bring participants up to date. The investigator will discuss with the medical monitor any individual participant circumstances relevant to the vaccination requirements that would make the above schedule not possible or reasonable, of if the investigator has any questions or concerns about the vaccination requirements. If local or national guidelines for immunizations differ from the ACIP recommendations, the differences should be discussed with the medical monitor to determine an appropriate course of vaccinations. On an ongoing basis, including upon entry into a long-term extension, participants should be reevaluated for the need for any additional vaccinations or boosters on the basis of ACIP recommendations.

Vaccination serum samples will be collected on the day of vaccination before receiving vaccinations on that visit. These samples will be analyzed to evaluate response to vaccinations if the participant tests positive for infection with *S pneumoniae*, *N meningitidis*, or *H influenzae*.

8.2.1. 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.

8.3. Concomitant Medications

All medications administered (including over the counter or prescription medicines, vitamins, and/or herbal supplements) and all 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 final visit (the week 60 exit visit, an exit visit following early discontinuation as described in Section 7.3.1, or the final visit before transition to the long-term extension study, as applicable) are regarded as concomitant and will be documented.

8.3.1. Treatment Regimens for C3G or IC-MPGN

Participants should be on stable doses of all medications relevant to their renal disease for at least 12 weeks prior to randomization, as described in Section 7.1. During the screening period and the RCP, changes to the baseline treatment regimens for C3G/IC-MPGN (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 participant (with the exception of posttransplant immunosuppression—see below). During the open-label period, if the investigator plans to make changes to the baseline treatment regimen, these should be approved by the sponsor before implementation.

8.3.1.1. Posttransplant Immunosuppression

If the participant is in a posttransplant 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 posttransplant care. For all posttransplant participants, the plan for posttransplant 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.

Posttransplant participants with evidence of rejection on the baseline biopsy collected during screening 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 repeat biopsy to serve as the baseline (refer to Section 10.5 for further details). Participants with evidence of subclinical rejection on the biopsy collected during screening may proceed with pegcetacoplan treatment, at the discretion of the investigator, provided no treatment is initiated for the rejection.

8.3.2. Rescue Therapy

In the event of an increase in serum creatinine to at least 2× the baseline level that in the opinion of the investigator is due to the underlying C3G/IC-MPGN disease, rescue therapy may be considered, such as high-dose corticosteroids and/or C5 inhibitor treatment.

If the participant receives rescue therapy that is not a prohibited concomitant medication, then they will be allowed to remain on study drug. If a participant receives rescue therapy that is a prohibited concomitant medication, they will be discontinued from study drug, as described in Section 8.3.3.

8.3.3. Prohibited Medications

The use of rituximab, belimumab, or any approved or investigational anticomplement therapy other than pegcetacoplan (including, but not limited to, eculizumab and/or ravulizumab) is prohibited within 5 half-lives of that product prior to screening and for the duration of the study.

If a participant receives a prohibited concomitant medication, they will be discontinued from study drug and the procedures described in Section 7.3 should be followed.

Analysis of results from participants receiving prohibited medications is described in Table 8 and Table 9.

8.4. Treatment Compliance

Participants must be instructed to bring their empty/unused study drug packaging and diaries to every visit. The pharmacist/nominated person will record drug accountability information in the interactive response technology.

8.5. Measures to Minimize Bias: Study Treatment Assignment

8.5.1. Randomization

Participants will be randomized to receive pegcetacoplan or placebo in a ratio of 1:1 via a computer-generated randomization schedule. The randomization will be performed centrally. To achieve balance between the arms, 2 stratification factors will be applied to the randomization. The first stratification factor examines participants with posttransplant recurrence versus nontransplant participants; at least 78 participants with C3G or IC-MPGN in a native kidney will be enrolled. This is followed by the second stratification factor, which examines participants with baseline renal biopsies (either collected during screening or a historic biopsy collected within 28 weeks prior to randomization) versus participants without baseline renal biopsies. The stratification will ensure balance between treatment groups for the stratification factors.

8.5.2. Blinding

Dosing will be double-blinded in the RCP; the open-label period is not blinded. All central evaluations (including evaluation of renal biopsies by the central pathologist) will be blinded to treatment assignment.

Participants, the sponsor, investigators, and all study site personnel conducting study-related activities (including carrying out study procedures, evaluating participants, and entering and/or evaluating study data) will remain blinded to treatment allocations during the RCP at least until all participants have completed the week 26 assessments and the RCP portion of the database has been locked. Although treatment in the open-label period is not blinded, investigators, study site personnel, and participants will remain blinded to the RCP treatment assignment until the blind has been broken. Only the drug supply distributor/logistics personnel who are not site personnel will be unblinded to study treatment. These individuals are not allowed to discuss treatment and/or participant outcome with blinded study staff, including the evaluating physician. Active and placebo product labels will not include any information which would unblind the treatment assignment during the RCP, as described in Section 9.2.2.

8.5.2.1. Study Drug Unblinding

Except as noted below, investigators shall not break the study blind. If knowledge of the participant's treatment assignment is necessary for clinical management, the investigator should first attempt to contact the medical monitor or designee to discuss the need for unblinding to occur. The medical monitor or designee will be available at all times for such discussions. If the investigator is unable to reach the medical monitor or designee, or in the case of a medical emergency, the investigator should use their best judgment based on the nature and urgency of the clinical situation, and if necessary may proceed with unblinding without having successfully contacted the medical monitor or designee. If a participant's treatment assignment is unblinded under these circumstances, the medical monitor and study coordinator must be notified within 24 hours.

Information describing the unblinding (eg, date and time of the call to the medical monitor by the investigator, reason for unblinding, and date and time of unblinding) must be clearly recorded in the participant's study file. In addition, the investigator should consider whether the clinical event prompting unblinding should be considered an AE or an SAE according to the definitions in Section 11.2.1; if so, such events must be recorded and reported as described in Section 11.2.2 and Section 11.2.3.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Study Drug

The investigational product is pegcetacoplan (APL-2). The study drug may be pegcetacoplan or placebo during the RCP, depending on the treatment assignment. The study drug will be pegcetacoplan during the OLP.

Pegcetacoplan will be provided as a sterile solution in single-use glass vials. Each vial contains an isotonic sterile solution of pegcetacoplan 1080 mg/20 mL (54 mg/mL) in 10 mM acetate buffer, pH 5.0, containing 4.1% sorbitol. Additional information is provided in the pegcetacoplan IB.

Placebo will be provided as a sterile solution of 10 mM acetate buffer, pH 5.0, containing 4.1% sorbitol supplied in single-use glass vials.

9.2. Study Drug Packaging and Labeling

9.2.1. Packaging

Both pegcetacoplan and placebo will be 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.

9.2.2. Labeling

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

All investigational product (pegcetacoplan drug product or placebo) is labeled with a minimum of the following items: 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, 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 participant identifier and date dispensed by the site to the participant.

Additional labels may, on a case-by-case basis, be applied to the investigational product to satisfy national, local, or institutional requirements but must not contradict the clinical study label, obscure the clinical study label, unblind the treatment assignment during the RCP, or identify the participant by name.

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

9.3. Study Drug Storage

The study drug 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 study drug is maintained within an established temperature range.

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

- ensuring that the study drug 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 study drug appropriately
- dispensing the vials of study drug to the participant
- entering the unique participant identifier on the study drug bottle/carton labels as they are distributed

When the participant receives the study drug 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 participant's residence, but a log will be kept for every infusion to ensure that all study drug was kept refrigerated.

With sponsor prior approval, investigational product and/or ancillary supplies may be shipped from the study site to a participant's designated location. Such shipments will only be implemented at sites where this activity is approved by the IRB/IEC and health authority (if required). Participant consent will be required prior to any participant information being provided to a courier. The responsibility to return both empty vials and any unused investigational product as described in Section 8.4 shall remain unchanged.

9.4. 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.

9.5. Study Drug Administration

Study drug will be administered as an SC infusion. The infusion volume depends on the dose received, as described in Section 8.1.

The preferred site of infusion will be the anterior abdominal wall. If administration into the abdomen is not feasible, alternative appropriate sites are acceptable. Alternative sites include the anterior aspects of the thighs or upper arms (see Study Medication Administration Instructions—Participant's Guide for more details). It is advisable to change infusion site after each drug administration in order to avoid skin irritation. Research nurses or other appropriately qualified research personnel will administer the SC infusions (as needed) and will qualify and supervise the self-administration. Study drug administration may also be conducted by a caregiver or a member of the participant's household, etc, who will undergo the same training (training is not intended to be restricted to the participant).

These qualified personnel will be made available for a minimum of 6 days on treatment (2 doses) to ensure the participant or caregiver has been qualified to conduct administration, but duration could be shortened if qualification happens sooner or extended if the participant or caregiver requires further training. During qualification, the participant or caregiver must demonstrate to the research personnel their ability to safely and effectively administer study drug using the infusion pump. Following administration qualification, the participant or caregiver may administer the SC infusions without supervision. Once qualified, the participant or caregiver will continue to administer infusions at the clinic on those days when a clinic visit occurs on a dosing day and at an off-site location convenient to the participant on all other days. Self-administration or caregiver administration conducted at the clinic will be supervised to ensure that the participant or caregiver continues to remain compliant with the administration guidelines.

9.6. Study Drug Accountability

Accountability for the study drug at the study center is the responsibility of the investigator. The investigator will ensure that the study drug is used only in accordance with this protocol. Where allowed, the investigator may choose to delegate drug accountability responsibilities to a pharmacist or other appropriate individual.

Investigators will be provided with sufficient amounts of the study drug to carry out this protocol for the agreed number of participants. The investigator or designee will acknowledge receipt of the investigational product and placebo, documenting shipment content and condition. Accurate records of all study drug dispensed, used, returned, and/or destroyed must be maintained. Accountability records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and participant numbers. The sponsor or its designee will review study drug accountability at the study center on an ongoing basis during monitoring visits.

Study drug must not be used for any purpose other than the present study. Study drug that has been dispensed to a participant and returned unused must not be redispensed to a different participant.

The investigator is responsible for ensuring the retrieval of all returnable study supplies from participants.

9.7. Study Drug Handling and Disposal

All unused and used study drug vials should be retained at the center until they are inventoried by the study monitor. All used, unused, or expired study drug vials will be returned to the sponsor or its designee for destruction and destruction will be documented, or if authorized, disposed of at the study center per the center’s standard operating procedures and documented.

10. ASSESSMENT OF EFFICACY

10.1. Retrospective Data Collection for eGFR and Measured Glomerular Filtration Rate

Retrospective data will be collected on glomerular filtration rate (GFR) to calculate historical eGFR for up to 3 years prior to study entry, depending on the date of diagnosis (for renal transplant recipients, this refers to diagnosis of recurrent disease, not diagnosis of the original disease in native kidneys). Three years of retrospective data will be collected to calculate eGFR for those diagnosed at least 3 years prior to randomization. Retrospective data for the period between randomization and diagnosis will be collected for those diagnosed less than 3 years prior to randomization. For historical eGFR calculations, data will be collected to enable calculation of eGFR by CKD-EPI (with serum creatinine) in adults and by the Bedside Schwartz equation in adolescents. Specifically, age, sex, race, height (adolescents only), serum creatinine, serum blood urea nitrogen (adolescents only), and serum cystatin C (if available) will be collected. For each participant, eGFR will be calculated using the same formula for the duration of the study; the choice of formula will be determined by the participant's age at study entry.

If a participant has historical data on measured GFR, then this data, including the method used to measure GFR, should also be collected (in addition to the data required to calculate eGFR in that participant) for the same timeframe.

10.2. 24-Hour Urine Collection

A 24-hour urine collection is defined as collection of all urine produced over a 24-hour period. As 24-hour urine collections will be done at home, participants will be provided with containers for the collection as well as an instruction sheet that details the collection procedure. The 24-hour urine collection should begin following the first urinary output for the day, and then continue for a 24-hour period. Samples should be collected within ±1 week of the clinic visit (except for the week 24 collection, which cannot be earlier than week 24).

In brief, the first urine (on the day of collection) must be discarded (as this is urine made prior to the start of the collection date/time). The time and date of this discarded void must be recorded, as it represents the start of the collection. The participant should then collect all urine over the next 24 hours. At the 24-hour time point, the participant should empty their bladder and collect this urine as the final void of the 24-hour urine collection. The date and time of this last collected void should be recorded, as it represents the end of the 24-hour urine collection.

There will be six 24-hour urine collections, at the visits outlined in the schedule of activities (Table 2):

- screening (between week –8 and week –4 and before the renal biopsy)
- week 12
- week 24 (before the week 26 renal biopsy)
- week 36
- week 48 (before the week 52 renal biopsy, if performed)
- week 60

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 participant's source document. Urine must be stored at 2 to 8 °C (ie, in refrigerator). Courier arrangements can be made by the site to pick up the collection container from the participant's home and return it to the site, or the participant may return it directly to the site. Total urine volume, total protein concentration, total albumin concentration, total β-2 microglobulin, and total creatinine concentration will be measured on the 24-hour urine collections, with calculation of total protein excretion, total albumin excretion, total creatinine excretion, total β-2 microglobulin excretion, uPCR, urinary albumin-to-creatinine ratio (uACR), and urinary β2-microglobulin–to-creatinine ratio (uBCR) based on the 24-hour collection.

10.3. Triplicate FMU Collections

Triplicate FMU collection is defined as a collection of first-morning urine on 3 consecutive mornings, with each morning urine sample collected into a separate container. Samples should be collected within ±1 week of the clinic visit (except for weeks 24 to 26, when sample collection should be within ±3 days of the clinic visit).

It is important that each of these collections represent the first urinary output upon awakening, after an extended period of rest. The date and time of each collected sample should be recorded. In the event that a participant 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 documented in the source document. If menses are repeatedly occurring at the scheduled times of a triplicate FMU collection, the collection dates should be adjusted to avoid collection during menses to the extent possible, with this information recorded in the participant's source document.

After FMU collection, the urine samples must be stored at 2-8 °C (ie, in a refrigerator). Courier arrangements can be made by the site to pick up the collection containers from the participants, or the participant may return them directly to the site. Urine protein, albumin, β-2 microglobulin, and creatinine concentrations should be measured on all spot urine samples, with calculation of uPCR, uACR, and uBCR values.

Triplicate FMU collections should be before each clinic visit (ie, approximately every 4 weeks), with an additional triplicate to be collected at week 25. At each scheduled clinic visit, the site will dispense the number of spot urine containers needed before the next scheduled visit (dispense 3 containers at each visit except week 24, when 6 containers should be dispensed); participants will return the triplicate spot urine collections at their next visit.

10.4. Random Spot Urine Collection

At each clinic visit, participants 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 to 8 °C (ie, in a refrigerator). Urine protein, albumin, β-2 microglobulin, and creatinine concentrations should be measured on all spot urine samples, with calculation of uPCR, uACR, and uBCR values.

10.5. Renal Biopsy

The renal biopsy procedure should be performed according to the local standard practices at the site, including use of anesthesia/sedation, pre-procedure evaluation (eg, laboratory testing prior to renal biopsy), and post-procedure 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.

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 participants participating in this study because of the potential for interference with pegcetacoplan.

10.5.1. Renal Biopsies in Adults

For adult participants, a percutaneous biopsy will be performed at the visits indicated in the schedule of activities (Table 2).

A renal biopsy will be performed during screening to confirm diagnosis and eligibility, and to serve as the baseline renal biopsy. Once participant eligibility has been confirmed on the basis of the assessments from screening visit 1 and the initial 24-hour urine collection is complete as described in Section 10.2, the baseline renal biopsy may be conducted at any time during screening. A prior renal biopsy done within 28 weeks of randomization may be used for eligibility confirmation and serve as the baseline biopsy, if confirmed as adequate per central pathology review. Copies of prior renal biopsy reports will be requested for review by the central pathology laboratory. If a prior renal biopsy is used to establish eligibility and/or will serve as the baseline biopsy, images and/or slides from that biopsy will also be required. Tissue blocks and/or unstained slides may also be requested for staining at the central pathology laboratory.

Follow-up renal biopsies will be performed at week 26 and week 52. The week 26 biopsy is required for participants aged 18 years and older. The week 26 renal biopsy need not occur on the same day as all other assessments for that visit. However, the week 26 biopsy must occur after the week 26 triplicate FMU collections and before the first visit of the open-label period at week 28. The week 52 biopsy is optional. If performed it should be after collection of the week 48 24-hour urine and not more than 8 weeks after the week 52 visit.

In the event that a participant has a renal biopsy as part of their clinical management, biopsy samples should be reviewed by the central pathology laboratory and the results should be entered into the study database, if possible. If this biopsy includes the required components for this study and is collected within the window defined above, it may serve as the week 52 biopsy.

10.5.2. Renal Biopsies in Adolescents

Participants younger than 18 years will be requested to provide renal biopsies in countries and at sites where permitted but are not required to do so, and refusal of a participant younger than 18 years to provide any or all renal biopsies will not be considered noncompliance. Renal biopsies will not be collected for research purposes from adolescent participants in the US or from adolescent participants at sites where not permitted by national or local regulations.

An adequate prior renal biopsy will be used to establish the diagnosis and eligibility for adolescent participants who do not provide a baseline renal biopsy during screening, even if the prior biopsy was performed more than 28 weeks prior to randomization. Copies of prior renal biopsy reports will be requested for review by the central pathology laboratory. If a prior renal biopsy is used to establish eligibility and/or will serve as the baseline biopsy, images and/or slides from that biopsy will also be required. If the historical biopsy was performed more than 28 weeks prior to randomization, then eligibility will be determined on the basis of alternative evidence of active renal disease as described in Section 7.1.

Participants younger than 18 years may advance to the open-label period upon completion of all week 24 though week 26 assessments other than the renal biopsy. Participants younger than 18 years who did not have a baseline biopsy within 28 weeks of day 1 will not have week 26 or week 52 biopsies under any circumstances. Participants under the age of 18 who had a baseline biopsy within 28 weeks of day 1 will be requested to provide week 26 and week 52 renal biopsies, in countries and at sites where allowed. When collected, renal biopsies in adolescent participants should be collected within the windows defined in Section 10.5.1 for biopsies in adult participants.

In the event that a participant younger than 18 years has a renal biopsy as part of their clinical management, biopsy samples should be reviewed by the central pathology laboratory and the results should be entered into the study database, if possible. If this biopsy includes the required components for this study and is collected within the windows defined in Section 10.5.1 for biopsies in adult participants, it may serve as one of the study biopsies.

10.6. Ophthalmologic Evaluation

Ophthalmologic evaluation is an optional assessment and will be performed at selected sites. If performed, participants should have a baseline ophthalmologic 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 participants with drusen prior to pegcetacoplan administration, a followup- ophthalmologic evaluation, including a basic ophthalmologic examination, SD-OCT, and color fundus photography, is requested to occur at a convenient time 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 examination with comment on presence or absence of pigment, drusen, hemorrhage, atrophy, or other evidence of macular degeneration.

10.7. Measured GFR

Measured 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 participant's source document) once prior to the first pegcetacoplan dose (but no more than 10 weeks prior to the first dose), again at week 26, and a third time between week 42 and week 52, inclusive. In the event that retrospective measured GFR data are available, these should be collected for the same time frame as retrospective data for calculation of eGFR (see Section 10.1).

10.8. Health-Related Quality of Life Assessments

Health-related quality of life (HRQoL) assessments will be completed during clinic visits as outlined in the schedule of activities (Table 2).

10.8.1. Functional Assessment of Illness Therapy–Fatigue Scale

The FACIT-Fatigue scale is a 13 item Likert scaled instrument that is self-administered by participants. Participants are presented with 13 statements and asked to indicate their responses as it applies to the past 7 days. The 5 possible responses are “Not at all” (0), “A little bit” (1), “Somewhat” (2), “Quite a bit” (3) and “Very much” (4). With 13 statements the total score has a range of 0 to 52. Before calculating the total score, some responses are reversed to ensure that the higher score corresponds to a higher quality of life.

10.8.2. 5-Level EuroQol-5 Dimension

The EQ-5D-5L assessment is a standardized measure of health status developed to assess HRQoL by the EuroQoL Group. The questionnaire consists of a descriptive system and a visual analog scale. The descriptive system contains 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with 5 levels in each dimension.

10.8.3. Kidney Disease Quality of Life

The KDQOL survey is a kidney disease-specific measure of HRQoL developed by the RAND Corporation, which is self-administered by participants. It includes a generic chronic disease core, and additional items relevant to patients with kidney disease, such as symptoms, burden of illness, social interaction, staff encouragement, and patient satisfaction. Scores are reported separately for each of 5 subscales.

10.8.4. Patient Global Impression of Change

The Patient Global Impression of Change is a 1-item questionnaire that measures the participant’s impression of the change in their health and assesses whether there has been an improvement or decline in clinical status since the start of the study.

10.8.5. Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

The Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) is a patient-reported quantitative assessment of the amount of absenteeism, presenteeism, and daily activity impairment attributable to a specific health problem for working patients. It includes 6 questions assessing health-related work productivity loss over the previous 7 days.

11. ASSESSMENT OF SAFETY

11.1. Safety Parameters

11.1.1. Demographic/Medical History

Medical history will be recorded at screening. Investigators should document the occurrence, signs, and symptoms of the participant's preexisting conditions, including all prior significant illnesses, up to and including 1 year 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.

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. Available disease medical history for the 3 years preceding screening will be requested. Submission of additional historical data is encouraged, when available. Copies of prior renal biopsy reports will be requested for review by the central pathology laboratory. If a prior renal biopsy is used for eligibility and/or will serve as the baseline biopsy, images and/or slides from that biopsy will also be required. Tissue blocks or unstained slides may also be requested for staining at the central pathology laboratory.

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 11.2.2.

Additionally, demographic data will be collected for all participants, as allowed per applicable regulations.

11.1.2. 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 2). All vital signs will be measured after the participant 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.

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. Following the infusions on day 1 and on the first day of open-label dosing (week 26 or week 28, depending on whether a week 26 renal biopsy is required and when it is performed), vital signs will also be measured approximately 30 minutes to 1 hour after dosing.

11.1.3. Weight and Height

Body weight will be recorded at each visit. Height will be recorded at screening for adults and every 12 weeks throughout the study for adolescents. Height will be measured using a calibrated stadiometer. Both body weight and height will be assessed without shoes on.

11.1.4. 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 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 2) for the details regarding which type of physical examination should be given at each visit.

11.1.5. Menses

For WOCBP, the start and stop date of each menstrual period will be recorded in the participant's source document for the duration of the study.

11.1.6. Electrocardiograms

All 12-lead ECGs will be measured once, prior to dosing, at the visits outlined in the schedule of activities (Table 2). The ECG will be taken following resting in the supine position for 10 minutes in a quiet environment and prior to any blood sampling procedures.

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 internal (uncorrected and corrected using Fridericia's method [QTcF]) will be reviewed for eligibility and ongoing safety.

11.1.7. Chest Radiography

Chest radiography will be performed prior to dosing at the visits outlined in the schedule of activities (Table 2). Posterior-anterior and lateral views of the chest will be recorded via chest radiography; both views are required. The actual chest radiography technical procedure should be performed according to the site's standard protocol. The radiographs will be classified as normal, having a not clinically significant abnormality, or having a clinically significant abnormality per radiology report, and this classification should be included in the source documentation.

11.1.8. Infusion Site/Pump Safety Assessment

On the days of clinic visits, pump use safety will be reviewed 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 participant will be asked about any issues related to pump use.

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

11.1.9. Laboratory Assessments

Laboratory assessment samples (Table 4) are to be obtained at designated visits as detailed in the schedule of activities (Table 2).

Table 4: Laboratory Assessments

Hematology	Serum chemistry	Urine studies
Hb Hematocrit Platelet count RBC count Reticulocytes WBC count with differential	Albumin ALT ALP AST Bicarbonate Bilirubin (total, direct, and indirect) BUN C3 C4 Calcium Chloride Creatinine Creatine kinase Cystatin C Estimated GFR (using CKD-EPI formula for adults; Bedside Schwartz for adolescents) GGT Glucose HDL LDH LDL Phosphorus Potassium Sodium Triglycerides Total cholesterol Total protein Uric acid	Urinalysis • Blood • Bilirubin • Glucose • Ketones • Leukocyte esterase • Nitrite • pH • Pregnancy, when applicable • Protein • Specific gravity • Urobilinogen • Microscopic examination of urine sediment, including for presence of RBCs, WBCs, and casts, will be performed on all urinalyses Spot Urines (First-Morning and Random) • ACR • BCR • PCR • Total albumin concentration • Total β-2 microglobulin concentration • Total creatinine concentration • Total protein concentration 24-Hour Urine • ACR • BCR • PCR • Total albumin concentration • Total β-2 microglobulin concentration • Total creatinine concentration • Total protein concentration • Total volume

Table 4: Laboratory Assessments

Hematology	Serum chemistry	Urine studies
Coagulation[a]	**Additional**	
PT	FSH (postmenopausal women)[b]	Serum pregnancy test[b]
aPTT	Hepatitis B panel[b,c]	Complement tests (serum/plasma)[e]
INR	Hepatitis C panel[b,d]	Anti-drug antibodies
	HIV antibodies[b]	Vaccination response[f]
	SPEP[2]	
	ANA (with reflex anti-dsDNA)[b]	
	ANCA (with reflex anti-MPO and anti-PR3)[b]	

Abbreviations: ACR = albumin-to-creatinine ratio; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANA = antinuclear antibodies; ANCA = antineutrophil cytoplasmic antibodies; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BCR = β-2 microglobulin:creatinine ratio; BUN = blood urea nitrogen; CKD-EPI = Chronic Kidney Disease–Epidemiology Collaboration; ds DNA = double stranded DNA; FSH = follicle-stimulating hormone; GFR = glomerular filtration rate; GGT = γ-glutamyltransferase; Hb = hemoglobin; HBcAb = hepatitis B core antibody; HbsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HDL = high-density lipoprotein; Hib = *Haemophilus influenzae* type B vaccine; HIV = human immunodeficiency virus; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; MPO = myeloperoxidase; PCR = protein-to-creatinine ratio; PCV13 = pneumococcal conjugate vaccine; PPSV23 = pneumococcal polysaccharide vaccine 23; PR3 = proteinase 3; PT = prothrombin time; RBC = red blood cell; SPEP = serum protein electrophoresis; WBC = white blood cell.

a. The use of silica reagents in coagulation panels should be avoided in participants participating in this study because of the potential for interference with pegcetacoplan.
b. Screening only. SPEP will be evaluated only in adult participants.
c. HbsAg and HbcAb.
d. Hepatitis C antibody with reflex HCV RNA polymerase chain reaction.
e. Complement tests (serum/plasma): AH50, CH50, C3a, C3b/iC3b, C5a, sC5b-9, C3NeF, and potentially additional complement components. C3NeF will only be assayed in samples collected at the baseline (screening) visits.
f. Serum samples will be collected to evaluate response to vaccinations to *N. meningitidis* (types A, C, W, Y, and B), PCV13 or PPSV23, and Hib. Samples will only be analyzed in the event that the participant has a positive infection for *Streptococcus pneumoniae*, *Neisseria meningitidis*, or *Haemophilus influenzae*.

Blood and urine samples will be analyzed at a central or local laboratory facility, as defined in the laboratory manual. 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 participant'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.

11.1.9.1. Pregnancy Screen

For WOCBP, a serum pregnancy test will be performed at screening. Participants with a positive result will be excluded or discontinued from the study as described in Section 7.3. A urine pregnancy test will also be performed starting at baseline and then at all visits through the end of the study, including the follow-up visits. Male participants will be counseled to avoid donating semen during the time between the first screening and the final week 60 exit visit and for the 90 days after their last dose of study drug.

11.1.10. Pharmacokinetic Assessment

Blood samples for PK assessment of pegcetacoplan will be collected before dosing via direct venipuncture at the visits delineated in the schedule of activities (Table 2).

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

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 in the final clinical study report.

11.1.11. Pharmacodynamic Assessment

Blood samples for assessment of the effects of pegcetacoplan on the complement profile (CH50 and AH50, sC5b-9, and potentially additional complement components) will be collected before dosing via direct venipuncture at the visits delineated in the schedule of activities (Table 2).

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

PD assessment results will be included in the final clinical study report.

11.1.12. Blood Volume for Study Assessments

Table 5 presents the approximate blood volume to be collected for this study. See the laboratory manual for additional details regarding the blood volume required throughout the study.
The maximum volume of blood drawn at any single visit is 24.7 mL for adult participants and 22.2 mL for adolescent participants and occurs at the first screening visit. For the remainder of the study, the maximum volume of blood drawn at any single visit is 18.2 mL for both adult and adolescent participants. For an adolescent participant at the minimum permitted body weight of 30 kg, the 22.2-mL and 18.2-mL volumes would be 0.74 and 0.61 mL of blood per kg of body weight, respectively. Over a 4-week period, the maximum blood volume to be drawn is approximately 55 mL for adult participants and 52.5 mL for adolescent participants. This would occur only if the first screening visit was 4 weeks before the start of the RCP. For an adolescent participant at the minimum permitted body weight of 30 kg, this would be a maximum of 1.75 mL/kg in a 4-week period.

Table 5: Approximate Blood Volume Collected

Sample type	Approximate volume per visit	Collections during screening	Collections during main period	Collections during follow-up	Approximate volume over course of study
Serum chemistry (with serum complement profile)	5 mL	2	12	3	85 mL
Serum chemistry (without serum complement profile)	3.5 mL	0	2	0	7 mL
Plasma complement profile	1 mL	1	9	2	12 mL
Hematology	1 mL	2	14	3	19 mL
Serum coagulation	2.7 mL	2	14	3	51.3 mL
Additional screening tests	15 mL[a]	1	0	0	15 mL[a]
PK samples	2.5 mL	0	8	1	22.5 mL
PK and immunogenicity (antidrug antibodies) combined	8.5 mL	0	6	2	68 mL
Vaccination response samples	3.5 mL	1	1	0	7 mL
Approximate blood volume per visit		**12-25 mL**	**10-18 mL**	**11-18 mL**	
Total approximate blood volume for study					**287 mL**

Abbreviation: PK = pharmacokinetic.
[a] 12.5 mL for adolescent participants.

11.1.13. Antidrug Antibody Assessment

Blood samples for assessment of antidrug antibodies (ADAs) will be collected at the visits indicated in the schedule of activities (Table 2). Samples will be assayed for both antibodies against polyethylene glycol (PEG) (anti-PEG antibodies) and antibodies against the peptide moiety of pegcetacoplan (anti–pegcetacoplan peptide antibodies).

The proposed ADA sampling schedule was established to capture the ADA signal at baseline, any potential early onset antibody formation, and the dynamic profile (transient or persistent) of antibody formation while minimizing pegcetacoplan level in the sample.

Participants who have a treatment-emergent or treatment-boosted antidrug antibody response at any time will have ADA samples collected approximately every 6 months until resolution (participants with a treatment-boosted response will be followed until the titer returns to within four-fold of baseline and participants with a treatment-emergent response will be followed until there is a negative sample). Antibody titers will be determined for any samples that are confirmed to be positive for anti–pegcetacoplan peptide or anti-PEG antibodies, and any samples that are confirmed to be positive for anti–pegcetacoplan peptide antibodies will be further characterized with a neutralizing antibody assay.

11.1.14. COVID-19 Assessments

If a participant has been tested for COVID-19, the results, if available, will be documented in the participant's source document.

11.2. Adverse and Serious Adverse Events

11.2.1. Definitions

11.2.1.1. 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 it is considered related to the investigational product. TEAEs are defined as AEs that develop or worsen after the first dose of study medication.

AEs can be reported spontaneously by the participant 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 participant's source document. Fluctuating or nonsignificant changes in laboratory values do not necessarily qualify for AE reporting. If these 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.

11.2.1.2. Serious Adverse Events

An SAE is any AE or suspected adverse reaction that, in the view of the investigator, results in 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, based upon appropriate medical judgment, they may jeopardize the participant 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, which, in the view of either the investigator or sponsor, places the participant 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.

All SAEs (irrespective of causality) must be reported to Apellis Safety immediately, no later than 24 hours of the investigator or their representative becoming aware of the event, as described in Section 11.2.3.

11.2.1.3. Unexpected AEs

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.

11.2.2. Recording and Reporting AEs

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

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 patient 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 and up to 56 days beyond the last dose of study medication will be recorded as TEAEs.

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 participant discontinued the study as a result of the event. AEs characterized as intermittent require documentation of the start and stop of each incidence.
If possible, the outcome of any AE resulting in permanent discontinuation or that was present at the end of the study should be reported. AEs resulting in interruption or discontinuation of study drug or that are present at the exit visit should receive follow-up as appropriate.

11.2.2.1. 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 6 should be considered when evaluating the relationship of AEs/SAEs to study treatment.

Table 6: 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

11.2.2.2. 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 11.2.1.2. An AE can be of severe intensity but not be considered serious.

Table 7 presents the definitions that should be considered when evaluating the severity of AEs and SAEs.

Table 7: 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 AEs

All SAEs must be reported to 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.

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

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

11.2.4. Pregnancy

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

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

The investigator should make every effort to obtain the consent from the pregnant woman to follow the status of the pregnancy until completion. The outcome of the pregnancy (eg, delivery, termination) and, as applicable, the neonatal outcome should be reported within 24 hours of awareness. In the event of an abnormal outcome (outcome other than live, healthy birth), an SAE report form must be reported within 24 hours of investigator awareness, as described in Section 11.2.3.

11.2.5. AEs of Special Interest

The following events are classified as AEs of special interest:

- Thrombocytopenia
- Severe infection (see Section 11.2.2.2 for a discussion of severity grading)
- Hypersensitivity, including pneumonitis
- Severe acute kidney injury (see Section 11.2.2.2 for a discussion of severity grading)

An AE of special interest can be serious or nonserious but must be reported to the sponsor/Apellis Safety in the same manner as an SAE, as described in Section 11.2.3.

11.2.6. Abuse, Misuse, Overdose, and Medication Errors

Occurrences of events of abuse or misuse of the medicinal product, overdose, 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 participant (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 abuse or misuse of the medicinal product, overdose, or medication error must be reported appropriately. 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 participant's source document.

12. STATISTICS

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 the final SAP or from what is outlined in the protocol will be discussed in the final study report.

12.1. Determination of Sample Size

Approximately 80 to 100 participants, including patients with native kidney disease or post-transplant, will be randomized 1:1 to pegcetacoplan or placebo with 40 to 50 participants per arm.

Based on preliminary data from Study APL2-201, a reduction of 60% in uPCR in the pegcetacoplan group at week 26 is assumed vs a reduction of 20% in uPCR in the placebo arm, which corresponds to mean log ratio to baseline of −0.92 vs −0.22 respectively, and a standard deviation of 0.88 (on log-scale). Based on this assumption, a sample size of 70 participants in total provides at least 90% power at 1-sided significance level of 0.025. Considering a 10% attrition to account for potential missing assessments and impact by COVID-19, it is expected that at least 78 participants with native kidney disease should be enrolled.

A minimum of 63 participants with C3G in native kidneys will be enrolled, which is approximately 80% of the enrolled participants with native kidney disease.

12.2. Analysis Set

12.2.1. Screened Set

The screened set will include all participants who provide written informed consent. This set will be used only for the purpose of describing participant disposition.

12.2.2. Safety Set

The safety set will include all participants who receive at least 1 dose of study drug in the RCP. Participants will be analyzed according to the treatment they received.

12.2.3. Intent-to-Treat Set

The intent-to-treat (ITT) set will include all randomized participants. Participants will be analyzed according to their assigned treatment, regardless of the treatment actually received. All efficacy analyses will be performed with the ITT set.

12.2.4. Per-Protocol Set

The per-protocol (PP) set will include all participants in the ITT set who have not violated any inclusion or exclusion criteria and/or deviated from the protocol in a way that could influence their efficacy assessment. Decisions concerning the exclusion of participants from the PP analysis set will be made and documented prior to database lock.

12.2.5. Pharmacokinetic Set

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

12.2.6. Pharmacodynamic Set

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

12.2.7. Data Review for Analysis Set

After all the data have been verified, coded, and entered into the database, a review will be performed to check the quality of the data, identify any outliers, and make decisions on how to deal with any data issues (eg, missing values, withdrawals, protocol deviations). After this review, resolution of all issues, and documentation of all decisions, the database will be locked.

12.3. Efficacy Analysis

12.3.1. Analysis of Primary Efficacy Endpoint

The targeted treatment regimen to be used for this study is pegcetacoplan or placebo plus stable regimen for C3G/IC-MPGN treatment. The primary estimand on the treatment effect of pegcetacoplan is for the participant population as defined through the study inclusion/exclusion criteria, with the primary endpoint based on the log-transformed ratio of uPCR (sampled from first-morning urine collections) at week 26 compared to baseline using an equal-weighted average over weeks 24, 25, and 26.

Population level summary is the treatment difference in the mean change from baseline in log-transformed ratio to baseline in uPCR of pegcetacoplan over placebo.

A hypothetical strategy will be used for addressing the intercurrent events (ICEs) that are listed in ICE categories 1 and 2 in Table 8. In the hypothetical strategy, uPCR data collected at visits after the occurrence of ICEs will be set as missing and will be imputed using different approaches as described in Table 8. A treatment policy strategy will be used for ICEs of premature discontinuation of treatment (ICE category 3). In the treatment policy strategy, any measured value will be used as is.

The primary endpoint will be analyzed using a mixed effect model for repeated measures (MMRM). The model will include fixed categorical effects for treatment group, visit, disease type (C3G vs IC-MPGN), stratification factors, and the visit-by-treatment group interaction, as well as the continuous, fixed covariate of baseline log-transformed uPCR. Initially, an unstructured covariance matrix will be investigated. If this analysis fails to converge, other covariance structures will be used; details will be provided in the statistical analysis plan. The difference between treatment groups using a composite contrast of equal-weighted average over weeks 24, 25, and 26 will be estimated with its 95% CI and corresponding *P* value. The model will be applied to each multiply imputed data set, and results from each imputed data set will be combined using Rubin's rule (Rubin 1976).

The primary efficacy analysis will be conducted using the ITT set. Supplemental analysis based on alternative estimands, analysis using the PP set, and sensitivity analyses for assessing the robustness of the primary analysis results will be performed and prespecified in the SAP.

Subgroup analyses will also be conducted to describe findings within both stratification factors in addition to other important prognostic factors such as disease type, age, sex, baseline uPCR, etc.

Table 8: Intercurrent Events During the Randomized Treatment Phase and Strategies Addressing Intercurrent Events for the Primary Efficacy Endpoint

ICEs	Strategies for addressing ICEs
ICE Category 1 Use of prohibited concomitant medication in the protocol (Section 8.3.3) Use of rescue therapies defined in the protocol (Section 8.3.2)	Hypothetical strategy will be used where all measurements after events under any ICE in this category will be set to missing. Missing data resulting from these ICEs will be imputed using reference-based imputation.
ICE Category 2 Start renal replacement therapy (dialysis)	Hypothetical strategy will be used where all measurements after the ICEs will be set as missing. Missing data resulting from these ICEs will be imputed based on the worst change of all participants across visits plus a random error.
ICE Category 3 Permanent discontinuation of study treatment.	Treatment policy strategy will be used whereby any measured value will be used as is. Missing data resulting from the ICEs will be imputed using reference-based imputation.

Abbreviations: ICE = intercurrent event.

12.3.2. Analysis of Secondary Efficacy Endpoints

To preserve the overall type I error among the primary endpoint and key and additional secondary endpoints, a fixed-sequence testing strategy will be used; hence, statistical significance of the first secondary endpoint will be evaluated only if statistical significance is achieved with the primary analysis of the primary endpoint. The remaining secondary endpoints will also adhere to this testing strategy, and their order will match the order in which they are presented in Section 5.2.1.

12.3.2.1. Key Secondary Efficacy Endpoints:

- The numbers and proportion of participants who meet the criteria for achieving a composite renal endpoint at week 26 will be tabulated by treatment group and analyzed using a logistic regression model with treatment group as the independent variable and adjusted for baseline eGFR values, baseline log-transformed uPCR values, disease type, and stratification factors. The *P* value and odds ratio of being a responder for the pegcetacoplan group to being a responder for the placebo group with associated 95% CI will be provided.

  A participant meets the requirements of the composite renal endpoint if he/she satisfies: (1) a stable or improved eGFR compared to baseline (≤15% reduction in eGFR), and (2) a ≥50% reduction in uPCR compared to baseline.

  A composite strategy will be used for addressing the ICEs listed in Table 9. In the composite strategy, the composite renal endpoint status at or after the occurrence of any of these ICEs below will be regarded as non-responder.

Table 9: Intercurrent Events During the Randomized Treatment Phase and Strategies Addressing Intercurrent Events for the Composite Renal Endpoint

ICEs	Strategies for addressing ICEs
Use of prohibited concomitant medication in the protocol (Section 8.3.3) Start renal replacement therapy (dialysis) Use of rescue therapies defined in the protocol (Section 8.3.2) Permanent discontinuation of study treatment	Composite strategy. The composite renal endpoint status at or after the initiation of any of ICEs will be regarded as non-responder.

Abbreviations: ICE = intercurrent event.

- The numbers and proportion of participants who achieve uPCR response at week 26 will be tabulated by treatment group and compared using a logistic regression model with treatment group as the independent variable and adjusted for baseline uPCR values, disease type, and stratification factors. The *P* value and odds ratio of being a responder for the pegcetacoplan group to being a responder for the placebo group with associated 95% CI will be provided. ICEs will be handled as described in Table 9.

  The uPCR response, defined as a reduction of at least 50% from baseline in uPCR at week 26, will be calculated using the following steps:

  1. Baseline uPCR value will be calculated as the average of the uPCR measurements from at least 6 of the 9 FMU samples collected between the start of screening and day 1, inclusive. The uPCR values used to calculate baseline should include those from the samples collected on day –2, day –1, and before dosing on day 1.
  2. Week 26 uPCR value will be calculated as the average of the uPCR measurements from at least 6 of the 9 FMU samples collected in week 24, week 25, and week 26.
  3. Each participant will be categorized as either a success or a failure according to whether the change from baseline in uPCR calculated from steps 1 and 2 is a reduction of at least 50%.

  For participants with evaluable renal biopsies, evaluation of the change from baseline to week 26 in the C3G histologic index activity score will use an analysis of covariance (ANCOVA) model with treatment as a fixed effect, adjusted for baseline C3G histologic index activity score, disease type, and stratification factors. Least-square (LS) means will be presented for each treatment group, along with the between-treatment difference, 95% confidence interval, and *P* value. The strategies to handle intercurrent events are the same as those for the primary endpoint. This endpoint will be evaluated based on adult participants only because neither the week 26 renal biopsy nor an on-study baseline renal biopsy are required for adolescent participants. All data, including any data from adolescent participants, will be included in a summary table.

For participants with evaluable renal biopsies, the numbers and proportion of participants showing decreases in C3c staining intensity of at least 2 orders of magnitude from baseline to the week 26 renal biopsy will be tabulated by treatment group and compared using a logistic regression model with treatment group as the independent variable and adjusted for baseline C3c staining, disease type, and stratification factors. The odds ratio of being a responder for the pegcetacoplan group to being a responder for the placebo group and associated 95% CI and *P* value will be provided. ICE will be handled the same as Table 9. This endpoint will be evaluated based on adult participants only because neither the week 26 renal biopsy nor an on-study baseline renal biopsy are required for adolescent participants.

- Change from baseline in eGFR at week 26 will be tabulated by treatment group and analyzed using a MMRM model. The model will include fixed categorical effects for treatment group, visit, disease type, stratification factors, and the visit-by-treatment group interaction, as well as the continuous, fixed covariate of baseline eGFR values. Initially, an unstructured covariance matrix will be investigated, if this analysis fails to converge, other covariance structures will be used, details will be provided in the statistical analysis plan. The difference between treatment groups will be estimated with its 95% CI and corresponding *P* value. The strategies to handle intercurrent events are similar to those for the primary endpoint.

12.3.2.2. Additional Secondary Efficacy Endpoints:

- The proportion of participants achieving proteinuria <1 g/d at week 26 will be analyzed using the same approach as the first key secondary endpoint.
- For participants with serum albumin levels below the LLN at baseline, the number and proportion of participants with normalization of serum albumin at week 26 will be calculated using the following steps:

  1. Baseline serum albumin value will be calculated as the average of up to 2 serum albumin measurements preceding and including day 1. Participants will be included in the denominator of this calculation only if the baseline albumin value is below the LLN.
  2. Week 26 serum albumin values will be calculated as the average of up to 2 serum albumin measurements preceding and including week 26.
  3. Each participant will be categorized as either a success or a failure according to the week 26 serum albumin values as calculated in Step 2. Values greater than or equal to the LLN will be categorized as a success; values less than the LLN will be categorized as a failure.

  For participants with serum albumin levels below the LLN at baseline, the numbers and proportion of participants with normalization of serum albumin at week 26 will be tabulated by treatment group and compared using a logistic regression model with treatment group as an independent variable and adjusted for baseline albumin value, disease type, and stratification factors. The *P* value and odds ratio of showing serum albumin above the LLN at week 26 for the pegcetacoplan group vs. the placebo group and associated 95% CI will be provided. The strategies to handle intercurrent events are the same as those for the first key secondary endpoint.

- For participants with low serum C3 levels at baseline, the number and proportion of participants with normalization of serum C3 levels at week 26 will be calculated using the following steps:

  1. Baseline serum C3 value will be calculated as the average of up to 2 serum C3 measurements preceding and including day 1. Participants will only be included in the denominator of this calculation if the baseline C3 value is below the LLN.
  2. Week 26 serum C3 value will be calculated as the average of up to 2 serum C3 measurements preceding and including week 26.
  3. Each participant will be categorized as either a success or a failure based on the week 26 serum C3 value as calculated in Step 2. Values greater than or equal to the LLN will be categorized as a success; values less than the LLN will be categorized as a failure.

  For participants with low serum C3 levels at baseline, the numbers and proportion of participants with normalization of serum C3 levels at week 26 will be tabulated by treatment group and compared using a logistic regression model adjusting for baseline serum C3 level, disease type, and stratification factors. The odds ratio of showing a serum C3 level above the LLN at week 26 for the pegcetacoplan group vs. the placebo group and associated 95% CI and *P* value will be provided. The strategies to handle intercurrent events are the same as those for the first key secondary endpoint.
- The change from baseline in FACIT-Fatigue score at week 26 will be analyzed using analysis of covariance (ANCOVA) model with treatment as a fixed effect, adjusted for baseline FACIT-Fatigue score, disease type, and stratification factors. LS means will be presented for each treatment group, along with the between-treatment difference and 95% confidence interval. The strategies to handle intercurrent events are the same as those for the primary endpoint.
- The change from baseline in KDQOL score at week 26 will be analyzed using analysis of covariance (ANCOVA) model with treatment as a fixed effect, adjusted for baseline KDQOL score, disease type, and stratification factors. LS means will be presented for each treatment group, along with the between-treatment difference and 95% confidence interval. The strategies to handle intercurrent events are the same as those for the primary endpoint.

12.3.3. Analysis of Exploratory Endpoints

Details regarding the analysis of exploratory endpoints will be presented in the SAP.

12.4. Safety Analysis

All safety analyses will be summarized for the safety set.

AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities at the time of analysis. TEAEs will be summarized by System Organ Class, Preferred Term, and treatment group for the number of participants and proportion reporting the event. A similar summary will be produced for SAEs, AEs leading to discontinuation of study drug, severe AEs, and AEs related to the investigational product.

The intensity of AEs and the relationship to investigational product will be summarized for each System Organ Class and Preferred Term by treatment group.

Withdrawals due to AEs will be summarized for each body system and Preferred Term by treatment group.

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

In participants who are post transplant, the number and incidence of rejection episodes at week 26, will be tabulated by treatment group and compared between treatment groups using Fisher's exact test or a stratified Cochran-Mantel-Haenszel χ-square test as appropriate. The number and incidence of rejection episodes at week 52 will be tabulated.

In participants who are post transplant, the number and incidence of graft loss at week 26 will be tabulated by treatment group, and the results for treatment groups will be compared using Fisher's exact test or a stratified Cochran-Mantel-Haenszel χ-square test as appropriate. The number and incidence of graft loss at week 52 will be tabulated.

Changes from baseline in clinical laboratory test results will be summarized, using descriptive statistics, by visit and nominal time postdose. Baseline will be taken as the measurement closest to but before randomization. Out-of-range values will be flagged in data listings.

ADA results, ECG results, and changes from baseline in vital sign measurements will be summarized by treatment group, using appropriate descriptive statistics. Baseline will be taken as the measurement closest to but before randomization.

Values of potential clinical significance (eg, increase in QTcF $\geq$30 milliseconds from baseline) will be flagged in listings and summarized by treatment.

ECG parameters will be analyzed using concentration effect models.

Changes in physical examination results will be described in a data listing.

12.5. Pharmacokinetic Analysis

The PK concentrations will be evaluated using the PK set.

Concentrations will be summarized, using descriptive statistics, over time, in the randomized treatment group (pegcetacoplan group).

Individual participant 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 guidances for both exposure-response and population PK (FDA Guidance for Industry: Population Pharmacokinetics; FDA Guidance for Industry: Exposure-Response Relationships).

12.6. Pharmacodynamic 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 by treatment group.

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

The PD endpoints will be compared between treatment groups using mixed effect repeated measures analyses.

12.7. Other Analyses

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

World Health Organization and Medical Dictionary for Regulatory Activities coding dictionaries will be used for the concomitant medications and medical histories, respectively.

12.8. Interim Analysis

An analysis will be conducted for administrative purposes or regulatory submissions when all participants have completed the randomized controlled period and the data is cleaned. No type I error adjustment is necessary.

12.9. Data Monitoring Committee

A formal independent data monitoring committee (DMC) will be used for this study. Representatives of Apellis Pharmaceuticals, Inc, will not participate in the review of unblinded data, but if requested by the DMC may participate in the review of blinded data or attend portions of DMC meetings at which blinded data are presented and discussed to facilitate or answer questions. In addition, external medical and scientific experts may be invited to participate in the reviews, as needed.

DMC meetings will be held according to the schedule in the DMC charter. The remit, roles, and responsibilities of the DMC will be specified in a DMC charter.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1. Study Monitoring

Before an investigational site can enter a participant into the study, a representative of Apellis Pharmaceuticals, Inc, will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Apellis Pharmaceuticals, Inc, or its representatives. This will be documented in a clinical study agreement between Apellis Pharmaceuticals, Inc, and the investigator.

During the study, a monitor from Apellis Pharmaceuticals, Inc, or representative will have regular contacts with the investigational site, for but not limited to the following:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that study drug accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the participant's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each participant (eg, clinic charts).
- Record and report any protocol deviations not previously sent to Apellis Pharmaceuticals, Inc
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to Apellis Pharmaceuticals, Inc, and those SAEs that met criteria for reporting have been forwarded to the IRB

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

13.2. Audits and Inspections

Authorized representatives of Apellis Pharmaceuticals, Inc, a regulatory authority, an Independent Ethics Committee, or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of an Apellis Pharmaceuticals, Inc, audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), and any applicable regulatory requirements. The investigator should contact Apellis Pharmaceuticals, Inc, immediately if contacted by a regulatory agency about an inspection.

13.3. Institutional Review Board

The principal investigator must obtain IRB approval for the investigation. Initial IRB approval and all materials approved by the IRB for this study, including the informed consent and assent forms and any recruitment materials, must be maintained by the investigator and made available for inspection.

14. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, Apellis Pharmaceuticals, Inc, may conduct a quality assurance audit. Please see Section 13.2 for more details regarding the audit process.

15. ETHICS

15.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The investigator must submit written approval to Apellis Pharmaceuticals, Inc, before he or she can enroll any participant into the study.

The principal investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit participants for the study. The protocol must be reapproved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The principal investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Apellis Pharmaceuticals, Inc, will provide this information to the principal investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

15.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the GCP guideline of the ICH, applicable regulatory requirements, and the Apellis Pharmaceuticals, Inc, policy on bioethics.

15.3. Written Informed Consent

The principal investigator(s) at each center will ensure that written informed consent is obtained for each participant before any study procedures are conducted. The informed consent process must at a minimum include the following:

- The investigator or his/her representative will explain the nature of the study to the participant and/or his or her legally authorized representative, including full and adequate oral and written information about the nature, purpose, and possible risks and benefits of the study, and answer all questions regarding the study. Participants and/or their legally authorized representatives or guardians should have the opportunity to consider the information provided before providing their consent.
- Participants must be informed that their participation is voluntary and that they are free to discontinue from the study at any time. Each participant or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of Chapter 50 of Title 21 of the US Code of Federal Regulations, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the requirements of the IRB/IEC or study center. Where appropriate, the participant must also give assent to participation in the study in accordance with local regulations.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- If the ICF is revised, participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- If informed consent is initially provided by a participant's legally authorized representative and the participant acquires the ability to provide informed consent during their participation in the study (eg, by reaching the age of majority), informed consent must be obtained from the participant before additional study-related activities are conducted.

The principal investigator(s) must maintain the original, signed ICF. A copy of the ICF must be given to the participant.

16. DATA HANDLING AND RECORDKEEPING

16.1. Inspection of Records

Apellis Pharmaceuticals, Inc, will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, participant charts and study source documents, and other records relative to study conduct.

16.2. Retention of Records

The principal investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Apellis Pharmaceuticals, Inc, or the regulatory authority to review any documentation relating to the study, the investigator must permit access to such records.

17. PUBLICATION POLICY

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 participant 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, participant to the terms of any such agreement. 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.

18. LIST OF REFERENCES

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19. APPENDICES

Appendix 1. Protocol Amendment History

A.1.1. Protocol Amendment History

DOCUMENT HISTORY	
Document	**Date**
Country-specific modifications to Protocol Amendment 3	
Amendment 3.1 DEU	02 November 2023
Amendment 3.1 CHE	12 September 2023
Amendment 3.1 FRA, NLD	31 July 2023
Addendum 3.1 ISR	06 April 2023
Addendum 3.1 JPN	06 April 2023
Addendum 3.1 CZE	06 April 2023
Addendum 3.1 CAN	06 April 2023
Amendment 3	03 March 2023
Amendment 2	14 August 2021
Amendment 1	12 March 2021
Original Protocol	26 September 2019

Country-specific protocol modifications are only listed for the most recent global amendment. Any outstanding country-specific modifications are evaluated at each global amendment and incorporated into the global amendment as appropriate.

Amendment 3: Summary of Changes From the Previous Version

Overall Rationale for the Amendment:

The protocol was amended to revise and reorganize the study endpoints in response to feedback and comments from the FDA. Strategies for the statistical analysis of the endpoints were updated to align with the revised endpoints. Additional revisions were made to clarify study procedures and activities in response to feedback from investigators and/or to align with current company practices.

Minor formatting and stylistic revisions were made to align with current templates, and any identified typographical errors were corrected; these are not identified individually in the descriptions below.

Description of change	Section(s) affected	Rationale for change
Study design and rationale changes		
Updated summary of clinical experience to include Study APL2-308	Section 4.3	Updated to reflect current clinical experience with pegcetacoplan
Increased duration of screening period from 8 to 10 weeks with a corresponding increase of total duration of study participation to 70 weeks	Synopsis, Section 6, Section 6.1.1, Figure 1	Updated to allow extra time for the transfer, processing, and reading of biopsy materials within the screening period
Increased the minimum number of adolescent participants from 8 to 10	Section 6, Section 6.2	Increased to align with the current pediatric investigational plan, and clarified that participants initially screened as adolescents will follow adolescent procedures and requirements through the duration of the study.
Revised study scheme diagram	Figure 1	Reflects revised screening period
Study endpoint changes		
Changed primary efficacy endpoint from the proportion of subjects with a reduction from baseline in uPCR of at least 50% to the log-transformed ratio of uPCR at week 26 compared to baseline	Synopsis, Section 5.2.1, Section 12.3.1	Dichotomization of continuous outcomes in clinical trials can result in loss of statistical power. Revised in response to FDA suggestion to assess the primary endpoint as a continuous variable
Changed key secondary efficacy endpoint to the proportion of participants who meet the criteria for achieving a composite renal endpoint (a stable or improved eGFR compared to the baseline visit (≤15% reduction in eGFR), and a ≥50% reduction in uPCR compared to the baseline visit.)	Synopsis, Section 5.2.1, Section 12.3.2	Revised to provide analysis of the population with reduced proteinuria who maintain a stable eGFR. Revised in response to FDA suggestion to redefine the criteria for a stable or improved eGFR; combined eGFR and uPCR responses in a new composite endpoint
Escalated change in eGFR to a key secondary endpoint	Synopsis, Section 5.2.1, Section 12.3.2	Reorganized secondary endpoints following the change to the primary endpoint
Added the proportion of participants with a reduction of at least 50% from baseline in uPCR as a key secondary endpoint	Synopsis, Section 5.2.1, Section 12.3.2	Reorganized secondary endpoints following the change to the primary endpoint

Description of change	Section(s) affected	Rationale for change
Removed change from baseline in uPCR as an additional secondary efficacy endpoint	Synopsis, Section 5.2.1, Section 12.3.2	Reorganized secondary endpoints following the change to the primary endpoint
Revised and reorganized exploratory endpoints to align with changes to primary and secondary endpoints	Section 5.2.1	Reorganized exploratory endpoints following the change to the primary and secondary endpoints
Reorganized pharmacokinetic, pharmacodynamic, and immunogenicity endpoints to appear in a single heading	Section 5.2.3	Organizational change in presentation of endpoints
Participant selection changes		
Clarified that biopsy-based inclusion criteria apply to both baseline biopsies collected as part of the study and historical biopsies collected within 28 weeks of randomization and used as baseline biopsies	Synopsis, Section 7.1	Clarified to provide additional guidance for investigators
Added sodium-glucose cotransporter-2 inhibitors to the description of stable treatment regimens for C3G/IC-MPGN	Synopsis, Section 7.1	Added to reflect recognition of treatment with sodium-glucose cotransporter-2 inhibitors as standard of care treatment for chronic kidney disease
Updated the time requirements for stable dosing regimens to remove reference to baseline renal biopsy; timing of stable treatment requirements is now based solely on randomization	Synopsis, Section 7.1	Clarified to provide additional guidance for investigators and for consistency with stable treatment requirement period
Added recent severe infection as an exclusion criterion	Synopsis, Section 7.2	Incorporated changes requested by health authorities
Study intervention changes		
Clarified when open-label dosing will begin	Synopsis, Section 6.1.3, Table 2 (Schedule of Activities), Section 11.1.2	Clarified that open-label dosing will begin at the first visit after the week 26 renal biopsy for adults and any adolescents providing renal biopsies. Open-label dosing for adolescents not providing renal biopsies should start at the week 26 visit. Clarified procedures and requirements for the transition to open-label dosing to provide additional guidance for investigators
Updated vaccination guidance to recognize the potential use of local guidelines as an alternative to ACIP guidelines	Section 8.2	Added to recognize that vaccination requirements and practices may differ between countries
Updated discussion of vaccination against *S pneumoniae* to reflect recent changes to ACIP guidelines	Section 8.2	Revised to reflect current ACIP guidelines

Description of change	Section(s) affected	Rationale for change
Study assessment changes		
Removed testing of C3Nef from samples collected after screening	Table 2 (Schedule of Activities), Table 4 (Laboratory Assessments)	Revised protocol to incorporate guidance in a previous protocol clarification letter, as the evidence suggests C3 inhibition does not change C3NF
Clarified the timing of the collection of baseline and week 26 renal biopsies and the requirements for using a prior biopsy as the baseline biopsy	Section 6.1.1, Section 10.5	Clarified the windows for collection of the baseline and 26-week renal biopsies.
Clarified requirements for chest radiography, moved baseline radiography to visit 2	Section 11.1.7, Table 2 (Schedule of Activities)	Clarified requirements for chest radiography to provide additional guidance for investigators. Moved collection of the baseline chest radiography to follow the initial screening visit for consistency with other invasive procedures (eg, vaccination, renal biopsy)
Safety reporting changes		
Updated discussion of assessment of severity of adverse events	Section 11.2.2.2	Updated to align with current company practices
Updated description of procedures for reporting SAEs to Apellis	Section 11.2.3	Updated to align with current company practices
Updated description of procedures for monitoring and reporting pregnancies to Apellis	Section 11.2.4	Updated to align with current company practices
Statistical analysis changes		
Updated discussion of the determination of sample size	Synopsis, Section 6, Section 6.2, Section 12.1	Updated to provide additional background, and to reflect determination of the sample size based on the revised primary endpoint. Changing the primary endpoint led to an increase in the number of participants with native kidney disease to 78. Also provided enrolment targets for participants with posttransplant recurrence and for participants with C3G in native kidneys.
Updated the discussion of the efficacy analyses	Synopsis, Section 12.3	Updated to reflect the revised the primary, key secondary, and additional secondary endpoints
Study conduct changes		
Clarified screening procedures, including rescreening activities	Section 6.1.1, Section 6.1.1.1	Clarified procedures based on feedback from investigational sites
Clarified discussion of study treatment discontinuation, study withdrawal, and the activities to be undertaken in these situations	Section 7.3	Updated to align with current company practices

Description of change	Section(s) affected	Rationale for change
Provided guidance for the resumption of dosing if regularly scheduled doses are missed	Section 8.1	Updated to provide additional guidance for investigators
Clarified discussion of study treatment blinding requirements	Section 8.5.2	Updated to align with current company practices
Added the potential to ship investigational product and/or ancillary study supplies directly to the participant, where permitted	Section 9.3	Updated to align with current company practices
Clarified guidance regarding infusion sites	Section 9.5	Updated to align with current company practices
Document organization changes		
Updated Responsible Medical Director	Signature Page	Updated to reflect organizational change in study management
Changed wording from “subjects” to “participants”	Global	Updated to align with current company practices

Amendment 2: Summary of Changes From the Previous Version

Overall Rationale for the Amendment:

The protocol was amended to address comments from the FDA. Additional revisions were made for clarification of study activities or to align with current company practices.

Minor formatting and stylistic revisions were made to align with current templates, and any identified typographical errors were corrected; these are not identified individually in the descriptions below.

Description of change	Section(s) affected by change
Study design and rationale changes	
Changed planned enrollment from 90 to 80-100 subjects	Synopsis, Section 6, Section 6.1.2, Section 6.2, Section 12.1
Clarified vaccination strategy and prophylactic antibiotic use in Risk/Benefit discussion	Section 4.4
Changed primary and key secondary objectives to align with endpoint changes	Synopsis, Section 5.1
Changed from 10 posttransplant minimum to 77 native kidney minimum	Section 6, Section 6.2, Section 8.5.1, Section 12.1
Added 8-adolescent minimum	Section 6, Section 6.2
Revised study scheme diagram	Section 6.1 (Figure 1)
Study endpoint changes	
Changed primary efficacy endpoint to remove eGFR component	Synopsis, Section 5.2, Section 12.3.1
Removed proportion of subjects with uPCR reductions of at least 50% as a secondary efficacy endpoint	Synopsis, Section 5.2, Section 12.3.2
Changed primary and key secondary efficacy endpoints from week 52 to week 26	Synopsis, Section 5.2, Section 12.3.1, Section 12.3.2
Revised and reorganized secondary and exploratory endpoints (including timing of evaluations)	Synopsis, Section 5.2, Section 12.3.1, Section 12.3.2
Subject selection changes	
Increased minimum body weight to 30 kg	Synopsis, Section 7.1, Section 8.1
Updated inclusion criteria to define evidence of active renal disease and remove central medical review	Synopsis, Section 7.1
Updated inclusion criteria to define acceptable stable regimens for treatment of C3G/IC-MPGN	Synopsis, Section 7.1
Revised replacement of subjects section to clarify that subjects who discontinue will not be replaced	Section 7.3.4
Study intervention changes	
Clarified wording of renal biopsies in adolescents section to explicitly note that biopsies will not be collected for research purposes from adolescent subjects in the US	Section 10.5.2

Description of change	Section(s) affected by change
Created separate subsection in Concomitant Medications describing permitted prior medications	Section 8.3
Added section discussing possible rescue treatment for C3G/IC-MPGN	Section 8.3.2
Study assessment changes	
Added specification of use of Bedside Schwartz equation in adolescents where missing	Synopsis, Section 6.1.1
Added chest radiography to schedule of activities and discussion of safety procedures	Table 2, Section 11.1.7, Table A1
Removed fibrinogen and added prothrombin time to coagulation section of laboratory assessments table	Section 11.1.9 (Table 4)
Safety reporting changes	
Added section describing AEs of special interest	Section 11.2.5
Statistical analysis changes	
Removed discussion of extrapolating placebo response rate from week 26 to week 52	Synopsis, Section 4.2.2, Section 12.3.1
Removed potential sample size revision	Synopsis, Section 6, Section 6.2, Section 12.8
Changed baseline, week 26, and week 52 uPCR calculations to the average of 6 to 9 samples from the average of 9 samples	Section 6.1.1, Section 12.3.1, Section 12.3.2
Added discussion of primary and alternate estimands	Section 12.3.1
Added discussion of intercurrent events and how they will be handled in assessment of the primary endpoint	Section 12.3.1
Updated descriptions of calculations of responder analysis for uPCR and eGFR endpoints	Section 12.3.1, Section 12.3.2
Revised and clarified descriptions of analysis of secondary endpoints	Section 12.3.2
Removed interim analyses (interim analysis 1 for sample size readjustment and interim analysis 2 for early efficacy assessment)	Synopsis, Section 12.8
Study conduct changes	
Added section describing maximum blood collection volumes	Section 11.1.12
Removed central medical review for confirmation of diagnosis and eligibility	Synopsis, Section 6.1.1, Section 7.1, Section 10.5.2, Section 11.1.2
Clarified that Apellis representatives will not review unblinded data	Section 12.9
COVID-19 continuity changes	
Added COVID-19 vaccine to COVID-19 risk mitigation section and COVID-19 Appendix	Section 4.4.1, Appendix 2
Document organization changes	
Added appendix listing prior revision history of the document	Appendix 1

Amendment 1: Summary of Changes From the Previous Version

Overall Rationale for the Amendment:

The protocol was amended to revise the study design and endpoints following discussions with regulatory authorities and internal evaluation of the study, and to provide guidance to investigators in the case of COVID-19–related restrictions. Additional revisions were made for clarification of study activities, or to align with current company practices.

Minor formatting and stylistic revisions were made to align with current templates, and any identified typographical errors were corrected; these are not identified individually in the descriptions below.

Description of change	Section(s) affected by change
Study design and rationale changes	
Updated study design so that the randomized controlled period is double-blinded and added justification of study design section.	Synopsis, Section 4.2.2, Section 6, Section 6.1, Section 8.5.2
Shortened the follow-up period for subjects who do not continue receiving pegcetacoplan from 24 to 8 weeks.	Synopsis, Section 6, Section 6.1, Section 6.1.4
Added requirement that the study will enroll at least 10 subjects with posttransplant recurrence of C3G or IC-MPGN.	Synopsis, Section 6, Section 6.2, Section 8.5.1
Added an interim analysis of efficacy when all subjects have completed the 26-week randomized controlled period.	Synopsis, Section 12.8
Added an optional renal biopsy at week 52 to support evaluation of the revised primary endpoint.	Synopsis, Section 6.1, Section 6.1.3, Table 1 (Schedule of Activities), Section 10.5
Study endpoint changes	
Revised the primary endpoint from the change from baseline in urine protein-to-creatinine ratio (uPCR) at week 26 to the proportion of subjects with a reduction in uPCR of at least 50% and an estimated glomerular filtration rate (eGFR) that is stable or improved from baseline at week 52.	Synopsis, Section 5.2.1
Extensively revised secondary efficacy endpoints, exploratory endpoints, and safety endpoints.	Synopsis, Section 5.2.2, Section 5.2.3, Section 5.2.4
Subject selection changes	
Amended inclusion criteria to allow enrollment of adolescents of 20 kg or more, rather than 42 kg or more.	Synopsis, Section 7.1
Amended inclusion criteria to include a definition of women of childbearing potential and provided a definition of childbearing potential.	Synopsis, Section 7.1, Section 7.1.1
Added inclusion criterion that subjects must be willing and able to self-administer pegcetacoplan or have an identified caregiver who can perform the administration.	Synopsis, Section 7.1
Added exclusion criterion requiring an absolute neutrophil count of at least 1000 cells/mm^3 at screening.	Synopsis, Section 7.2

Description of change	Section(s) affected by change
Added exclusion criterion for subjects with hypersensitivity to pegcetacoplan or excipients.	Synopsis, Section 7.2
Added exclusion criterion for subjects with a history of meningococcal disease.	Synopsis, Section 7.2
Added exclusion criterion excluding subjects with known or suspected hereditary fructose intolerance.	Synopsis, Section 7.2
Removed exclusion criterion for subjects with liver dysfunction.	Synopsis, Section 7.2
Replaced inclusion criterion for body mass index ≤35 kg/m^2 with exclusion criterion for weight >100 kg.	Synopsis, Section 7.1, Section 7.2
Study intervention changes	
Revised dosing recommendations, adding regimens for adolescent subjects ≥50 kg, 35 to <50 kg, and 20 to <35 kg.	Synopsis, Section 4.2.3, Section 8.1
Revised wording of vaccination requirements to cite Advisory Committee on Immunization Practices guidelines and align with current company practices.	Section 8.2
Added description of blinding and unblinding procedures.	Section 8.5.2
Study assessment changes	
Clarified instructions for triplicate first-morning spot urine collection.	Section 10.3
Provided additional guidance on the collection of renal biopsy samples, including clarification of the biopsy requirements for adolescent subjects.	Section 10.5
Added color fundus photography to the optional ophthalmologic evaluation; clarified that the evaluation should also include a basic ophthalmologic examination.	Table 1 (Schedule of Activities), Section 10.6
Safety reporting changes	
Update wording describing monitoring and reporting of AEs and SAEs to align with current company practices, including: • Updated wording defining terms • Updated description of evaluation and recording of adverse events • Clarified SAE reporting responsibilities and procedures	 Section 11.2.1 Section 11.2.2 Section 11.2.3
• Clarified pregnancy reporting responsibilities and procedures	Section 11.2.4
• Added guidance on the definition and reporting of abuse, misuse, overdose, and medication errors	Section 11.2.5

Description of change	Section(s) affected by change
Statistical analyses changes	
Updated descriptions of statistical analyses to align with revised endpoints.	Synopsis, Section 12.3, Section 12.4
Revised description of sample size evaluation and added a description of the interim analysis of efficacy.	Synopsis, Section 12.1, Section 12.8
Study conduct changes	
Updated and clarified procedures for obtaining informed consent.	Section 15.3
COVID-19 continuity changes	
Added wording describing risks related COVID-19 and activities to mitigate these risks.	Section 4.4.1, Appendix 1

Appendix 2. Country-Specific Protocol Modifications

Country-specific modifications to this protocol are listed below.

Additions to the protocol are marked by underlined text, and deletions of existing protocol text are marked by ~~strikethrough text~~.

Canada

Rationale for Modifications

These modifications to the APL2-C3G-310 protocol are being implemented in Canada to support the Investigational Testing Authorization for the Crono Super PID infusion pump and CRN Crono 20-mL syringe reservoir.

Summary of Changes

Changes in the sections noted below will be enacted by this addendum.

9.4 Infusion Supplies

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

The Crono Super PID infusion pump and the CRN Crono 20-mL syringe reservoir, which will be used during the clinical study to deliver each dose of the isotonic sterile solution of pegcetacoplan 1080 mg/20 mL (54 mg/mL) transferred from the vial to the syringe, do not have a medical device license authorizing their commercial sale in Canada and are therefore considered investigational medical devices. The infusion pump and reservoir will be used in conjunction with the Neria multi infusion set (MDL #88990; Unomedical Devices SA de CV, Aaholmvej 1-3, Osted, 4320 Lejre, Denmark) and the vial adaptor (MDL #70132; West Pharmaceutical Services IL, Ltd, 4 Hasheizaf St, Ra'Anana, Israel, 4366411), which are approved for use in Canada.

9.4.1. Investigational Medical Devices: Crono Super PID Infusion Pump and CRN Crono 20-mL Reservoir

9.4.1.1. Descriptions of the Investigational Medical Devices

The Crono Super PID infusion pump is an electromechanical, software-controlled, reusable infusion pump manufactured by Canè SpA Medical Technology (Via Cuorgnè 42/a, 10098 Rivoli, Cascine Vica [TO], Italy) that is supplied to the participant and used throughout the duration of the study. The CRN Crono 20-mL syringe reservoirs are sterile, nonpyrogenic, single-use syringes specifically for use with the Crono pumps and are supplied in individual sterile packaging. A new syringe reservoir is filled from the drug vial with the transfer set, used for one dose of pegcetacoplan, and then disposed of. During the study, infusion site/pump safety will be assessed during clinical visits, and any significant finding from the assessment will be recorded.

9.4.1.2. Justification for the Use of the Investigational Medical Devices

Apellis assessed the potential hazards associated with the delivery of the drug product in relation to the uses for which the pump carries a CE mark in the EU. The hazards evaluated were related to the required critical performance attributes, the user profile, and the use environment relevant to use with the drug product in the clinical trial. This assessment included testing to confirm performance to the required delivery requirements and the delivery process and evaluation of the user population in comparison with those for which these devices are already CE-marked for use.

The assessment concluded that the Crono Super PID infusion pump could meet the delivery requirements of Study APL2-C3G-310, does not present any unique usability issues to the user groups in Study APL2-C3G-310, and does not introduce any additional or residual risks.

The use of the investigational devices in human participants is justified on the basis of the design and intended uses of the device constituent parts (Canè Crono Super PID Infusion Pump and CRN Crono 20-mL syringe reservoir), which are appropriate.

9.4.1.3. Anticipated Exposure to the Investigational Medical Devices

The anticipated exposure to the investigational device is approximately 30 minutes per infusion twice weekly.

9.4.1.4. Anticipated Adverse Device Effects

The anticipated adverse device effects are discussed in Section 9.4.2.

9.4.1.5. Number of Investigational Devices to be Used

The sponsor plans to open 3 sites in Canada and expects to assign to treatment 2 participants across the sites in Canada. Each participant assigned to treatment will receive a primary pump, a backup pump, and enough infusion sets for 52 weeks of biweekly infusions. Sites will be provided with additional pumps and infusion supplies (approximately 20% overage, rounded up). Actual need will depend on enrollment, but 14 Super PID pumps and approximately 360 syringe reservoirs are planned for the study sites in Canada.

9.4.2. Risks of Investigational Medical Devices

The use of this delivery system with this drug in this clinical trial does not create any risks additional to the residual risk inherent with the current use of these devices. There is a possibility that participants could experience redness, swelling, and pain or tenderness at the site of infusion. There is also a slight possibility of infection. In addition, because pegcetacoplan is to be administered by SC infusion, participants may feel some discomfort from the infusion. None of these risks are affected by the use of these specific devices.

9.4.3. Reporting of Incidents Related to Investigational Medical Devices

All incidents related to investigational medical devices must be reported to Apellis immediately, within 24 hours of the investigator or their representative becoming aware of the event. The site must complete the complaints form and email it to complaints@apellis.com immediately, within 24 hours of becoming aware of the event.

The sponsor is responsible for submitting reports of incidents related to an investigational medical device to Health Canada and the device manufacturer within 72 hours of becoming aware of the issue. The device manufacturer will then further assess the incident according to the timelines in the guidance and report their findings accordingly.

9.4.4. Investigational Medical Device Accountability

Accountability for the investigational medical devices at the study center is the responsibility of the investigator. The investigator will ensure that the investigational medical devices are used only in accordance with this protocol. Where allowed, the investigator may choose to delegate accountability responsibilities to a pharmacist or other appropriate individual.

Investigators will be provided with sufficient amounts of the investigational medical devices to carry out this protocol for the agreed number of participants. The investigator or designee will acknowledge receipt of the investigational medical devices, documenting shipment content and condition. Accurate records of all the investigational medical devices provided, used, returned, and/or destroyed must be maintained. Accountability records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and participant numbers. The sponsor or its designee will review the investigational medical device accountability at the study center on an ongoing basis during monitoring visits.

The investigational medical devices must not be used for any purpose other than the present study. The investigational medical devices that have been provided to a participant and returned unused must not be provided to a different participant.

9.4.5. Investigational Medical Device Handling

All used and unused investigational medical devices should be retained at the study center until they are inventoried by the study monitor. All used, unused, or expired investigational medical devices will be returned to the sponsor or its designee for disposition. Disposition will be documented, or if authorized disposed of at the study center according to the center's standard operating procedures and documented.

Czech Republic

Rationale for Modifications

These modifications to the APL2-C3G-310 protocol are being implemented in the Czech Republic, as requested by the State Institute for Drug Control.

Summary of Changes

Enrollment of Adolescent Participants

As described in Section 7.1, Inclusion Criteria, adolescents (aged 12-17 years) may be enrolled where approved. The enrollment of adolescent participants is not approved in the Czech Republic, and therefore only adult participants, aged 18 years or older, will be enrolled in this country.

France, Netherlands, Germany

Rationale for Modifications

These modifications to the APL2-C3G-310 protocol are being implemented to temporarily allow participants in Study APL2-C3G-310 in France, the Netherlands, or Germany to continue to receive pegcetacoplan after the completion of the 52 weeks of treatment defined in Protocol APL2-C3G-310 if they are eligible and intend to enter Study CCI [redacted], the long-term extension study, but that study is not yet fully approved and active.

Summary of Changes

Changes in the sections noted below will be enacted by this addendum.

Section 6.1.3, Part 3: Open-Label Period (26 Weeks)

At the end of the RCP, participants from both groups will proceed to the 26-week open-label period, in which all participants will be treated with pegcetacoplan twice weekly. Open-label dosing will begin at the first visit after the week 26 renal biopsy for adults and any adolescents providing renal biopsies. Open-label dosing for adolescents not providing renal biopsies should start at the week 26 visit. At the end of the open-label period, there will be an optional renal biopsy. Participants younger than 18 years who did not have a baseline biopsy within 28 weeks of day 1 will not have a biopsy at the end of the open-label period. Upon completion of the open-label period, participants will enter the follow-up period (Part 4) unless they enter a long-term extension study.

Participants who have completed the planned 52 weeks study participation and are eligible and intend to enter Study CCI [redacted], the long-term extension study, may continue to receive pegcetacoplan in this study if immediate transition to the long-term extension study is not possible because that study is not yet fully approved and active. If this occurs, participants should continue study visits every 6 weeks, and investigators should collect at least the information defined for the week 42 visit in the schedule of activities, excluding any optional assessments. This extension period may continue for up to approximately 3 months.

Israel

Rationale for Modifications

These modifications to the APL2-C3G-310 protocol are being implemented in Israel to satisfy requirements of the Ministry of Health (MOH) and to clarify that only adolescent study subjects will be enrolled in Israel.

Summary of Changes

Enrollment of Participants

To comply with the Ministry of Health requirement that in-study renal biopsies must be optional, only adolescent participants will be enrolled at study sites in Israel. Enrolled participants must follow the procedures described in the protocol, including any specific notations or considerations for adolescent participants.

Because only adolescent participants will be enrolled, the following portions of the protocol are modified as indicated:

Synopsis and Section 7.1, Inclusion Criteria

1. ~~Aged at least 18 years; where approved, a~~Adolescents (aged 12-17 years) weighing at least 30 kg ~~may also be enrolled.~~

Section 10.5.1, Renal Biopsies in Adults, is no longer applicable and should be disregarded.

Japan

Rationale for Modifications

These modifications to the APL2-C3G-310 protocol are being implemented in Japan to satisfy requirements of the Pharmaceuticals and Medical Devices Agency and to clarify study procedures in Japan by considering Japanese regulatory rules and the actual situation of general medical practice.

Contraception Exceptions

The protocol includes implantable or injectable contraceptives and removable birth control devices as acceptable methods of contraception. These methods of contraception are not approved in Japan and therefore will not be allowed for Japanese participants included in this study.

Vaccinations

Meningitis caused by *Neisseria meningitidis* type B is not endemic to Japan, and the number of patients with meningitis caused by *N meningitidis* type B in Japan has been decreasing in recent years. Given this, the meningococcal B vaccine is not approved in Japan. Participants enrolled in Japan for this clinical trial must have received the meningococcal conjugate vaccine for *N meningitidis* A, C, W, and Y and do not need to have received the meningococcal B vaccine.

The schedule of vaccinations is consistent with the United States Centers for Disease Control and Prevention rationale as well as the Japanese Respiratory Society/Japanese Association for Infectious Diseases recommendation “Considerations of Pneumococcal Vaccination for Adults Aged 65 and Over.”

All other vaccinations defined in the protocol are marketed in Japan and should be administered as described in Section 8.2 of the global protocol. Investigators must follow the instructions in the package inserts of these vaccine products when planning vaccination schedules.

Summary of Changes

Changes in the sections noted below will be enacted by this addendum.

Contraception Exceptions

Section 7.1.1, Acceptable Methods of Contraception, is modified as below:

7.1.1. Acceptable Methods of Contraception

Women of childbearing potential (WOCBP) and male participants with female partners of childbearing potential will be instructed to practice an acceptable method of birth control throughout the duration of the study and for 90 days following the end of study drug administration.

A woman is considered to be of childbearing potential following menarche and until becoming postmenopausal, unless she is 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 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 participants with female partners of childbearing potential only)

Not all methods of contraception may be available in all of the countries in which this study is being conducted.

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

Vaccinations

Vaccinations are discussed in multiple locations in the global protocol. The affected sections are modified as below:

Study Design: Protocol Synopsis and Section 6.1.1

Part 1: Screening Period; last bullet

- Vaccinations against *S pneumoniae*, *N meningitidis* (types A, C, W, and Y~~, and B~~), and *H influenzae* (type B) are mandatory unless documented evidence exists that participants are nonresponders to vaccination. If required, vaccination series should be initiated at least 14 days prior to randomization. Vaccinations are discussed in more detail in Section 8.2.

Inclusion Criteria: Protocol Synopsis and Section 7.1

Inclusion Criterion 8

8. Have received vaccinations against *S pneumoniae*, *N meningitidis* (types A, C, W, and Y~~, and B~~), and *H influenzae* (type B) as per ACIP recommendations for adults or children with complement deficiencies. Vaccination series should be initiated at least 14 days prior to randomization. Vaccination is mandatory unless documented evidence exists that participants are nonresponders to vaccination.

Vaccinations: Section 8.2

8.2. Vaccinations

To receive study drug, participants will be required to be vaccinated as follows on the basis of ACIP recommendations for adults or children with complement deficiencies (available at https://www.cdc.gov/vaccines/schedules/hcp/index.html) or other similar local guidelines.

- *N meningitidis* types A, C, W, and Y: First dose at least 14 days prior to randomization with a second dose 2 months later, and then boosters every 5 years.
- ~~*N meningitidis* type B: First dose at least 14 days prior to randomization 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*: pneumococcal conjugate vaccine (PCV13, PCV15, or PCV20, depending on participant age and vaccine availability) and/or pneumococcal polysaccharide vaccine ~~23~~ (PPSV23). Adults who have not previously received any pneumococcal vaccine may receive PCV20, if the site is able to procure it, and a subsequent dose of PPSV23 would not be required. Multiple scenarios exist depending on previous vaccination history and investigators should consult ACIP guidelines for adults or children with complement deficiencies or other similar local guidelines.
- *H influenzae* type B: Documentation of childhood vaccination or one dose at least 14 days prior to randomization.

Vaccination is mandatory, unless documented evidence exists that participants have received the recommended vaccinations or are nonresponders to vaccination. For participants who do not have this documented evidence, the required missing vaccination(s) will be administered as needed to bring participants up to date. The investigator will discuss with the medical monitor any individual participant circumstances relevant to the vaccination requirements that would make the above schedule not possible or reasonable, or if the investigator has any questions or concerns about the vaccination requirements. If local or national guidelines for immunizations differ from the ACIP recommendations, the differences should be discussed with the medical monitor to determine an appropriate course of vaccinations. On an ongoing basis, including upon entry into a long-term extension, participants should be reevaluated for the need for any additional vaccinations or boosters on the basis of ACIP recommendations.

Vaccination serum samples will be collected on the day of vaccination before receiving vaccinations on that visit. These samples will be analyzed to evaluate response to vaccinations if the participant tests positive for infection with *S pneumoniae*, *N meningitidis*, or *H influenzae*.

Laboratory Assessments: Section 11.1.9

Table 4: Laboratory Assessments, Footnote f

f. Serum samples will be collected to evaluate response to vaccinations to *N meningitidis* (types A, C, W, and Y~~, and B~~), PCV13, PCV20, or PPSV23, and Hib. Samples will only be analyzed in the event that the participant has a positive infection for *Streptococcus pneumoniae*, *Neisseria meningitidis*, or *Haemophilus influenzae*.

Switzerland

Rationale for Modifications

These modifications to the APL2-C3G-310 protocol are being implemented in Switzerland to support the Investigational Testing Authorization for the Crono Super PID infusion pump (version 2).

Summary of Changes

Changes in the sections noted below will be enacted by this addendum.

Section 9.4, Infusion Supplies

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

This clinical study is a combined trial with medical devices. The Crono Super PID infusion pump (version 2) is an electromechanical, software-controlled, reusable infusion pump manufactured by CANÈ S.p.A. Medical Technology (Via Cuorgnè 42/a, 10098 RIVOLI - Cascine [TO] – Italy) that is supplied to the participant and used throughout the duration of the study. The CRN Crono 20 mL syringe reservoirs are sterile, nonpyrogenic, single-use syringes, specifically for use with Crono infusion pumps. Since the initiation of this clinical study, CANÈ S.p.A. Medical Technology has modified the intended use of the Crono Super PID infusion pump, and it is no longer licensed for administration of immunoglobulins and drugs in general, but only for the administration of immunoglobulins. Given this change, the use of the Crono Super PID infusion pump in this study is considered to be investigational.

The infusion pump and syringe reservoirs will be used in conjunction with the Neria multi-infusion set (Unomedical Devices S.A de C.V, Aaholmvej 1-3, Osted, 4320 Lejre Denmark). And the vial adaptor (West Pharma. Services IL, Ltd., 4 Hasheizaf St., Ra'Anana, Israel, 4366411), which are *conformité européenne* (CE)-marked and approved for use in Switzerland.

9.4.1 Investigational Medical Devices: Crono Super PID Infusion Pump and CRN Crono 20 mL Syringe Reservoir

9.4.1.1 Justification for the Use of the Investigational Medical Devices

The Crono Super PID infusion pump was selected for use in this trial as it is the only available subcutaneous infusion pump that enables blinded administration of pegcetacoplan or the placebo used in this study by allowing the same delivery time despite their differing viscosities.

Apellis assessed the potential hazards associated with the delivery of the drug product in relation to the uses for which the pump carries a CE mark in the European Union. The hazards evaluated were related to the required Critical Performance Attributes, the user profile, and use environment relevant to use with the drug product in the clinical trial. This assessment included testing to confirm performance to the required delivery requirements and the delivery process and evaluation of the user population compared with those for which these devices are already CE-marked for use.

The assessment concluded that the Crono Super PID infusion pump could meet the delivery requirements of Study APL2-C3G-310, does not present any unique usability issues to the user groups in Study APL2-C3G-310, and does not introduce any additional or residual risks.

The use of the investigational devices in human participants is justified based on the design and intended uses of the device constituent parts (Crono Super PID infusion pump and CRN Crono 20 mL syringe reservoir), which are appropriate.

9.4.1.2 Risks of Investigational Medical Devices

The use of this delivery system with this drug in this clinical trial does not create any risks additional to the residual risk inherent with the current use of these devices. There is a possibility that participants could experience redness, swelling, and pain or tenderness at the site of infusion. There is also a slight possibility of infection. In addition, as pegcetacoplan is to be administered by subcutaneous infusion, participants may feel some discomfort from the infusion. None of these risks are affected by the use of these specific devices.

9.4.2 Reporting of Device Deficiencies and Adverse Events Related to Investigational Medical Devices

All device deficiencies and serious adverse events where a relationship with the use of investigational medical devices cannot be ruled out must be reported to Apellis immediately, within 24 hours of the investigator or their representative becoming aware of the event. The site must complete the complaints form and email it to Complaints@Apellis.com immediately, within 24 hours of becoming aware of the event.

The sponsor is responsible for submitting reports of device deficiencies and serious adverse events related to the use of investigational medical devices, as described in according to Art. 33 para. 1 of the ClinO-MD, to SwissMedic and the device manufacturer within 72 hours of becoming aware of the issue. The device manufacturer will then further assess the incident per the timelines in the guidance and report their findings accordingly.

9.4.2.1 Definitions for Reporting of Safety Events Related to Investigational Medical Devices

For the purpose of reporting safety events related to investigational medical devices, the following definitions will apply:

Investigational Device

A device that is assessed in a clinical investigation.

Adverse Event

Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs, including an abnormal laboratory finding, in participants, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device. Note that this definition includes events that are anticipated as well as unanticipated events. This definition also includes events occurring in the context of a clinical investigation related to the investigational device, the comparator, or the procedures involved.

Adverse Device Effect

Any adverse event related to the use of an investigational medical device or a comparator.

Anticipated Serious Adverse Device Effect

Any serious adverse device effect which by its nature, incidence, severity, or outcome has been identified in the last risk assessment document upon serious adverse device effect occurred.

Causality Assessment

Safety events related to investigational medical devices should be classified as not related, possibly related, probably related, or definitely related to the use of the investigational medical device, according to the definitions in section 9 of the EU guidance (Safety Reporting in Clinical Investigations of Medical Devices Under the Regulatory [EU] 2017/745, MDCG2020-10/1, 2020).

Device Deficiency

Any inadequacy in the identity, quality, durability, reliability, safety, or performance of an investigational device, including malfunction, use errors, or inadequacy in information supplied by the manufacturer.

Incident

Any malfunction or deterioration in the characteristics or performance of a device made available on the market, including use-error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side-effect.

Reportable Serious Adverse Device Effect

Serious adverse event that is either possibly, probably, or definitely related to the use of the investigational medical devices. This includes relationship to the device or the procedure.

Serious Adverse Device Effect

Any adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Serious Incident

Any incident that directly or indirectly led, might have led, or might lead to any of the following:

- the death of a participant, user, or other person
- the temporary or permanent serious deterioration of a participant's, user's, or other person's state of health
- a serious public health threat

Appendix 3. COVID-19 Study Continuity Plan

A.3.1. Protocol Changes to be Followed During COVID-19 Restrictions

A.3.1.1. Overview

As a response to the COVID-19 global public health emergency, Apellis will implement the measures outlined in this addendum to safeguard the rights, welfare, and safety of Study APL2-C3G-310 participants and investigative site staff when and if deemed necessary. These measures are based on guidance issued by global regulatory health authorities regarding the impact of COVID-19 on the management of clinical trials and can only be implemented at each clinical investigative site after written approval from the sponsor.

A.3.1.2. Minimum Study Requirements

A.3.1.2.1. Safety Assessments

When feasible, the full list of protocol assessments should be conducted; however, the following are the **minimum** study safety requirements for Study APL2-C3G-310:

1. **Maintain** dosing schedules and management per protocol guidelines
2. **Obtain** key safety laboratory assessments:
    a. All laboratory assessments will be drawn at the frequency required by the minimized Schedule of Events (see Table A1), at a minimum. Collection of more than the minimum activities described in Table A1 should continue to the extent possible, and investigators should resume following the full schedule of activities as soon as possible.
    b. In the event that the clinical investigative site is closed and/or participants are unable or unwilling to travel, participants will be referred to a certified local laboratory that can perform the required safety testing specified in Table A1. Alternatively, a home health care provider may be sent to the participant's home to draw samples for the minimum laboratory tests required for safety testing (see Section A.3.1.5), which may then be sent to the central laboratory or to a local laboratory. Use of the central laboratory is preferable whenever feasible. In the event that a local laboratory is used, the investigator will collect the local laboratory reports, which must be redacted in accordance with local privacy requirements. The laboratory results, reference ranges, units of measure, and format of laboratory values are to be filed with the study records.
3. **Perform** minimal medical safety assessments:
    a. If the participant is unable to have an in-person assessment, the investigator (or delegated site staff) will have a telephone and/or video contact at the frequency noted in the protocol (at minimum) to solicit adverse events (including serious adverse events) and concomitant medications. The appropriate forms in the electronic case report form will be completed.

b. Serious adverse event reporting requirements are unchanged, and all serious adverse events are still required to be reported to Apellis within 24 hours of the investigator or their representative becoming aware of the event(s).

4. **Document** appropriate contact with the participant:

    a. At least 3 documented attempts, including a certified letter with return receipt, must be made to solicit adverse events and concomitant medications before considering the visit missed. If contact with the participant still cannot be established for the following visit after another 3 documented attempts, participant is considered lost to follow-up. The clinical research associate and medical monitor must be notified of any participants lost to follow-up.

    b. All communication with the participant (including failed attempts at contact) must be documented in the study records.

A.3.1.2.2. Efficacy Assessments

The participants must be able to complete the following assessments to continue in the trial:

- Renal biopsies during screening and at week 26 (adult participants only)
- Triplicate first-morning urine collection during screening and at weeks 26 and 52
- Serum chemistry and hematology during screening and at weeks 26 and 52

A.3.1.3. Screening

A.3.1.3.1. Study Screening

A participant cannot be considered for screening using the minimum study requirements. The screening and baseline assessments must remain unchanged and must be completed in their entirety. The sponsor may decide to pause screening at any point because of the COVID-19 pandemic, at which point sites will be notified and should not attempt to screen new participants.

For sites continuing at full capacity (and not using the minimum study requirements), the investigator should assess and appropriately document the risk/benefit of participants continuing to come to the clinic for visits. These sites may continue to screen new participants using the protocol-outlined procedures.

A.3.1.3.2. Institutional Screening for Public Health or Clinical Purposes

A.3.1.3.2.1. Mandatory Clinical Screening Procedures

According to local guidance, if an institution implements mandatory public health screening procedures related to a public health emergency (eg, COVID-19, measles, etc) for all individuals coming into that institution, inclusive of research participants, IRB approval is not required before screening procedures are implemented. Additionally, because these screening procedures are not research procedures, the institution does not require IRB approval to share results with a public health authority or research participants, although adherence to other permissions or notice restrictions remain under applicable law and/or policy (see Section A.3.1.12).

A.3.1.3.2.2. Excluded Public Health Surveillance Activities

Some types of public health surveillance activities, including collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority, may be conducted per local, regional, and national regulation and guidance as applicable (see Section A.3.1.12).

If a public health authority authorizes general screening for COVID-19 for public health surveillance purposes and requests that test results be shared as necessary with a public health authority to allow the public health authority to identify, monitor, assess, or investigate the COVID-19 outbreak, an investigator may incorporate these activities into an existing research visit without prior IRB review and approval.

Note, however, that US Food and Drug Administration regulations may apply if the screening procedure involves use of an investigational in vitro diagnostic device.

A.3.1.4. Participants Testing Positive for COVID-19

The following are considerations and changes that might need to be made for participants who test positive for COVID-19.

If a research participant tests positive for COVID-19

1. Follow the clinical recommendations of the study site and public health authorities to manage the infection.
2. Follow the notification requirements of the study site and public health authorities. Investigators should inform the participant of the required reporting of results. Note: The results of the COVID-19 test should be recorded in the COVID-19 electronic case report form and documented as an adverse event if the result is positive.
3. Determine whether a positive test result meets criteria for withdrawal from the study, or for reporting as a serious adverse event by contacting the sponsor and notifying IRBs/ethics committees and/or health authorities as required per local guidelines.

A.3.1.5. COVID-19 Vaccination

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 participant, with consideration of local and national vaccination recommendations and a benefit-risk assessment. Vaccination is not mandatory for continued study participation.

Apellis is currently not aware of any contraindications to vaccination (of any modality) and concurrent treatment with pegcetacoplan. Precaution should be taken when vaccinating participants with any concurrent illnesses that may affect the efficacy or safety of vaccination (eg, complement-activating condition) and as indicated by the labeled prescribing information.

All vaccinations (including boosters) should be recorded as concomitant medications. The information should include the type of COVID-19 vaccination administered. Any untoward medical events related to vaccination should be captured in the participants source document and should include the timing in relation to the vaccine. Any questions should be directed to the medical monitor or study team.

A.3.1.6. Home Health Care Provider

In the event that the clinical investigative site is closed and/or participants are unable or unwilling to travel, home health care providers (HHCPs) may be used to perform study activities, such as the below, with participants' consent:

- Blood draw
- Investigational product administration
- Investigational product accountability
- Study assessments

HHCPs will be required to follow all safety precautions set by the local guidance/regulations prior to and after contact with participant(s). HHCPs will summarize the activities completed, including any reported AEs, at the visit in a home visit report, which will be provided to the clinical investigative site for review and to file in the study records.

A.3.1.7. Monitoring

Remote monitoring measures may be implemented with participants' consent in accordance with local and institutional guidelines. Methods to review and perform remote monitoring will be outlined in the sponsor's clinical monitoring plan.

A.3.1.8. Investigational Product

To ensure that participants can continue treatment during the COVID-19 public health emergency and the associated changes with these clinical trials, additional study drug may need to be dispensed to participants or shipped to their homes. Additional dispensation of study drug and/or direct shipment of study drug to participants' homes will only be implemented if permitted by local regulations, in conjunction with participant consent and corresponding ethics committee and competent authority approval, as required. Participants are to return all study drug to the investigator site once on-site visits are permitted to enable full study drug accountability.

A.3.1.9. Regulatory Considerations

Actions taken as a result of the COVID-19 public health emergency (protocol deviations, urgent safety measures, etc) that fall outside of standard clinical trial conduct guidance and regulations should be documented as appropriate in the study file. Ensure compliance with all local, regional, and national regulation and guidance, as applicable.

A.3.1.10. Statistical Considerations

In accordance with the local, regional, and national guidelines, the SAP for the study might need to be updated on the basis of the guidance provided by regulatory authorities related to the COVID-19 public health emergency.

A.3.1.11. Schedule of Activities—Minimum Study Requirements

For all screening visits, day 1, and week 26, the visits must occur in clinic, and all assessments on those days are required. Every effort should be made to conduct a full and in-person visit at week 52, but if COVID-19 restrictions make that impossible, the visit may be conducted virtually or by an HHCP after consultation with the medical monitor. The remainder of the required visits can be done virtually or by an HHCP, and for these visits, the required assessments are indicated. Visits and/or assessments not required as part of the minimum activities are shown in strikethrough text in Table A1.

Table A1: Revised COVID-19 Minimum Schedule of Activities

Study period	Screening period[a]		Randomized controlled period								Open-label period						Follow-up period		
Study week	**–10 to –4**	**–2**	**1**	**4**	~~**8**~~	**12**	~~**16**~~	**20**	**24**	**26**	**28**	**32**	~~**36**~~	**42**	**48**	**52**	~~**54**~~	**56**	**60 Exit**
Study day	**–70**	**–14**	**1**	**28**	~~**56**~~	**84**	~~**112**~~	**140**	**168**	**182**	**196**	**224**	~~**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[b]**		**0**	**3**	~~**7**~~	**7**	~~**7**~~	**7**	**3**	**3**	**3**	**7**	~~**7**~~	**7**	**7**	**7**	~~**3**~~	**3**	**7**
Assessments																			
Informed consent	X																		
Demographics	X																		
Medical history	X																		
Post-transplant immunosuppression plan documentation[c]		X																	
Inclusion/exclusion	X	X	X																
Vaccination[d]		X[b]				X													
Adverse events	X	X	X	X	~~X~~	X	~~X~~	X	X	X	X	X	~~X~~	X	X	X	~~X~~	X	X
Concomitant medications	X	X	X	X	~~X~~	X	~~X~~	X	X	X	X	X	~~X~~	X	X	X	~~X~~	X	X
Physical examination (full)[e]	X		X							X[e]						X			
Physical examination (brief)[e]		X		~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~		~~X~~[e]	~~X~~	~~X~~	~~X~~	~~X~~			~~X~~	~~X~~	~~X~~
12-lead ECG	X		X		~~X~~		~~X~~		~~X~~	X	~~X~~		~~X~~		~~X~~	X	~~X~~		~~X~~
Chest radiography		X[b]								X						X			
Renal biopsy[f]	X[b]									X[g]						~~X~~[h]			
Randomization			X																
Study drug administration[i]			X	X	~~X~~	X	~~X~~	X	X	X	X	X	~~X~~	X	X	X			
Infusion site/pump safety assessment[j]			X	X	~~X~~	X	~~X~~	X	X	X	X	X	~~X~~	X	X	X	~~X~~		
Vital sign measurements[k]	X	X	X	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	X	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	X	~~X~~	~~X~~	~~X~~
HRQoL[l]		X								X						X			

Table A1: Revised COVID-19 Minimum Schedule of Activities

Study period	Screening period[a]		Randomized controlled period								Open-label period						Follow-up period		
Study week	**–10 to –4**	**–2**	**1**	**4**	~~**8**~~	**12**	~~**16**~~	**20**	**24**	**26**	**28**	**32**	~~**36**~~	**42**	**48**	**52**	~~**54**~~	**56**	**60 Exit**
Study day	**–70**	**–14**	**1**	**28**	~~**56**~~	**84**	~~**112**~~	**140**	**168**	**182**	**196**	**224**	~~**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[b]**		**0**	**3**	~~**7**~~	**7**	~~**7**~~	**7**	**3**	**3**	**3**	**7**	~~**7**~~	**7**	**7**	**7**	~~**3**~~	**3**	**7**
Urine																			
24-hour urine collection[m]	X					X			X				~~X~~		X				X
Triplicate FMU uPCR[n]	X	X	X[o]	X	~~X~~	X	~~X~~	X	X	X	X	X	~~X~~	X	X	X	~~X~~	X	X
In-clinic (random) uPCR	X	X	X	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	X	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	X	~~X~~	~~X~~	~~X~~
Urinalysis (dipstick & microscopic)[p]	X																		
Urine pregnancy test		X	X	X	~~X~~	X	~~X~~	X	X	X	X	X	~~X~~	X	X	X	~~X~~	X	X
Blood																			
Hematology[p] & chemistry[p]	X	X	X	X	~~X~~	X	~~X~~	X	X	X	X	X	~~X~~	X	X	X	~~X~~	X	X
PK sample collection			X	X	~~X~~	X	~~X~~	~~X~~	~~X~~	X	X	X	~~X~~	~~X~~	~~X~~	X	~~X~~	X	X
ADA assays[q]			X	~~X~~			~~X~~		~~X~~				~~X~~			X	~~X~~		X
Serum complement profile[p]	X	X	X	~~X~~	~~X~~	X	~~X~~	~~X~~	~~X~~	X	X	~~X~~	~~X~~		~~X~~	X	~~X~~	X	X
Plasma complement profile[p]	X		X		~~X~~		~~X~~		~~X~~	X	~~X~~		~~X~~		~~X~~	X	~~X~~		X
eGFR[r]	X	X	X	X	~~X~~	X	~~X~~	X	X	X	X	X	~~X~~	X	X	X	~~X~~	X	X
Pregnancy (β-HCG)	X																		
Screening assays[s]	X																		
Optional assessments																			
~~Ophthalmologic evaluations[t]~~		~~X[t]~~												~~X[t]~~					
~~Measured GFR[u]~~			~~X[u]~~							~~X[u]~~				~~X[u]~~					

Table A1: Revised COVID-19 Minimum Schedule of Activities

Abbreviations: Ab = antibodies; ADA = antidrug antibodies; AE = adverse events; AH50 = 50% alternative hemolytic complement pathway activity; ANA = antinuclear antibodies; ANCA = antineutrophil cytoplasmic antibodies; β-HCG = beta human chorionic gonadotropin; CH50 = 50% classical hemolytic complement pathway activity; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EQ-5D-5L = 5-Level EuroQol-5 Dimension; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy- Fatigue Scale; FMU = first-morning spot urine; FSH = follicle-stimulating hormone; GFR = glomerular filtration rate; HIV = human immunodeficiency virus; HRQoL = health-related quality of life; KDQOL = Kidney Disease Quality of Life; N/A = not applicable; PGIC = Patient Global Impression of Change; PK = pharmacokinetic; SC = subcutaneous; SD-OCT = spectral domain optical coherence tomography; SPEP = serum protein electrophoresis; uPCR = urine protein-to-creatinine ratio; WPAI = Work Productivity and Activity Impairment.

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

a) All visit 2 assessments need not occur in a single visit and visit 2 can be split into multiple visits (eg, visit 2a, visit 2b).

b) Vaccinations, baseline renal biopsy, and screening chest radiography can occur any time during screening after confirmation of eligibility based on visit 1 data.

c) For transplant participants only. Must be documented prior to randomization.

d) Vaccine series should be initiated at least 14 days prior to randomization; additional vaccines may be required at visit 6. Please see Section 8.2 for more details on vaccination requirements. Vaccination serum samples will be collected on the day of vaccination prior to receiving vaccinations on that visit. These samples will be analyzed to evaluate response to vaccinations in the event that the participant has a positive infection for *Streptococcus pneumoniae*, *Neisseria meningitidis*, or *Haemophilus influenzae*.

e) A full physical examination is required at visits 1, 3 (week 1), 10 (week 26), and 16 (week 52). A full physical examination should also be conducted on the first day of open-label dosing, if that not at the week 26 visit. Brief physical examinations, including weight (kg) and assessment of edema, will be conducted at all other visits noted. A symptom-driven physical examination may be performed at any time, at the investigator's discretion. Body height (cm) will be measured only during screening for adults but will be measured at screening as well as every 12 weeks throughout the study for adolescents; weight (kg) will be measured throughout study, during brief and full physical examinations for all participants. Both body weight and height will be assessed without shoes on; height will be measured using a calibrated stadiometer. Edema should be assessed at every visit.

f) Renal biopsies will not be required for participants under the age of 18, provided they have an adequate prior renal biopsy to establish the diagnosis as per the central pathology laboratory.

g) The week 26 renal biopsy need not occur on the same day as all other assessments for that visit. However, the week 26 triplicate uPCR collections must occur prior to the renal biopsy. In addition, the week 26 biopsy must occur prior to the first visit of the open-label period at week 28. Participants younger than 18 years are not required to provide renal biopsies and may advance to the open-label period upon completion of all assessments for weeks 24 through 26 other than the renal biopsy.

h) The week 52 renal biopsy is optional for all participants. If performed it should be after collection of the week 48 24-hour urine and FMU samples and not more than 8 weeks after the week 52 visit, In the event that a participant has a renal biopsy as part of their clinical management within this window, it may serve as the week 52 biopsy provided that it includes the required components for this study.

i) Study drug will be self-administered by the participant or administered by their caregiver, after receiving appropriate training and sign-off by a research nurse (or other qualified personnel) in their first treatment week, as described in Section 9.5. Once qualified, the participant or caregiver should administer study drug at site visits (as done at home) on those days when a clinic visit occurs on a dosing day. In the event that a home nurse is administering study drug on nonvisit days, then the site staff may administer study drug on days of site visits.

j) Between site visits, participants will be instructed to report any infusion site reaction to the study staff. Pump use safety will be reviewed by licensed health care professionals (ie, investigator or nurse) for each study drug administration at clinic visits and during at-home qualification.

k) Vital signs should be measured a maximum of 2 hours before study drug infusion. On day 1 and on the first day of open-label dosing (week 26 or week 28, depending on whether a week 26 renal biopsy is required and when it is performed), vital signs should also be measured approximately 30 minutes to 1 hour after the first infusion of study drug dosing, timed from the completion of the study drug administration. Blood pressure and heart rate should be evaluated after the participant has been resting in a seated 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.

l) FACIT-Fatigue, EQ-5D-5L, KDQOL, PGIC, and WPAI.

Table A1: Revised COVID-19 Minimum Schedule of Activities

m) The screening 24-hour urine collection may be done any time between screening visit 1 and screening visit 2. After week 1 collections should be within ±1 week of the visit (except for the week 24 collection, which cannot be earlier than week 24). Courier arrangements can be made to pick up the collection container from the participant, or the participant may return the container directly to the site.

n) Triplicate FMU samples will be collected by the participant at home on 3 consecutive days throughout the duration of the study. These should be the first urinary output of the day. An additional triplicate FMU uPCR sample will be collected at week 25. Samples should be collected within ±1 week of the clinic visit (except for weeks 24 through 26, when sample collection should be within ±3 days of the clinic visit). Courier arrangements can be made by the site to pick up the collection containers from the participants, or the participant may return them directly to the site. At every visit, enough uPCR collection containers need to be dispensed to the participant to enable all at-home uPCR collections until the next clinic visit.

o) The day 1 triplicate FMU uPCR samples should be collected before the first dose of study drug (eg, day –2, day –1, and before dosing on day 1).

p) Serum complement profile includes AH50, CH50, and C3NeF; C3NeF will only be assayed in samples collected at the baseline (screening) visits. Plasma complement profile includes C3a, C3b/iC3b, C5a, and sC5b-9. See laboratory assessments (Table 4) for more details.

q) The day 1 samples should be collected before dosing with study drug. Participants who discontinue dosing will have ADA samples collected at 2 and 8 weeks after the last treatment. Participants who have a treatment-emergent or treatment-boosted antidrug antibody response at any time will have ADA samples collected approximately every 6 months until the antibody levels revert to baseline.

r) eGFR will be calculated using the Chronic Kidney Disease–Epidemiology Collaboration creatinine equation for adults or the Bedside Schwartz equation for adolescents. For each participant, eGFR will be calculated using the same formula for the duration of the study; the choice of formula will be determined by the participant's age at study entry.

s) Serum FSH (to be measured in female participants only), hepatitis B panel, hepatitis C panel, HIV antibodies, SPEP (adult participants only), ANA, and ANCA (see Table 4 and laboratory manual for more details).

t) Ophthalmologic evaluations are optional and will be performed at selected sites. If evaluations are performed, each participants should have a baseline ophthalmologic 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 participants with drusen prior to pegcetacoplan administration, a follow-up ophthalmologic evaluation, including an SD-OCT and color fundus photography, should occur at a convenient time between weeks 42 and 52.

u) Measured GFR is an optional assessment that, if performed, should occur at 3 time points: once on day 1 or within 10 weeks before day 1, again at week 26, and a third time between week 42 and week 52, inclusive. Measured GFR should only be done at sites where it is routinely performed, as per the site's standard protocol.

A.3.1.12. Regulatory Guidances

European Medicines Agency. Guidance on the management of clinical trials during the COVID-19 (Coronavirus) pandemic. Published 28 April 2020. Accessed 24 August 2020. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf

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Office for Human Research Protections, US Department of Health and Human Services. OHRP guidance on coronavirus. Published 2020. Updated 08 April 2020. Accessed 24 June 2020. https://www.hhs.gov/ohrp/regulations-and-policy/guidance/ohrp-guidance-on-covid-19/index.html

Office for Human Research Protections, US Department of Health and Human Services. Unanticipated problems involving risks & adverse events guidance. Published 2007. Updated 21 March 2016. Accessed 24 June 2020. https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html