# Protocol No.: APL2-201

# A PHASE 2 STUDY TO EVALUATE THE SAFETY AND BIOLOGIC ACTIVITY OF PEGCETACOPLAN IN PATIENTS WITH IGA NEPHROPATHY, LUPUS NEPHRITIS, PRIMARY MEMBRANOUS NEPHROPATHY, OR C3 GLOMERULOPATHY (C3 GLOMERULONEPHRITIS AND DENSE DEPOSIT DISEASE)

**Phase:** 2

**Protocol Amendment 7**

**Approval Date:** 07 July 2022

# INVESTIGATOR AGREEMENT

| | |
|---|---|
| **Long Title:** | A Phase 2 Study to Evaluate the Safety and Biologic Activity of Pegcetacoplan in Patients With IgA Nephropathy, Lupus Nephritis, Primary Membranous Nephropathy, or C3 Glomerulopathy (C3 Glomerulonephritis and Dense Deposit Disease) |
| **Protocol Number/Version/Date** | APL2-201/Amendment 7/07 July 2022 |
| **Study Phase:** | Phase 2 |
| **Sponsor Name and Address:** | Apellis Pharmaceuticals, Inc<br>100 5th Avenue<br>Waltham, MA 02451 |
| **Investigational Test Article:** | Pegcetacoplan Subcutaneous Infusion |
| **US IND#:** | 136409 |
| **Indication Studied:** | IgA Nephropathy, Lupus Nephritis, Primary Membranous Nephropathy, C3 Glomerulopathy |
| **Investigator Agreement:** | I have read the clinical study protocol described herein, recognize its confidentiality, and agree to conduct the described trial in compliance with Good Clinical Practices (GCP), the ethical principles contained within the Declaration of Helsinki, this protocol, and all applicable regulatory requirements. |

**Principal Investigator:**

Name: _____

Signature: _____

Date: _____/_____/_____ (DD/MMM/YYYY)

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# PROTOCOL AMENDMENT SUMMARY OF CHANGES

## Protocol Amendment 7 (Approval date 07 July 2022)

### Overall Rationale for the Amendment:

The protocol was amended to permit the shipping of investigational product and/or ancillary supplies from the study site to a subject's home or other designated location in situations other than COVID-19-related disruptions to study conduct. Additional revisions were made to align the endpoints and analyses with the Statistical Analysis Plan and to align study procedures 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 |
|---|---|---|
| Adding the option to ship investigational product and/or ancillary supplies from the study site to a subject's home or other designated location in situations other than COVID-19-related disruptions to study conduct. | Section 12.3.4, Section A1.1.5.4 | Align with current company practice permitting direct-to-subject shipments, where permitted. |
| Remove measurement of C3Nef after Part A of the study. | Synopsis, Section 9.2.3, Section 16.2.2.3, Table A1, Table A3 | Recommended to remove C3NF testing post-dose as pegcetacoplan interferes with the assay performance. Testing in Part A is already completed and reported so is retained. |
| Add CH50 to the list of pharmacodynamic assays. | Synopsis, Section 9.2.5, Section 14.3 | Previously omitted from list of complement assays to be evaluated. |
| Updated description of the analyses of pharmacokinetic parameters. | Synopsis | Align with description in Section 16.2.4. |
| Updated procedures for reporting SAEs. | Section 15.2 | Align with current company practices. |
| Update procedures for reporting changes in severity of AEs. | Section 15.2.2 | Align with current company practices. |
| Updated procedures for reporting pregnancies. | Section 15.3 | Align with current company practices. |
| Updated definition of TEAEs to include events up to 8 weeks after the last dose of study medication. | Section 16.2.3.1 | Align with current understanding of pegcetacoplan pharmacology and with company reporting practices. |
| Reduce frequency of collection of ADA samples in the long-term extension portion of the study to approximately every 24 weeks. | Table A1, Table A3 | Minimize unnecessary blood collections; reduced frequency should be sufficient to effectively monitor immunogenic responses. |
| Add recommendations regarding vaccination against COVID-19. | Section A2.1.5 | Align with current company practices. |

Abbreviations: ADA = antidrug antibody; AE = adverse event; C3Nef = C3 nephritic factor; CH50 = total hemolytic complement activity assay; COVID-19 = coronavirus disease 2019; SAE = serious adverse event.

# 1. SPONSOR INFORMATION

**Sponsor:**

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

**Sponsor Representative:**

PPD

Date: 07-Jul-2022 | 10:17 EDT

# 2. ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| ACIP | Advisory Committee on Immunization Practices |
| ACR | albumin-to-creatinine ratio |
| ADA | antidrug antibody |
| AE | adverse event |
| AH50 | complement alternative pathway assay |
| ALT | alanine aminotransferase |
| aPTT | activated partial thromboplastin time |
| AST | aspartate aminotransferase |
| AUC | area under the serum concentration versus time curve |
| $AUC_{0-\infty}$ | area under the serum concentration versus time curve, from time 0 to infinity |
| $AUC_{tau}$ | area under the serum concentration versus time curve, over the dosing interval |
| β-HCG | beta human chorionic gonadotropin |
| C3G | C3 glomerulopathy |
| C3GN | C3 glomerulonephritis |
| C3NeF | C3 nephritic factor |
| CH50 | total hemolytic complement activity assay |
| $C_{max}$ | maximum observed serum concentration |
| CKD/EPI | Chronic Kidney Disease Epidemiology Collaboration |
| CL | clearance |
| CL/F | apparent total body clearance after extravascular administration |
| CRF | case report form |
| DDD | dense deposit disease |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| eGFR | estimated glomerular filtration rate |
| ESRD | end-stage renal disease |
| Gd-IgA1 | galactose-deficient IgA |
| GGT | gamma-glutamyl transferase |
| GLP | Good Laboratory Practice |
| GMP | Good Manufacturing Practice |
| Hb | hemoglobin |
| HBsAg | hepatitis B surface antigen |
| HCV | hepatitis C |

| Abbreviation | Definition |
|---|---|
| hERG | human ether-à-go-go-related gene |
| HIV | human immunodeficiency virus |
| IB | investigator's brochure |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IEC | independent ethics committee |
| IgAN | immunoglobulin A nephropathy |
| IND | investigative new drug |
| INR | international normalized ratio (for coagulation) |
| IRB | institutional review board |
| ITT | intent-to-treat |
| IV | intravenous |
| LDH | lactate dehydrogenase |
| LN | lupus nephritis |
| MBL | mannose-binding lectin |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NOAEL | no-observed-adverse-effect level |
| NOEL | no observed effect level |
| PCR | protein-to-creatinine ratio |
| PD | pharmacodynamic(s) |
| PI | primary investigator |
| PLA2R | phospholipase A2 receptors |
| PK | pharmacokinetic(s) |
| PNH | paroxysmal nocturnal hemoglobinuria |
| primary MN | primary membranous nephropathy |
| RBC | red blood cell |
| SAP | statistical analysis plan |
| SC | subcutaneous |
| $t_{½}$ | terminal elimination half-life |
| $T_{max}$ | time at which maximum serum concentration is observed |
| ULN | upper limit of normal |
| uPCR | urine protein-to-creatinine ratio |
| $V_z/F$ | apparent volume of distribution after extravascular administration |
| WBC | white blood cell |
| WOCBP | women of childbearing potential |

# 3. SYNOPSIS

**Protocol Number:**

APL2-201

**Protocol Title:**

A Phase 2 Study to Evaluate the Safety and Biologic Activity of Pegcetacoplan in Patients With IgA Nephropathy, Lupus Nephritis, Primary Membranous Nephropathy, or C3 Glomerulopathy (C3 Glomerulonephritis and Dense Deposit Disease)

**Version Number:**

Amendment 7

**Investigational Product, Dose, and Route of Administration:**

1. Pegcetacoplan (APL-2)
2. 360 mg daily; may transition to 1080 mg twice weekly
3. Subcutaneous infusion

**Study Phase and Type:**

Phase 2 study consisting of an open-label, nonrandomized group of patients with complement-mediated nephropathies.

**Number of Planned Subjects:**

Up to approximately 48 patients (pegcetacoplan treatment naive) with clinical diagnosis (confirmed by renal biopsy) of IgA nephropathy (IgAN), lupus nephritis (LN), primary membranous nephropathy (primary MN), or C3 glomerulopathy (C3G), with 6-12 patients per disease.

**Treatment Groups:**

1. Pegcetacoplan in patients with IgAN, LN, primary MN, or C3G

**Duration of Study Participation:**

The planned length of participation in the study for each subject is 76 weeks, including an approximate 4-week screening period, 48-week treatment period and 24-week follow-up period (Part A, Core Study Phase). Any subject who, in the opinion of the investigator, is experiencing clinical benefit from pegcetacoplan administration will be invited to participate in Part B, a Long-Term Extension Phase in order to continue to receive treatment with pegcetacoplan until it is commercially available for the disease under treatment. If invited to participate in Part B, the subject can enter the Long-Term Extension Phase as soon as they complete the 48-week treatment period and do not need to participate in the 24-week follow-up period.

**Study Population:**

Patients, at least 18 years of age with either IgAN, LN, primary MN, or patients at least 16 years of age with C3G.

**Rationale for the Study:**

The 4 diseases of IgAN, LN, primary membranous nephropathy (primary MN) and C3 glomerulopathy (C3G) have a shared pathogenesis of activation of the central complement component, C3. These diseases all involve activation of either 2 or 3 of the pathways to C3 activation (classical, lectin, or alternative complement activation). Complement activation in glomeruli induces the inflammatory cascade, which results in renal injury and loss of function. Both decreased circulating C3 levels and mesangial C3 deposition are independently associated with poor renal outcome in patients with complement-mediated glomerulopathies, which suggests that systemic and local activation of complement play a role in the disease progression. Genetic mutation also supports the importance of the complement alternative pathway in complement-mediated glomerulopathies. By targeting therapy directly to the key junction of the classical, lectin, and alternative complement activation pathways, pegcetacoplan documented C3 inhibitory activity may control the C3-mediated inflammatory response and the downstream inflammatory events responsible for the renal manifestations of injury common to all these diseases. To date, no safety signals have emerged from ongoing studies in paroxysmal nocturnal hemoglobinuria (PNH) or age-related macular degeneration that preclude further development with pegcetacoplan in other indications. Thus, this proposed Phase 2 study's aim is to explore treatment efficacy and safety of pegcetacoplan for the treatment of IgAN, LN, primary MN, and C3G.

**Study Objectives and Endpoints:**

**Objectives**

The primary objectives of this study are to establish preliminary efficacy and safety of pegcetacoplan in patients with IgAN, LN, primary MN, and C3G.

**Endpoints**

*Primary efficacy endpoint:*

- Proteinuria reduction from baseline to Week 48, based on urinary protein-to-creatinine ratio (uPCR)

*Secondary efficacy endpoints:*

- All disease groups: changes of disease-specific biomarkers:
  - Serum C3 levels
  - AH50 and C3a concentrations
  - Serum albumin levels
- All disease groups: complete clinical remission defined as normalization of proteinuria as defined by <200 mg/g uPCR at Week 48
- All disease groups: stabilization or improvement in estimated glomerular filtration rate (eGFR) from baseline to Week 48

*Exploratory endpoints:*

- Complete renal response: defined as <200 mg/g uPCR and stabilization or improvement in eGFR from baseline to Week 48

- Changes of disease-specific biomarkers:
  - LN: autoantibodies to double-stranded DNA, C3, and C1q
  - Primary MN: autoantibodies to phospholipase A2 receptors (PLA2R)
  - C3G: C3 nephritic factor (Part A only)

*Pharmacokinetic endpoint:*

- Pegcetacoplan pharmacokinetic concentrations

*Pharmacodynamic endpoints:*

- Pegcetacoplan activity: Absolute levels, change from baseline, and % change from baseline in CH50, C3, C3a, C4, C5a, and soluble C5b9 complex (sC5b9)
- Immunogenicity: Presence of autoantibodies to polyethylene glycol and pegcetacoplan throughout treatment and follow-up periods

*Safety endpoints:*

- Physical examination; incidence and severity of adverse events (AEs)
- Changes from baseline in laboratory parameters
- Changes from baseline in electrocardiogram parameters

**Study Design:**

This is a prospective Phase 2 study, consisting of a single cohort with a total of approximately 48 patients among the 4 indications. This is an open-label study, with 48 patients clinically diagnosed with IgAN, LN, primary MN, or C3G (with 6-12 patients per disease). Each clinical diagnosis must be confirmed by renal biopsy prior to dosing with pegcetacoplan. Subject participation will include a Part A Core Study Phase that consists of an approximate 4-week screening period, 48-week treatment period, and 24-week safety follow-up. During the treatment period, patients will receive subcutaneous (SC) once daily infusions of 360 mg pegcetacoplan. Following the completion of 48-week treatment period in Part A Core Study Phase, if invited, subjects may participate in Part B, the Long-Term Extension Phase, in order to continue to receive treatment with pegcetacoplan until it is commercially available for the disease under treatment. If they are invited to participate in Part B, they do not need to complete the 24-week follow-up period.

For each indication, patients whose underlying renal disease is stable for at least 2 months prior to the first dose may enter the study. In this trial, stable renal disease should include stable eGFR, proteinuria, and blood pressure, as well as a stable and optimized treatment regimen for their renal disease, in the opinion of the primary investigator (PI) (see Section 10.1 for the complete detailed eligibility information). Upon completion of the screening period, patients who meet all of the inclusion and none of the exclusion criteria will begin the treatment phase of the study. The treatment phase will consist of once daily, self-administered, SC dosing of 360 mg pegcetacoplan at home, with the exception of all scheduled clinic visits. During scheduled Visit 4 only, the site staff will assist in administering the first SC dose of pegcetacoplan. At Visits 5-

15 subjects will self-administer pegcetacoplan in the presence of the site staff and undergo various safety and efficacy assessments by qualified site staff. Subjects may be switched over to twice-weekly dosing as early as Week 24. Any subject who is invited to participate in Part B who has not already switched over to twice-weekly dosing, must do so at the beginning of Part B. If a subject transitions to the twice-weekly dosing, they need to follow the dose transition visits (T1, T2, and T3) as outlined in Section 10.1, Table 2 (during Part A) or Appendix 1, Table A1 (for Part B). The change in proteinuria from baseline through the end of treatment will be assessed as the primary endpoint. Urinary protein-to-creatinine ratio (PCR) will be used to measure changes in proteinuria for the primary endpoint.

After completion of the 48-week treatment period, each subject will have the opportunity to enter Part B, the Long-Term Extension Phase (see Appendix 1), at the discretion of the investigator. If the subject does not enter Part B, he or she will enter into a 24 week follow-up period, consisting of 6 clinic visits at weeks 50, 52, 54, 60, 66, and 72 (Exit Visit). Various safety assessments will be undertaken during these clinic visits, and follow-up phone calls will be performed to gain relevant safety information. Patients will be maintained on their baseline treatment regimen during treatment and the follow-up period, as determined by the PI in consultation with the medical monitor. During the study, changes to the baseline treatment regimen should be avoided to the extent possible and made only when required for the well-being of the patient, in the opinion of the PI.

Safety summaries will be presented over the screening period, 48 weeks of treatment and 24 weeks of follow-up, as well as the overall duration of the study.

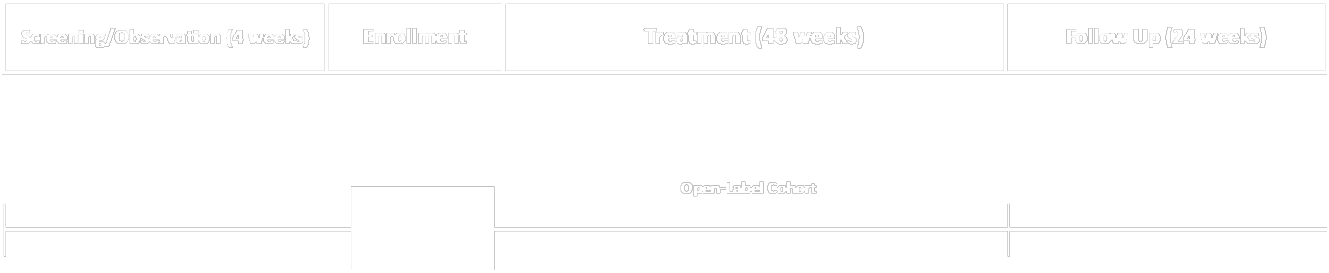
An external, independent safety monitoring committee will assess the safety/tolerability data of the study.

Subject level discontinuation will occur for any subject who develops a serious adverse event (SAE) due to infection confirmed to be caused by encapsulated organisms (see Section 8.3 for further information) or any subject with a sustained and significant reduction in renal function, as defined by one of the following: initiation of chronic dialysis, a confirmed and sustained eGFR ≤15 mL/min/1.73 $m^2$ or a confirmed and sustained reduction in eGFR of at least 30% which is drug related in the opinion of the PI. A reduction in eGFR would be considered confirmed if present on 2 separate consecutive measurements and considered sustained if the 2 measurements are at least 1 week apart. Subject level discontinuation can also occur for any individual for whom the PI deems it in the best interest of the patient to not continue in the study. Indication level discontinuation will occur if 2 or more subjects in a particular indication are discontinued by these criteria.

Subjects who do not meet the criteria for participation in the study (screen failure) may be rescreened. The timeframe and scope of eligibility reassessment will be determined by the sponsor. Any requests to rescreen an individual more than one time must be approved by the sponsor. For each rescreening, the individual must sign a new informed consent form and will be assigned a new identification number. Record of the subject's prior identification number and screening should be maintained with the source documents. Subjects who received vaccinations per protocol within 2 years of their rescreening date do not need to have the respective vaccination repeated but may do so at the discretion of the investigator.

**Study Outline**

The following study outline is for Part A, the Core Study Phase. Appendix 1 (Section A1.1) presents the information for Part B, the Long-Term Extension Phase.




**Inclusion Criteria:**

At specified screening visit(s) all subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study:

1. Patients of at least 18 years of age at screening (16 years of age for C3G), able to provide written informed consent, and able to understand and comply with all scheduled procedures and other requirements of the study by the opinion of PI
2. Patients must have a diagnosis of IgAN, LN, primary MN, or C3G confirmed by renal biopsy and required measurements performed prior to study participation
   - IgAN: Prior biopsy results for C3 and C4d staining should be made available
   - LN: Diagnostic biopsy showing proliferative focal, diffuse, or membranous lesions (Class III, IV, or V, respectively) by renal biopsy. Subject should have either a biopsy in the last 6 months, or evidence of disease activity (nephritic changes on urinalysis or nephrotic changes)
   - Primary MN: PLA2R positive titer plus nephrotic range proteinuria (defined as uPCR >2350 mg/g)
   - C3G plus one of the following: Low serum C3 level or historical renal biopsy within the last 3 years
3. Have proteinuria >750 mg/g (calculated by uPCR on 24-hour urine collection) collected during the first screening visit (Visit 3a)
4. eGFR ≥30 mL/min/1.73 $m^2$ calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation at Screening Visit 3a and currently not on dialysis
5. Must have stable or worsening renal disease, on stable and optimized treatment, in the opinion of the PI, for at least 2 months prior to the first dose of pegcetacoplan (Visit 4); treatments may include, but are not limited to, immunosuppressive agents, antihypertensives and/or antiproteinurics

6. Willing to receive vaccinations against *Neisseria meningitidis* at least 2 weeks prior to dosing on Day 1 with a booster on Day 56 (for both vaccinations) and Pneumococcal and Hib vaccines at least 2 weeks prior to dosing on Day 1
7. Women of childbearing potential (WOCBP) must have a negative blood pregnancy test at screening (and negative urine pregnancy at Visit 4) and must agree to use protocol defined methods of contraception from screening through 3 months after last dose of pegcetacoplan
8. Males must agree to use protocol defined methods of contraception and agree to refrain from donating sperm from screening through 3 months after receiving last dose of pegcetacoplan
9. Willing and able to give informed consent
10. Willing and able to self-administer pegcetacoplan (administration by caregiver will be allowed)

**Exclusion Criteria:**

1. Absolute neutrophil count <1000 cells/$mm^3$ at screening Visits 3a and 3b
2. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3.0× the upper limit of normal at screening Visits 3a and 3b
3. Previous treatment with pegcetacoplan
4. History of solid organ transplant
5. Diagnosis of human immunodeficiency virus (HIV), hepatitis B, or hepatitis C infection, or positive serology at screening Visits 3a and 3b (previous hepatitis B or hepatitis C diagnosis cleared by treatment is allowed)
6. Malignancy except for cured basal or squamous cell skin cancer, curatively treated in situ disease, or have been disease-free for ≥5 years or more from cancer, and off ongoing treatment
7. Renal disease secondary to another condition (eg, infection, malignancy, monoclonal gammopathy, or a medication)
8. Presence or suspicion of active bacterial or viral infection or severe recurrent bacterial infections
9. Participation in any other investigational drug trial or exposure to other investigational agent, device, or procedure within 30 days prior to screening period
10. Pregnant, breastfeeding, or intending to conceive during the course of the study
11. Inability to cooperate or any condition that, in the opinion of the investigator, could increase the patient's risk by participating in the study or confound the outcome of the study
12. Unwillingness to receive or intolerant of SC infusions of study medication or known allergy to ingredients in pegcetacoplan

13. Positive results for drug abuse (upon urinary drug screen) or alcohol dependence at screening (Visit 3a). Documented evidence of prescribed marijuana use is not exclusionary

**Sample Size:**

A sample size of 6-12 subjects will be recruited from each of the 4 disease types. As these complement-mediated glomerulopathies are rare diseases it may be difficult to recruit subjects from 1 or more of the disease types; hence the range of 6-12 subjects per type. The intention is to obtain safety, pharmacokinetic (PK), pharmacodymanic (PD), and efficacy data to support the progress of pegcetacoplan into further clinical studies.

With 6 subjects treated with pegcetacoplan in each disease type there is a 95% chance of an AE being reported if its true incidence is over 40%. Similarly, there is a 47%, 74% and 88% chance if the true incidence is 10%, 20% or 30% respectively. With 12 subjects treated in each disease type the chance increases to >93% for true incidences over 20% and 72% if the true incidence is 10%.

**Statistical Methods:**

Given the exploratory nature of the study no formal statistical hypothesis testing will be performed. Data will be presented by disease type (IgAN, LN, primary MN, or C3G), study day, and nominal time postdose (if appropriate).

Continuous variables will be summarized using descriptive statistics (eg, median and mean) whilst for categorical variables the frequency and percentage in each category will be displayed. Summaries may also be presented pooling data from the different disease types.

Treatment-emergent AEs will be summarized by System Organ Class and Preferred Term, according to the current version of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of analysis. The number of patients reporting each AE Preferred Term will be tabulated for all treatment-emergent adverse events and separately for those considered as possibly related to study treatment by the investigator. Number of patients reporting SAEs will also be tabulated.

The number and percentage of patients achieving partial clinical remission of proteinuria will be tabulated. Similarly the number and percentage of patients will be tabulated for secondary responder endpoints.

Changes from baseline in continuous efficacy and pharmacodynamics endpoints will be summarized and plotted (individual and mean) over time.

PK concentrations will be summarized and concentration profiles over time (individual and median) will be plotted.

# 4. SCHEDULE OF EVENTS

Table 1, below, represents the Schedule of Events for Part A, the Core Study Phase. The Study Flow Chart for Part B (Long-Term Extension Phase) is provided in Appendix 1 (Section A1.1).

**Table 1: Schedule of Events, Part A, Core Study Phase**

| Study Period | Screening Period: 4 Weeks[a] | | Treatment Period: 48 Weeks | | | | | | | | | | | | Follow-up & Exit: 24 Weeks | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Week | -4 | -2 | 1 | 2 | 4 | 8 | 12 | 16 | 20 | 24 | 30 | 36 | 42 | 48 | 50 | 52 | 54 | 60 | 66 | 72 (Exit) |
| Study Day | -28 | -14 | 1 | 14 | 28 | 56 | 84 | 112 | 140 | 168 | 210 | 252 | 294 | 336 | 350 | 364 | 378 | 420 | 462 | 504 |
| Study Visit | 3a | 3b | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 |
| Visit Window (±Days) | 0 | 3 | 0 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 7 | 7 | 7 |
| Informed Consent | X | | | | | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | | | | | | | |
| Inclusion/Exclusion[b] | X | X | X | | | | | | | | | | | | | | | | | |
| Vaccination[c] | | X | | | | X | | | | | | | | | | | | | | |
| Concomitant Medications | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | |
| Physical Examination[d] | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | |
| 12-Lead Electrocardiogram[e] | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

**Table 1: Schedule of Events, Part A, Core Study Phase**

| Study Period | Screening Period: 4 Weeks[a] | | Treatment Period: 48 Weeks | | | | | | | | | | | | Follow-up & Exit: 24 Weeks | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Week | -4 | -2 | 1 | 2 | 4 | 8 | 12 | 16 | 20 | 24 | 30 | 36 | 42 | 48 | 50 | 52 | 54 | 60 | 66 | 72 (Exit) |
| Study Day | -28 | -14 | 1 | 14 | 28 | 56 | 84 | 112 | 140 | 168 | 210 | 252 | 294 | 336 | 350 | 364 | 378 | 420 | 462 | 504 |
| Study Visit | 3a | 3b | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 |
| Visit Window (±Days) | 0 | 3 | 0 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 7 | 7 | 7 |
| Investigational Drug Product Administration (Daily)[f] | | | Daily Administration ----------> | | | | | | | | | | | | | | | | | |
| Injection Site/Infusion Pump Safety Assessment[g] | | | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | |
| Vital Sign Measurements[h] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Urine | | | | | | | | | | | | | | | | | | | | |
| 24-Hour Urine Collection[i] | X | | | | | | | | | | | | | X | | | | | | X |
| Dispense uPCR containers | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Return uPCR samples[j] | | | X | X | X | X | X | X | X | X | X | X | X | | X | X | X | X | X | |
| Arrange home uPCR Courier pickup[k] | | | | | X | X | X | X | X | X | X | X | X | | | | X | X | X | |
| Urinalysis– microscopic & Dipstick[l] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

**Table 1: Schedule of Events, Part A, Core Study Phase**

| Study Period | Screening Period: 4 Weeks[a] | | Treatment Period: 48 Weeks | | | | | | | | | | | | Follow-up & Exit: 24 Weeks | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Week | -4 | -2 | 1 | 2 | 4 | 8 | 12 | 16 | 20 | 24 | 30 | 36 | 42 | 48 | 50 | 52 | 54 | 60 | 66 | 72 (Exit) |
| Study Day | -28 | -14 | 1 | 14 | 28 | 56 | 84 | 112 | 140 | 168 | 210 | 252 | 294 | 336 | 350 | 364 | 378 | 420 | 462 | 504 |
| Study Visit | 3a | 3b | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 |
| Visit Window (±Days) | 0 | 3 | 0 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 7 | 7 | 7 |
| Blood[m] | | | | | | | | | | | | | | | | | | | | |
| Hematology[n] and Chemistry[o] | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Vaccination Titer Sample[p] | | X | | | | X | | | | | | | | | | | | | | |
| Pharmacokinetic Sample Collection[q] | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Antidrug Ab assays[r] | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| PD for Complement Profile | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | X |
| Disease-Specific Biomarkers[s] | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| eGFR[t] | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Pregnancy (β-HCG) | X | | X | | | | | | | | | | | X | | | | | | |
| Urine pregnancy test | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| FSH, HIV, HCV, HBsAg[u] | X | | | | | | | | | | | | | | | | | | | |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

Abbreviations: Ab = antibodies; ACR = albumin-to-creatinine ratio; ADA = antidrug antibody; AE = adverse events; ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = fibrinogen activated partial thromboplastin time; AST = aspartate aminotransferase; β-HCG = beta human chorionic gonadotropin; BP = blood

pressure; BUN = blood urea nitrogen; CDC = Centers for Disease Control and Prevention; Chem = serum chemistry; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; Coag = coagulation; ECG = electrocardiogram; FSH = follicle-stimulating hormone; GGT = gamma-glutamyl transferase; HBsAg = hepatitis B surface antigen; HCV = hepatitis C; Hem = hematology; HIV = human immunodeficiency virus; HR = heart rate; INR = international normalized ratio; LDH = lactate dehydrogenase; PCR = protein-to-creatinine ratio; PD = pharmacodynamic; PI = primary investigator; PK = pharmacokinetics; RBC = red blood cell(s); RR = respiration rate; T = temperature; UA = urinalysis; uPCR = urine protein-to-creatinine ratio; WBC = white blood cell(s); WOCBP = women of childbearing potential.

Note: When multiple assessments occur at the same time, order of collection will be: vital signs, ECGs, and blood collection/sampling. Further information can be found in schedule section.

a Patients who meet the medical history requirements will enter the screening period at Visit 3a and return for Visit 3b.

b Specific inclusion/exclusion criteria will be measured during screening, and some of them require confirmation on Visit 4 (Day 1) prior to performing any activities of Day 1 procedures. See the inclusion/exclusion criteria in Section 11 for further detail.

c *Neisseria meningitidis* vaccine(s) will be administered during screening (Day –14); a booster for Neisseria vaccination(s) should be administered at Visit 7. Additionally, pneumococcal vaccine PCV13 will be administered at least 2 weeks prior to Day 1, and a dose of PPSV23 will be administered at least 8 weeks later unless documented evidence exists that patients are nonresponders to vaccination as evidenced by titers or display titer levels within acceptable local limits. *Haemophilus influenzae* Type B (Hib) vaccinations will be administered at Day –14. Subjects who withdraw from the study prior to any vaccine booster will be offered the opportunity to return to the site as recommended by current CDC Adult Immunization schedule to receive the booster shot. Subjects who are being rescreened for the trial will not require repeat vaccination for those vaccines documented as given during a previous screening visit.

d Full physical examination will be performed at Visits 4 and 15. Brief physical examinations will be conducted at all other clinic visits as noted above in the schedule of events. A symptom-driven physical examination may be performed at other times, at the PI's discretion. (Body height [cm] and weight [kg] will be measured at Visit 3a, and body weight will be measured throughout study, during brief and full physical examinations.)

e Triplicate 12-lead ECGs (which have a ±5-minute start window) are to be performed: D1 (V4) and Week 48 (V15): –45, –30, –15 minutes predose and before dosing at all other treatment visits. Once each triplicate ECG begins, subsequent ECGs should be at least one minute and no more than 2 minutes apart. During screening and follow-up periods, triplicate ECGs will be collected immediately after vital measurements.

f Patients will self-administer SC pegcetacoplan after receiving appropriate training and sign-off by a research nurse or other personnel in their first treatment week. During site visits patients will self-administer pegcetacoplan at the site, with the exception of the very first dose.

g Between site visits, patients will be instructed to report any injection site reaction to the study staff. Pump use safety assessment will be performed by licensed health care professional (ie, investigator or nurse) within 30 min following study drug administration at all clinic visits and during at-home qualification (Days 2-7).

h Vital signs will be measured before venipuncture and ECG; vital signs measured post dose will be timed from the completion of the study drug administration. Additional monitoring of vital signs will occur on D1 and Visit 15 (predose and 30 minutes, 2 hours, and 4 hours post dose), Days 2 to 7 (at home, predose and 30 minutes post dose) by the health care professional conducting the self-administration qualification (ie, in-home nurse). At all other visits where pegcetacoplan is administered at the study site, vital signs will be measured predose and 30 minutes post dose. Blood pressure and heart rate should be evaluated after the subject has been resting in a seated, recumbent, or supine position for at least 5 minutes. All of these vital sign measurements have a ±15-minute start window.

i 24-hour urine collected for ACR and PCR, defined as collection for a 24-hour period in a urine pooling container following the first urinary output on that day (first urinary output is discarded). Courier arrangements will be made by site personnel to pick up urine containers from patient's home. Urine ACR and PCR will be calculated on 24-hour urine collections for accuracy in estimating 24-hour proteinuria.

j Urinary PCR samples (first urinary output for the day) should be collected on 3 consecutive days, biweekly, for both uACR/uPCR analysis with a ±3-day window. On weeks of scheduled clinic visit, samples will be brought with patient during the site visit.

k On weeks when no clinic visit is scheduled, courier service will be arranged for urine sample pickup and delivery to the site.

l Urinalysis—routine dipstick for protein, glucose, hemoglobin, blood, ketones, ACR, pH, bilirubin, urobilinogen, leukocyte esterase, specific gravity.

m All blood samples will be taken predose.

n Hematology consists of hemoglobin, hematocrit, RBC count, platelet count, WBC count with differential (basophils, eosinophils, monocytes, lymphocytes, neutrophils), aPTT, INR. The use of silica reagents in coagulation panels should be avoided in subjects treated with pegcetacoplan.

o Chemistry consists of BUN, creatinine (b), bilirubin (total and conjugated), uric acid, albumin, ALP, LDH, creatine kinase, AST, ALT, GGT, glucose, sodium, potassium, chloride, bicarbonate.

p Vaccination serum samples (for antibody titer) will be collected prior to patient receiving vaccinations on that study visit.

q All PK collections will be taken predose for treatment visits and following ECGs at all other visits. Predose PK collections to occur within 1 hour before dose.
r Patients who discontinue dosing will need to have ADA samples collected at 6 and 12 weeks after the last treatment. Patients who test positive for ADAs at any time will be followed up with ADA samples being collected every 6 months until the antibody levels revert to baseline.
s Biomarkers for primary MN (PLA2R) and C3G (serum C3) should be collected for screening, while all secondary/exploratory disease-specific biomarkers should be collected throughout the treatment and follow-up period.
t CKD-EPI creatinine equation (see https://www.niddk.nih.gov/); the CKD-EPI creatinine-cystatin C equation (if confirmation required).
u Serum FSH to be performed on females only. Blood HIV, HCV, and HBsAg to be performed on all patients.

# 5. INTRODUCTION

## 5.1. Background

This study is being conducted as part of a series of studies for the clinical development of pegcetacoplan (APL-2). The study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and applicable regulatory requirements. The subject population will be comprised of adult male and female subjects with either of 4 different complement-mediated dependent glomerulopathies: IgA nephropathy (IgAN), lupus nephritis (LN), primary membranous nephropathy, and C3 glomerulopathy (C3 glomerulonephritis and dense deposit disease).

## 5.2. Complement-Mediated Glomerulopathy Disease Overview

### 5.2.1. IgA Nephropathy

IgAN, also known as Berger's disease, is a rare autoimmune disease and is the most common cause of chronic glomerulonephritis (GN). It is characterized by a predominant deposition of IgA and complement C3 alone or with IgG or IgM in the glomerular mesangium (Rauen and Floege 2017). In the United States, IgAN incidence is estimated at 2.1 per 100,000 (Swaminathan et al. 2006). The clinical and pathological manifestations are highly variable and may include asymptomatic hematuria, proteinuria, hypertension, interstitial fibrosis, glomerulosclerosis, and a slow progression to chronic kidney disease (Haas 1997). Within 10-20 years of diagnosis, 10% to 40% of patients with IgAN progress in kidney failure or end-stage renal disease (Wyatt and Julian 2013; Hastings et al. 2007).

In IgAN, B cells synthesize antibodies to galactose-deficient IgA (Gd-IgA1) and these Gd-IgA1-containing immune complexes are deposited in the glomerular mesangium, which causes local inflammation and kidney damage (Wyatt and Julian 2013; Rauen and Floege 2017; Nasri et al. 2013). Consistent with IgA's ability to activate lectin (Roos et al. 2001) and alternative complement pathways (Hiemstra et al. 1987), it contributes to C3 activation. Mesangial co-deposits of properdin, a natural activator of C3 through the alternative pathway, are observed in about 60% of patient biopsies (Segarra-Medrano et al. 2017) while the deposition of mannose-binding lectins (MBL), activators of the complement lectin pathway, is observed in 20% to 25% of cases (Roos et al. 2006; Wyatt et al. 1987).

### 5.2.2. Lupus Nephritis

LN is one of the most serious manifestations of systemic lupus erythematosus (SLE). LN is caused by complement-mediated inflammation and damage of the kidney. Approximately 44% of patients with diffuse proliferative LN will progress to end-stage renal disease (ESRD) within 15 years of diagnosis (Tektonidou et al. 2016). In SLE autoantibodies are generated against various nuclear self-antigens such as histones and double-stranded DNA, and against proteins of the classical and alternative complement pathways (Vasilev et al. 2015; Nozal et al. 2015; Kenyon et al. 2011; Pang et al. 2014; Chen et al. 2012). Autoantibodies and self-antigens form immune complexes that deposit at the glomerular basement membrane, the mesangium, and the endothelium and within the proximal tubular epithelial cell membrane (Weening et al. 2004).

Deposited immune complexes initiate local inflammation through activation of the complement cascade which causes a chronic inflammatory response. Patients with LN have low levels of C3 proteins as all 3 pathways (classical, lectin, and alternative pathways) play a role in disease progression and damage (Sato et al. 2011). In the United States, LN prevalence is estimated at 30.9 per 100,000, or 76,000 persons, and LN incidence is estimated at 6.9 per 100,000, or 17,000 persons (Feldman et al. 2013). Approximately 18% to 22% overall and 44% patients with diffuse proliferative glomerulonephritis (Class IV) lupus will progress to ESRD within 15 years of diagnosis (Tektonidou et al. 2016).

All 3 pathways of complement activation have been implicated in LN pathogenesis, disease progression, and damage (Sato et al. 2011). Renal biopsies display IgG, IgA, and IgM deposition associated with C3 and C1q, and MBL deposition as well as high levels of glomerular C3aR (Nisihara et al. 2013; Mizuno et al. 2007).

### 5.2.3. Primary Membranous Nephropathy

Primary MN is the second most common nephrotic syndrome in adults worldwide. Primary MN is a slow progressive, chronic, autoimmune disease of the kidney. It is predominantly mediated by autoantibodies directed against phospholipase A2 (PLA2) receptors on podocytes that play an important role in kidney filtration. Though mediated by autoantibodies directed to antigens on the podocytes the immune complex induced complement activation may occur by several pathways. The lectin pathway activated by anti-PLA2R (most common autoantibodies) and IgG4 immune complexes binding to MBL leading to complement activation (Ma et al. 2013; Bally et al. 2016). Patients with high urinary C3dg levels and/or C5b-9 have a poor clinical prognosis (Brenchley et al. 1992).

Direct evidence shows the implication of the lectin and alternative pathways in primary MN pathogenesis while the classical pathway is typically absent in primary MN (Ma et al. 2013). High urinary C3dg levels in patients with primary MN correlate with the presence of proteinuria and a poor clinical prognosis (Brenchley et al. 1992).

In the United States, incidence of primary MN is estimated at 1.2 per 100,000; it accounts for about 3,000 persons. Current data indicate that after 5 years of treatment, approximately 20% of patients achieve remission, 40% of patients have stable to slowly decreasing renal function, and 40% have persistent nephrotic leading to ESRD (Ruggenenti et al. 2012; Glassock 2003). Approximately 40% to 50% of patients with primary MN progress to ESRD and renal failure within 15 years (Glassock 2003). Mortality for primary MN is estimated at approximately 9.8% per 100 person years (O'Shaughnessy et al. 2015).

### 5.2.4. C3 Glomerulopathy

C3G includes C3 glomerulonephritis (C3GN) and dense deposit disease (DDD). Both types of C3G are characterized by dense or isolated deposits of C3, and either the presence of autoantibodies called C3 nephritic factors or genetic mutations of complement inhibitory proteins that sustain complement activation (Servais et al. 2012). The key abnormality in both C3GN and DDD is an uncontrolled amplification of fragment C3b in the circulation and/or along the glomerular basement membrane (Servais et al. 2012). C3b and its breakdown fragments, and the terminal component of the complement system lead to impairment of kidney function (Bomback et al. 2012). Although there is no formal US registry for C3G, the National

Organization for Rare Disorders estimates C3G prevalence at 2-3 per 1,000,000 persons; it accounts for over 850 persons in the United States with a median diagnosis at 12 years of age for DDD and 26 years of age for C3GN (Lu et al. 2012).

Patients with C3G have either C3 nephritic factor (C3NeF), complement factor H (CFH), or complement factor I(CFI) autoantibodies and/or mutations in complement inhibitory proteins and regulatory factors (CFH, CFI, and membrane cofactor protein) that inhibit the regulation of convertases and lead to C3b-mediated activation of the amplification loop (Servais et al. 2012). In the absence of tight regulation, the amplification loop will consume all C3 available and maintain an ongoing activation of C3. Production of C3b and its breakdown fragments, and membrane attack complex leads to impairment of kidney function.

## 5.3. Pegcetacoplan

Pegcetacoplan is a PEGylated cyclic peptide inhibitor of complement C3. Pegcetacoplan is formed by 2 identical pentadecapeptides (combining a cyclic tridecapeptide active C3-inhibiting moiety and a 2-amino acid linker) covalently coupled to each end of a linear 40 kDa polyethylene glycol (PEG) chain. The bioactive tridecapeptide moiety binds to C3 to effect broad inhibition of the complement cascade. The PEGylation greatly improves solubility of the peptide and slows elimination in vivo following administration.

Pegcetacoplan solution for injection or infusion, 40 mg/mL (drug product) will be supplied as a sterile presentation of pegcetacoplan in acetate-buffered sorbitol or acetate-buffered mannitol solution, pH 5.0, contained in individual vials. It is designed for administration by subcutaneous administration.

## 5.4. Rationale for Treatment with Pegcetacoplan

Activation of the complement pathway through C3 appears to be a common pathogenic mechanism for the complement-mediated glomerulopathies IgAN, LN, primary membranous nephropathy, and C3 glomerulopathy (C3 glomerulonephritis and DDD). Pegcetacoplan therefore has potential in the treatment of these complement-mediated glomerulopathies. Complement-mediated glomerulopathies include inflammatory kidney disorders that represent a significant unmet medical need. Based on the key role of complement activation in these renal diseases pegcetacoplan has the potential to prevent the C3-mediated inflammatory response associated with kidney injuries.

# 6. NONCLINICAL DATA

The nonclinical effects of pegcetacoplan are summarized below; further details can be found in the pegcetacoplan Investigator's Brochure (IB).

## 6.1. Pharmacology

Pegcetacoplan binds to C3 and C3b and retains the human and nonhuman primate-specific inhibition of classical and alternative pathway activation of compstatin derivatives, but with a longer half-life and greater aqueous solubility than that of nonPEGylated peptides. Pegcetacoplan inhibits alternative and classical complement pathway activation, resulting in a decrease of the complement activation protein C3a, indicative of reduced C3 cleavage, and an increase in C3, indicative of target engagement resulting in decreased clearance of C3. On the basis of the absence of signals suggestive of off-target pharmacological effects in toxicology and safety pharmacology studies, it can be concluded that pegcetacoplan is a selective complement inhibitor.

## 6.2. Safety Pharmacology

Safety pharmacology studies indicate that pegcetacoplan does not inhibit the hERG (fast potassium [IKr]) channel or pose an acute cardiovascular or respiratory functional risk.

## 6.3. Pharmacokinetics and Drug Metabolism

In monkeys (the pharmacologically human-relevant test species), pegcetacoplan is readily and extensively absorbed following SC injection with an estimated bioavailability >85%. Pegcetacoplan distributes widely in tissues at concentrations lower than circulating drug but not to the brain and minimally to the eye. The pharmacokinetic (PK) behavior of pegcetacoplan is typical of a PEGylated peptide and is characterized by a prolonged systemic half-life ($t_{½}$) and slower clearance in vivo than that of the unPEGylated peptide. The main route of elimination is urinary excretion. Minimal, non–pharmacologically significant pegcetacoplan placental transfer and excretion in milk (<1% of maternal serum concentrations) were demonstrated in monkeys. Results of in vitro absorption, distribution, metabolism, and excretion testing (hepatic cytochrome P450 enzymes and transporter proteins) suggest minimal potential for clinical drug-drug interactions.

## 6.4. Toxicology

In toxicology studies, repeated daily SC doses up to 140 mg/kg/day to rabbits and monkeys were well tolerated and did not induce injection site reactions. After 28-day and chronic dosing, the principal findings were nonreversible renal tubular degeneration (considered adverse) and nonreversible multitissue microscopic vacuolation (considered an adaptative change related to the PEG40 moiety and not adverse). The no-observed-adverse-effect level (NOAEL) for renal degeneration in monkeys was 7 mg/kg/day (maximum concentration [$C_{max}$] and area under the concentration-time curve [AUC] margins over clinical exposure were approximately 1.4-fold, according to data from PNH patients). Renal tubular degeneration at 28 mg/kg/day was minimal and nonprogressive (a >5-fold margin over clinical exposures for monthly PEG load). Significance to humans of the minimal renal degeneration observed in the animal studies is not

known. No signal to suggest disturbed renal function has been detected in the current cumulative clinical safety database for pegcetacoplan. Population PK analysis demonstrated that renal function had no statistically significant impact on the PK parameters of pegcetacoplan among healthy adults and adult patients with PNH.

Pegcetacoplan was weakly to moderately antigenic in rabbits but minimally antigenic in monkeys. Negative results of in vitro and in vivo assays indicate that pegcetacoplan is not genotoxic.

Pegcetacoplan had no effect on embryofetal development in rats, rabbits, or monkeys, but SC doses of 28 mg/kg/day were associated with an increase in abortions and stillbirths in monkeys dosed during gestation. This is not considered a predicted on-target pharmacological effect of pegcetacoplan because complement-cascade regulation is recognized as potentially beneficial to pregnancy maintenance. The no-effect dose for abortions and stillbirths was 7 mg/kg/day (representing AUC and $C_{max}$ margins over clinical exposure of approximately 1.3-fold, according to data from PNH patients). Clinical relevance of the increase in abortions and stillbirths observed in monkeys is not known.

# 7. CLINICAL DATA

The effects of pegcetacoplan in humans are summarized below; further details can be found in the pegcetacoplan IB.

## 7.1. Pegcetacoplan Pharmacokinetic Effects in Humans

Following single ascending doses of SC pegcetacoplan from 45 to 1440 mg in healthy subjects (Study CCI ), absorption was slow (median time to reach maximum concentration [$T_{max}$] ranged from 108 to 144 hours [4.5 to 6.0 days]), exposure metrics increased with dose in a proportional manner, geometric mean for apparent clearance (CL/F) ranged from 11.1 to 17.2 mL/h, apparent volume of distribution ($V_z$/F) ranged from 3.6 to 4.8 L, and geometric mean of the terminal elimination half-life ($t_{½}$) ranged from 194 to 235 hours (8.1 to 9.8 days).

SC pegcetacoplan liquid formulations have been demonstrated to be well absorbed. Bioavailability of the SC dose was estimated at approximately 87% by comparing the dose-normalized AUC from zero to infinity ($AUC_{0-\infty}$) from an SC study (Study CCI ) and an IV study (Study CCI ) in healthy subjects.

In a multiple ascending dose study of daily SC doses of pegcetacoplan from 30 to 270 mg for 28 days in healthy subjects (Study CCI ), geometric means for exposure metrics, the area under the concentration-time curve over the dosing interval ($AUC_{tau}$) and $C_{max}$, increased in a generally proportional manner, and no time-dependent PK was evident, as displayed by the similar CL/F and $V_z$/F values being similar to those of single dosing. The geometric mean of CL/F ranged from 15.7 to 20.7 mL/h, $V_z$/F ranged from 5.2 to 6.1 L, and the geometric mean of the $t_{½}$ ranged from 197.8 to 237.2 hours (8.2 to 9.9 days). The disposition of pegcetacoplan after multiple doses was confirmed in another study in healthy subjects (Study CCI ), which included a regimen of SC 1080 mg twice weekly.

In PNH subjects given SC pegcetacoplan at 1080 mg twice weekly for a 16-week period (Study APL2-302), steady-state exposure was reached after 4 to 6 weeks of dosing. Geometric mean steady-state serum concentrations ranged from 655.3 to 706.3 µg/mL. A population PK analysis was performed on the basis of pooled data from 10 clinical studies in healthy adults, adults with renal impairment, and adult patients with PNH. The results demonstrated that patients with PNH had lower pegcetacoplan exposure than healthy volunteers because of increased CL/F without meaningful differences in $V_z$/F. The effective half-life of pegcetacoplan at an SC dose of 1080 mg twice weekly was estimated as 8.0 days for adult PNH patients and 10.1 days for healthy adults.

Evaluations of PK properties of pegcetacoplan in other disease populations are ongoing.

## 7.2. Pegcetacoplan Pharmacodynamics and Efficacy in Humans

Consistent changes in complement pharmacodynamic parameters were observed after SC dosing of pegcetacoplan in both healthy subjects and PNH subjects.

Complement C3 levels increased with increasing pegcetacoplan dose in both single and multiple-dose SC studies. An increase in serum C3 of more than 150% from baseline levels was observed at SC doses of 270 mg/day or higher, indicating that pegcetacoplan interacts with complement C3 and is likely to slow down its clearance (CL) from circulation.

Mean alternative complement pathway hemolytic activity (as determined by the AH50 assay) decreased from baseline levels with increasing pegcetacoplan dose. A decrease of 50% or more from baseline level was generally observed at SC doses of 270 mg/day or higher doses, tested in healthy volunteers and patients with PNH, indicating that repeated dosing of pegcetacoplan can achieve significant inhibition of the hemolytic activity via the alternative pathway.

No meaningful effect on classical complement pathway activity (as determined by the total hemolytic complement activity assay [CH50] assay) was noted during SC administration of pegcetacoplan at any of the doses evaluated using this assay.

Evaluations of pharmacodynamic (PD) properties of pegcetacoplan in other disease populations are ongoing.

Clinical data from studies with pegcetacoplan in subjects with PNH indicate that pegcetacoplan is effective in providing broad control of intravascular and extravascular hemolysis, as evidenced by increased and stable Hb levels and improvement in Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue Scale score, normalization of LDH, normalization of absolute reticulocyte count, and normalization of total bilirubin levels, along with reduction in C3 fragment opsonization and increased numbers of PNH RBCs.

## 7.3. Pegcetacoplan Safety in Humans

Available safety data from nonclinical and clinical studies have not indicated any serious safety concern in subjects treated with pegcetacoplan. As with other complement-inhibiting drugs, there is a potential increased risk of infections with encapsulated pathogens, however, there have been no reports of serious infections due to encapsulated bacteria to date.

Overall, SC administration of pegcetacoplan in clinical studies has been generally safe and well tolerated.

# 8. RATIONALE

The 4 diseases of IgAN, LN, primary membranous nephropathy (primary MN), and C3 glomerulopathy (C3G) have a shared pathogenesis of activation of the central complement component, C3. In IgAN antibodies to galactose-deficient IgA (Gd-IgA1) are deposited as immune complexes in the glomerular mesangium. In LN anti-DNA and antihistone autoantibodies form immune complexes that are deposited in the glomerular basement membrane. In primary membranous nephropathy autoantibodies to self-antigens on the podocyte such as PLA2 receptors form in-situ immune complexes. In C3 glomerulopathy activated C3 is directly deposited in renal glomerulus. All these diseases involve activation of either all 3 or 2 of the 3 pathways to C3 activation (classical, lectin, or alternative complement pathway). By targeting C3 at the point of convergence of all 3 pathways, pegcetacoplan has the potential to prevent C3 activation and C3-mediated inflammatory effects responsible for the renal manifestations of injury common to all these diseases. To date, no safety signals have emerged from ongoing studies that preclude further development. Thus, this proposed Phase 2 study's aim is to explore treatment efficacy and safety of pegcetacoplan for the treatment of IgAN, LN, primary MN, and C3G.

## 8.1. Purpose of the Study

The purpose of this study is to establish the preliminary efficacy and safety of pegcetacoplan as a potential treatment for patients with IgAN, LN, primary membranous nephropathy (primary MN), and C3 glomerulopathy (C3G), which are all complement-mediated glomerulopathies.

## 8.2. Dose Selection

The toxicological data accumulated from the animal studies were used to guide dose selection during the Phase 1 single ascending dose and multiple ascending dose studies in healthy volunteers (Protocols CCI respectively). In particular, the highest doses were selected based on exposure predicted by a PK model and compared with the exposures observed at the NOAEL in cynomolgus monkeys.

The planned dose of pegcetacoplan is subcutaneous 360 mg/day. Dose selection was based on past clinical experience with SC pegcetacoplan coupled with nonclinical toxicological studies. Daily doses up to 360 mg/day have been tested in past and ongoing clinical trials and have been found to be well tolerated, with exposures that are well below the pegcetacoplan levels associated with the NOAEL in monkeys. Doses of 180 mg/day and above have been shown to be pharmacologically active in both healthy volunteers and PNH patients, with clinical and biomarker responses increasing in a dose dependent manner. Therefore while no safety concern has been associated with a dose of 360 mg/day in the clinical testing conducted to date, that dose is expected to maximize any potential clinical response in these patients and provide an optimal risk/benefit profile.

### 8.2.1. Transition to Twice-Weekly Dosing

Patients may transition to twice-weekly dosing as early as Week 24, at the discretion of the sponsor. Such a dose transition from daily to twice-weekly pegcetacoplan has been safely implemented in PNH patients, and this study aims to follow a similar process when transitioning patients. In PNH patients transitioning from daily to twice-weekly dosing, the starting dose was

1080 mg twice weekly, with the option to adjust the dose, to a maximum dose of 1080 mg every 3 days. As illustrated in Figure A1, the PK exposure ($C_{max}$) with 1080 mg every 3 days will still be lower than that observed in Study CCI (1300 mg twice weekly) and will be safely below that observed at the NOAEL dose (7 mg/kg/day) in cynomolgus monkeys.

Additional information on the selection of the 1080 mg dose can be found in Appendix 1 (Section A1.1.3.2), and additional details around the dose transition process can be found in Section 10.1.

## 8.3. Risk/Benefit

A number of safety monitoring practices are being employed by this protocol (including, but not limited to, physical examination, vital signs monitoring at specified intervals, triplicate 12-lead electrocardiogram (ECG), hematology (including coagulation), serum chemistry, urinalysis, prompt reporting of predefined adverse events (AEs) of special interest, and AE collection) in order to ensure the subjects' safety.

Injection/infusion site and pump use safety will be assessed during clinical visits, and any significant finding from the assessment will be reported as an AE (see Section 14.1.10).

The volume of blood planned for collection from each subject over the course of the study (see Section 14.1.6) will be minimized in order to limit the impact on the overall health of these anemic subjects.

Systemic complement inhibition might predispose individuals to infections caused by encapsulated organisms, including *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*. Vaccinations against these organisms will be taken to minimize potential risk of infection. Body temperature and vital signs will be monitored periodically, and relevant blood parameters monitored regularly throughout the study to assess for signs of infection. The primary investigator (PI) should be contacted immediately in the event of a suspected infection for guidance on appropriate action to be taken.

While no cardiac safety signal has emerged from preclinical or clinical experience to date, the current clinical experience is not sufficient to negate any potential unanticipated risks. Therefore, cardiac risk will be evaluated as part of this study and cardiac monitoring has been implemented.

### 8.3.1. COVID-19 Risk Mitigation Measures

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

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

- Collection of AEs or SAEs should be done over the phone and documented in the source documents and in the applicable case report form (CRF) page.
- A minimized schedule of events is presented in Table A2 of Appendix 2, including identification of laboratory tests that can be performed at a certified local laboratory.
- Any activities not performed because of COVID-19–related restrictions will be identified in the electronic data capture (EDC) system.
- Any change in COVID-19 status (serology or antigen), if available, will be captured separately in the EDC system.
- 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.

These measures are described in more detail in Appendix 2.

# 9. STUDY OBJECTIVES AND ENDPOINTS

## 9.1. Study Objectives

The primary objectives of this study are to establish preliminary efficacy and safety of pegcetacoplan in patients with complement-mediated glomerulopathies (IgAN, LN, primary MN, and C3G).

## 9.2. Study Endpoints

### 9.2.1. Primary Efficacy Endpoints

- Proteinuria reduction from baseline to Week 48, based on urinary protein-to-creatinine ratio (uPCR)

### 9.2.2. Secondary Efficacy Endpoints

- All disease groups: changes of disease-specific biomarkers:
  - Serum C3 levels
  - AH50 and C3a concentrations
  - Serum albumin levels
- All disease groups: complete clinical remission defined as normalization of proteinuria as defined by <200 mg/g uPCR at Week 48
- All disease groups: stabilization or improvement in estimated glomerular filtration rate (eGFR) from baseline to Week 48

### 9.2.3. Exploratory Endpoints

- Complete renal response: defined as <200 mg/g uPCR and stabilization or improvement in eGFR from baseline to Week 48
- Changes of disease-specific biomarkers:
  - LN: autoantibodies to double-stranded DNA, C3, and C1q
  - Primary MN: autoantibodies to PLA2R
  - C3G: C3NeF (Part A only)

### 9.2.4. Pharmacokinetic Endpoints

- Pegcetacoplan pharmacokinetic concentrations

### 9.2.5. Pharmacodynamic Endpoints

- Pegcetacoplan activity: Absolute levels, change from baseline, and % change from baseline in CH50, C3, C3a, C4, C5a, and soluble C5b9 complex (sC5b9)
- Immunogenicity: Presence of autoantibodies to PEG and pegcetacoplan throughout treatment and follow-up periods

### 9.2.6. Safety Endpoints

- Physical Examination; Incidence and severity of AEs
- Changes from baseline in laboratory parameters
- Changes from baseline in ECG parameters

# 10. STUDY DESIGN

This is a prospective Phase 2 study, consisting a single cohort with a total of approximately 48 patients (pegcetacoplan treatment native). This is an open-label study, with 48 patients clinically diagnosed with IgAN, LN, primary MN, or C3G (with 6-12 patients per disease). Subject participation will include a Part A, Core Study Phase which is an approximately 4-week screening period, 48-week treatment period, and 24-week safety follow-up. During the treatment period, patients will receive SC once daily dosing of 360 mg pegcetacoplan. Following the completion of the 48-week treatment period, any subject who, in the opinion of the investigator, is experiencing clinical benefit from pegcetacoplan administration will be invited to participate in Part B, the Long-Term Extension Phase in order to continue to receive treatment with pegcetacoplan until it is commercially available for the disease under treatment. If invited to participate in Part B, subjects do not need to complete the 24-week follow-up period of Part A.

For each indication, patients who have sufficient medical history may enter the study. In this trial, sufficient medical history is defined as having stable proteinuria with a uPCR >750 mg/g, stable and optimized treatment regimen for their disease, stable eGFR or renal function, and stable blood pressure. Patients entering the 4-week screening period will begin screening at Visit 3a and return for Visit 3b. Upon completion of the screening period, patients who meet all of the inclusion and exclusion criteria will begin the treatment phase of this study. The treatment phase will consist of once daily, self-administered, SC dosing of 360 mg pegcetacoplan at home, with the exception of all scheduled clinic visits. During scheduled Visit 4 only, the site staff will assist in administering the first SC dose of pegcetacoplan. At Visits 5-15 subjects will self-administer pegcetacoplan in the presence of the site staff and undergo various safety and efficacy assessments by qualified site staff. The change in proteinuria from baseline through the end of treatment will be assessed as the primary endpoint. Urinary protein-to-creatinine ratio (PCR) will be used to measure changes in proteinuria.

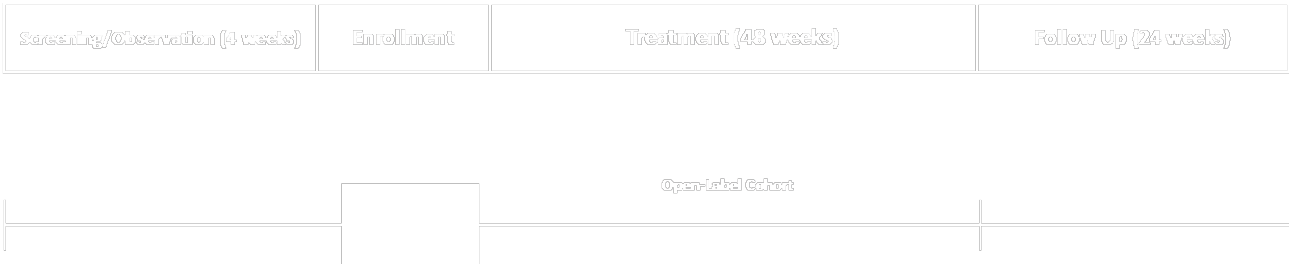
After completion of the 48-week treatment period, any subject who, in the opinion of the investigator, is experiencing clinical benefit from pegcetacoplan treatment, will be invited to participate in Part B, the Long-Term Extension Phase (see Appendix 1 [Section A1.1]). If the subject does not enter Part B, he or she will enter the 24-week follow-up period, consisting of 6 clinic visits at weeks 50, 52, 54, 60, 66, and 72 (Exit Visit). Various safety assessments will be undertaken during this visit clinics. Patients will be maintained on the standard of care during treatment and the follow-up period, as determined by the PI in consultation with the medical monitor.

An external, independent safety monitoring committee (SMC) will assess the progress and cumulative safety/tolerability data of the study at specified times described in Section 13.4.3.

Any subject with a sustained and significant reduction in renal function, as defined by one of the following: initiation of chronic dialysis, a confirmed and sustained eGFR ≤15 mL/min/1.73 $m^2$ or a confirmed and sustained reduction in eGFR of at least 30% which is drug related in the opinion in the PI. A reduction in eGFR would be considered confirmed if present on 2 separate consecutive measurements and sustained if the 2 measurements are at least 1 week or apart. Subject level discontinuation can also occur for any individual for whom the PI deems it in the best interest of the patient to not continue in the study. Indication level discontinuation will occur if 2 or more subjects in a particular indication are discontinued by these criteria.

Subjects who do not meet the criteria for participation in the study (screen failure) may be rescreened. The timeframe and scope of eligibility reassessment will be determined by the sponsor. Any requests to rescreen an individual more than one time must be approved by the sponsor. For each rescreening, the individual must sign a new informed consent form and will be assigned a new identification number. Record of the subject's prior identification number and screening should be maintained with the source documents. Subjects who received vaccinations per protocol within 2 years of their rescreening date do not need to have the respective vaccination repeated but may do so at the discretion of the investigator.

**STUDY OUTLINE**




## 10.1. Transition to Twice-Weekly Dosing

Patients are able, at the discretion of the sponsor, to transition to twice-weekly dosing with 1080 mg pegcetacoplan prior to the Long-Term Extension Phase, but not earlier than Week 24. If a dose transition occurs during Part A, the subject will need to follow the dose transition visits, outlined in Table 2 below. Dose can be adjusted, as needed, to maintain clinical response.

Transition Visits (T1, T2, and T3) should be scheduled for 1, 2, and 4 weeks after the first day on which their dose was adjusted. Additionally, subjects should be instructed to skip their Core Study Phase dose the day before the visit at which their dose will transition.

## Table 2: Part A, Dose Transition Visits

| | Dose Transition Visits | | |
|---|---|---|---|
| **Study Week** | **T+1W** | **T+2W** | **T+4W** |
| **Study Day** | **T+7D** | **T+14D** | **T+28D** |
| **Study Visit** | **T1** | **T2** | **T3** |
| **Visit Window (±Days)** | **2** | **2** | **2** |
| **Physical examination**[a] | | | |
| **Triplicate 12-lead electrocardiogram** | | | |
| **Pegcetacoplan administration**[b] | X | X | X |
| **Injection site assessment**[c] | X | X | X |
| **Concomitant medications** | X | X | X |
| **Vital sign measurements**[d] | X | X | X |
| **Urinalysis** | X | X | X |
| **Return uPCR samples** | | X | X |
| **Blood**[e] | X | X | X |
| **Pharmacokinetics**[f] | X | X | X |
| **Antidrug Ab assays**[g] | | | X |
| **Hematology and chemistry** | X | X | X |
| **PD for Complement profile**[f] | X | X | X |
| **Pregnancy (β-HCG and FSH)** | | | |
| **Urine pregnancy test**[h] | | | X |
| **Adverse events** | X | X | X |
| **Drug Dispensation for Home Administration** | X | X | X |

Abbreviations: β-HCG = beta human chorionic gonadotropin; ECG = electrocardiogram; IP = investigational product; PD = pharmacodynamic; PI = primary investigator; SC = subcutaneous; uPCR = urine protein-to-creatinine ratio; WOCBP = women of childbearing potential.

a Symptom-driven physical examinations may be performed at unscheduled time points if deemed necessary by the PI.
b Subjects will self-administer SC pegcetacoplan, after receiving appropriate training by a research nurse or other personnel. During site visits subject will self-administer pegcetacoplan at the site if the visit occurs on a dosing day. If the visit falls on a nondosing day, no IP administration is needed.
c Between site visits, subjects will be instructed to report any injection site reaction to the study coordinator.
d On clinic dosing days vital signs will be measured within 2 hours before dosing, venipuncture, and ECG assessments. On clinic dosing days, vital signs will be measured within 30 minutes after dosing.
e Blood samples will be taken predose.
f These tests should be performed at a central laboratory.
g For subjects with positive antidrug antibody in last dose samples, additional samples of 6 and 12 months from last dose will be collected for further assessments.
h Urine pregnancy test should be completed for WOCBP prior to dosing.

# 11. SUBJECT SELECTION

The study plans to enroll approximately 48 subjects with IgAN, LN, primary MN, or C3G (6-12 subjects per disease)

## 11.1. Inclusion Criteria

At specified screening and/or treatment visit(s) subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study:

1. Patients of at least 18 years of age at screening (16 years of age for C3G), able to provide written informed consent, and able to understand and comply with all scheduled procedures and other requirements of the study by the opinion of PI
2. Patients must have a diagnosis of IgAN, LN, primary MN, or C3G confirmed by renal biopsy and required measurements performed prior to study participation
   - IgAN: Prior biopsy results for C3 and C4d staining should be made available
   - LN: Diagnostic biopsy showing proliferative focal, diffuse, or membranous lesions (Class III, IV, or V, respectively) by renal biopsy. Subject should have either a biopsy in the last 6 months, or evidence of disease activity (nephritic changes on urinalysis or nephrotic changes)
   - Primary MN: PLA2R positive titer plus nephrotic range proteinuria (defined as uPCR >2350 mg/g)
   - C3G plus one of the following: Low serum C3 level or historical renal biopsy within the last 3 years
3. Have proteinuria >750 mg/g uPCR (on 24-hour urine collection) collected during at the first screening visit (Visits 3a).
4. eGFR ≥30 mL/min/1.73 $m^2$ calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation at Screening Visit 3a, currently not on dialysis.
5. Must have stable or worsening renal disease, on stable and optimized treatment, in the opinion of the PI, for at least 2 months prior to the first dose of pegcetacoplan (Visit 4); treatments may include, but are not limited to, immunosuppressive agents, antihypertensives and/or antiproteinurics.
6. Willing to receive vaccinations against *Neisseria meningitidis* at least 2 weeks prior to dosing on Day 1 with a booster on Day 56 (for both vaccinations) and pneumococcal and Hib vaccines at least 2 weeks prior to dosing on Day 1.
7. Women of childbearing potential (WOCBP) must have a negative blood pregnancy test at screening (and negative urine pregnancy at Visit 4) and must agree to use protocol defined methods of contraception from screening through 3 months after last dose of pegcetacoplan.

8. Males must agree to use protocol defined methods of contraception and agree to refrain from donating sperm from screening through 3 months after receiving last dose of pegcetacoplan.
9. Willing and able to give informed consent
10. Willing and able to self-administer pegcetacoplan (administration by caregiver will be allowed)

### 11.1.1. Approved Methods of Contraception

Approved methods of contraception include: oral contraceptives, intrauterine device, medically acceptable barrier methods (diaphragm or condom), implantable or injectable contraceptives (like Depo-Provera), or removable birth control device (like NuvaRing or Ortho Evra patches); and/or surgical sterilization (at least 6 months before dosing). Subjects practicing abstinence and coitus interruptus (pull out method) must agree to use an approved method of contraception during the study.

## 11.2. Exclusion Criteria

Subjects will be excluded from the study if there is evidence of any of the following criteria at specified screening and/or treatment visits as appropriate.

1. Absolute neutrophil count <1000 cells/$mm^3$ at screening Visits 3a and 3b
2. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3.0× the upper limit of normal at screening Visits 3a and 3b
3. Previous treatment with pegcetacoplan
4. History of solid organ transplant
5. Diagnosis of human immunodeficiency virus (HIV), hepatitis B (HBV), or hepatitis C (HCV) infection, or positive serology at screening Visits 3a and 3b (previous HBV or HCV diagnosis cleared by treatment is allowed)
6. Malignancy except for cured basal or squamous cell skin cancer, curatively treated in situ disease, or have been disease-free for ≥5 years or more from cancer, and off ongoing treatment.
7. Renal disease secondary to another condition (eg, infection, malignancy, monoclonal gammopathy, or a medication)
8. Presence or suspicion of active bacterial or viral infection or severe recurrent bacterial infections
9. Participation in any other investigational drug trial or exposure to other investigational agent, device, or procedure within 30 days prior to screening period
10. Pregnant, breastfeeding, or intending to conceive during the course of the study
11. Inability to cooperate or any condition that, in the opinion of the investigator, could increase the patient's risk by participating in the study or confound the outcome of the study

12. Unwillingness to receive or intolerant of SC infusions of study medication or known allergy to ingredients in pegcetacoplan.
13. Positive results for drug abuse (upon urinary drug screen) or alcohol dependence at screening (Visit 3a). Documented evidence of prescribed marijuana use is not exclusionary.

# 12. STUDY TREATMENTS

## 12.1. Identity of Investigational Product

The test product is pegcetacoplan, which will be provided as a sterile solution of pegcetacoplan in acetate-buffered mannitol or sorbitol, supplied in stoppered glass vials. Additional information is provided in the pegcetacoplan IB. Investigational product will be administered as a 9-mL mannitol SC infusion (for 360-mg daily infusions) or as a 20-mL sorbitol SC infusion (for 1080-mg twice-weekly infusions).

## 12.2. Administration of Investigational Product

### 12.2.1. Allocation to Treatment

All subjects who meet all the inclusion criteria and none of the exclusion criteria will receive open-label daily SC infusions of pegcetacoplan. Following completion of the 48-week treatment period, each subject will have the opportunity to enter Part B, the Long-Term Extension Phase (see Appendix 1 [Section A1.1]), at the discretion of the investigator. Any subject who does not enter Part B will enter the follow-up period, consisting of 6 clinic visits at Weeks 50, 52, 54, 60, 66, and 72 (Exit Visit).

### 12.2.2. Dosing

Starting on Day 1 (Visit 4), subjects will receive self-administered daily SC doses of 360 mg of pegcetacoplan until at least Week 24 (Visit 11) and then as directed based on the timing of transition to twice-weekly dosing, and whether they are following Part A (Follow-up) or Part B (Long-Term Extension). Of important note, patients may be switched over to twice-weekly dosing with 1080 mg, as early as Week 24, but no later than the entrance into the extension phase of the study; timing of the switch is at the discretion of the sponsor. If dose transition occurs, the subject will need to follow the dose transition visits (T1, T2, and T3), as outlined in Section 10.1, Table 2 (Part A) or Appendix 1, Table A1 (Part B). The dose can be adjusted, as needed, to maintain clinical response, but no more than 1080 mg every third day.

### 12.2.3. Investigational Product Administration

Investigational product will be administered as an SC infusion. For more details on infusion duration, pump specifications, and utilization, please see the instructions for use and pharmacy manual.

The preferred site of injection will be the abdomen, however, if a subject does not tolerate administration into the abdomen, alternative appropriate sites may be considered. Research nurses or other appropriately qualified research personnel will administer the SC infusions at Visit 4 and will qualify and supervise the self-administration (or caregiver administration) for a minimum of 6 days until the subject has been qualified to conduct self-administration. During qualification the subject (or caregiver) must demonstrate to the research personnel their ability to safely and effectively administer study drug using the infusion pump. Following self-administration qualification, subjects may self-administer the SC infusions without supervision. Once qualified, the patient will continue to self-administer infusions at the clinic on those days when a clinic visit occurs and at an off-site location convenient to the subject on all other days.

Self-administration conducted at the clinic will be supervised to ensure that the subject continues to remain compliant with the administration guidelines.

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

## 12.3. Labeling, Packaging, Storage, and Handling

### 12.3.1. Labeling

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

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

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

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

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

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

### 12.3.2. Packaging

Investigational product is packaged in the following labeled containers:

- 20-mL glass vials, 6 vials per carton.

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

### 12.3.3. Infusion Supplies

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

### 12.3.4. Storage and Handling

The investigational product should be stored refrigerated at 2-8 °C both at home and in the clinic.

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location at the site. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented.

A pharmacist or appropriately qualified designated person will be responsible for storing the investigational product appropriately and dispensing the vials of investigational product to the subject. The pharmacist/nominated team member will enter the unique subject identifier on the investigational product bottle/carton labels as they are distributed.

Temperature monitoring is required at the investigator site (or documented storage location) to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature in monitored throughout the duration of the study and that records are maintained.

The investigational product should be transported from the clinic to the subject's residence as described in the pharmacy manual, using the preconditioned phase change material plates and cooler bags. Temperature monitoring will not be required during transport or at the subject's residence, but a log will be kept for every infusion to ensure that all investigational product was kept refrigerated.

With sponsor prior approval, investigational product and/or ancillary supplies may be shipped from the study site to a subject's designated location. Such shipments will only be implemented at sites where this activity is approved by the IRB/EC and health authority (if required). Subject consent will be required prior to any subject information being provided to a courier. The responsibility to return both empty vials and any unused investigational product shall remain unchanged, as described in Section 12.5.

## 12.4. Investigational Product Accountability

Accountability for the study drug at the study center is the responsibility of the investigator, who must 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 investigational product to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the investigational product and document shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained. The investigator is responsible for ensuring the retrieval of all returnable study supplies from subjects. Study drug that has been dispensed to a subject and returned unused must not be re-dispensed to a different subject.

All unused and used study drug vials should be retained at the center until they are inventoried by the study monitor. At the conclusion of the study, any unused investigational product will either be destroyed at the investigator site or be returned to the sponsor or designee for destruction, and destruction will be documented appropriately. If no supplies remain, this fact will be documented appropriately.

## 12.5. Subject Compliance

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

## 12.6. Concomitant Medications

### 12.6.1. Rescue Antibiotics

Body temperature, vital signs, and relevant blood parameters will be monitored regularly throughout the study to assess for signs of infection. The PI 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 administration of a broad-spectrum antibiotic to cover possible resistant organisms such as resistant pneumococcus (eg, levofloxacin).

# 13. STUDY PROCEDURES

Please see the Schedule of Events in Section 4 for Part A, the Core Study Phase, for a summary of the schedule of study participation and procedures. The schedule of visit dates should be established either prior to or at the time of screening, allowing subjects an opportunity to assess whether there are likely to be significant conflicts with other activities or planned absences. To the extent possible, subjects will be expected to adhere to the visit schedule and any re-scheduling of visits must be agreed, in advance, with the PI and sponsor.

A summary of the schedule of study participation and procedures for the Part B Long-Term Extension Phase is provided in Appendix 1, Table A1.

## 13.1. Screening (Week –4 to Week –2)

The subject will be screened to confirm that the subject selection criteria for the study has been met. Informed consent will be obtained at screening prior to any study-related procedures being conducted (see Section 17.3.3). Patients with sufficient previous medical history (see Section 10 for details) will begin the 4-week screening period.

A screen failure is a subject who has given informed consent and failed to meet at least one of the inclusion and/or met at least 1 of the exclusion criteria and has not been randomized or administered investigational product(s).

Screening procedures are listed in the Schedule of Events in Section 4.

The following assessments will be performed at each visit:

- Informed consent
- Demographics
- Medical history (including current angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker therapy) (Visit 3a only)
- Review of inclusion/exclusion criteria
- Physical examination
- Begin 24-hour urine collection during scheduled clinic visit (Visit 3a only)
- Triplicate 12-lead ECG
- Prior and concomitant medications
- Vital sign measurements
- Urinalysis assessment (see schedule of events for details)
- Blood tests (see schedule of events for details)
- β-HCG pregnancy test, if applicable
- Follicle-stimulating hormone, HIV, HCV, HBsAg (see schedule of events for details)
- AE collection
- Vaccination Titer Serum Sample (Visit 3b only)

- Vaccination (see schedule of events for details)
- Dispense 3 uPCR containers for consecutive collection (Visit 3b only)

### 13.1.1. Vaccinations

Subjects will be required to be vaccinated as follows, according to Advisory Committee on Immunization Practices (ACIP) recommendations for vaccination in patients with immunocompromising conditions (available at https://www.cdc.gov/vaccines/schedules/hcp/imz/adult-conditions.html).

- *Neisseria meningitidis* types A, C, W, Y: Menactra®. First dose at least 2 weeks prior to dosing (Day –14) with a booster after 2 months (Day 56).
- *Neisseria meningitidis* type B: Bexsero®. First dose at least 2 weeks prior to dosing (Day –14) with a booster after 2 months (Day 56).
- *Streptococcus pneumoniae:* Prevnar 13®(PCV13) at least 2 weeks prior to dosing (Day –14) and Pneumovax® (PPSV23) after 2 months (Day 56).
- *Haemophilus influenzae* type B: ActHIB® at least 2 weeks prior to dosing (Day –14).

Vaccination is mandatory, unless documented evidence exists that subjects have received all recommended vaccines or are nonresponders to vaccination. All required vaccination(s) for which evidence is not available will be administered as needed to bring subjects up to date. The investigator should discuss with the medical monitor any individual patient circumstances that are relevant to the vaccination requirements or that would make the above schedule not possible or reasonable. On an ongoing basis, including upon entry into the long-term extension phase, subjects should be reevaluated for the need for any vaccinations based on ACIP recommendations. Subjects who withdraw from the study prior to any vaccine booster will be offered the opportunity to return to the site as recommended by current ACIP Adult Immunization schedule to receive the booster shot.

## 13.2. Treatment Period (Week 1 to Week 48)

### 13.2.1. Day 1 (Visit 4)

Following completion of the 4-week screening period, subjects will enter the treatment period and will receive pegcetacoplan. The following assessments outlined in the schedule of events (Section 4) will be performed:

Prior to treatment:

- Procure 3 previously collected consecutive uPCR samples
- Eligibility confirmation
- Triplicate 12-lead ECG at –45, –30, and –15 minutes predose
- Concomitant medications collection
- Vital sign measurements

- Urinalysis (See schedule of events for details)
- Blood tests (see schedule of events for details)
- Pregnancy (β-HCG)
- Urine pregnancy test, if applicable
- Predose PK collection (within 1 hour before dose)
- Dispense investigational product and infusion materials
- Train subject to perform home infusion
- Full physical examination

Following Treatment:

- Subjects will be contacted via phone by study staff 6 hours after the study treatment to collect safety information
- Vital sign measurements at 30 minutes, 2 hours, and 4 hours post dose
- Injection Site Assessment
- Collect AEs
- Dispense 3 uPCR containers for consecutive collection

### 13.2.2. Week 2 to Week 48 (Visits 5-15)

Subjects will self-administer once daily SC doses 360 mg of pegcetacoplan and will attend the investigator site at Visits 5-15 where the assessments outlined in the schedule of events (Section 4), will be performed.

Visit window: ±2 days.

Research nurses or other appropriately qualified research personnel will administer the SC infusions until the subject has been qualified to conduct self-administration. Following self-administration qualification, subjects may self-administer the SC infusions. The subject will continue to self-administer infusions at the clinic on those days when a clinic visit occurs and at an off-site location convenient to the subject on all other days. Subjects have the opportunity to transition to a biweekly 1080 mg SC infusion of pegcetacoplan, as early as Week 24 of Part A of the study. If this occurs, the subject will need to have 3 transition visits (T1, T2, and T3), the details of which are provided in Table A1 of Appendix 1.

The following assessments will be performed prior to investigational product administration:

- Procure 3 previously collected consecutive uPCR samples (except Visit 15)
  - Arrange courier pickup for all biweekly triplicate uPCR samples during non-clinic visit weeks
- Dispense 24-hour urine container at Visit 14 (for urine collection within 2 weeks prior to Visit 15)
- Vital sign measurements (to be performed prior to ECG and venipuncture)

- Triplicate 12-lead ECG 15 minutes predose
  - Visit 15: Triplicate 12-lead ECG at –45, –30, and –15 minutes predose
- PK sample predose (within 1 hour before dosing) to coincide with the 15 min predose ECG
- Concomitant medications review
- AE collection and review
- Urinalysis collection (See schedule of events for details)
- eGFR assessment
- Pregnancy (β-HCG) (Visit 15 only), if applicable
- Blood tests (see schedule of events for details)
- Urine pregnancy test, if applicable
- Physical examination (Full exam at Visit 15 only)
- Vaccination Titer Serum Sample (Visit 7 only)
- Vaccination(s) Booster (Visit 7 only)
- Dispense investigational product and infusion materials
- Observe Infusion of investigational product

After investigational product administration:

- Subjects will be contacted via phone by study staff 6 hours after the study treatment to collect safety information (Visit 15 only)
- Vital sign measurements at 30 minutes post dose
  - Visit 15 only: Vital sign measurements to be measured at 30 minutes, 2 hours, and 4 hours post dose
- Injection Site Assessment
- Collect AEs
- Dispense uPCR containers for consecutive collection
  - 3 uPCR containers (Visit 5 and 15 [for subjects entering the follow-up period]), 6 uPCR containers (Visits 6-10, Visit 14, and, for subjects entering Part B, Visit 15), 9 containers (Visits 11-13)

## 13.3. Part B: Long-Term Extension Phase (Week 48 and Beyond)

At Visit 15 (Day 336; Week 48) subjects will have the opportunity to enter Part B, the Long-Term Extension Phase, at the discretion of the investigator, in order to continue to receive treatment with pegcetacoplan until it is commercially available for the disease under treatment. Subjects who enter the Long-Term Extension Phase will complete study procedures as outlined in Appendix 1 and Table A1.

## 13.4. Follow-up (Visits 16-20)

All subjects who complete study treatment through Day 336/Week 48 but do not enter the Part B Long-Term Extension Phase will need to return to the clinical site for Follow-up Visits 16, 17, 18, 19, and 20, where the assessments outlined in the schedule of events (Section 4) will be performed.

Subjects who discontinue treatment early and do not continue their participation in the study should complete a follow-up visit 6 weeks after discontinuation of treatment and also the Exit Visit 6 weeks thereafter.

Visit window: ±2 days (Visits 16-18) ±7 days (Visits 19 and 20)

- Procure 3 previously collected consecutive uPCR samples to site (Visits 16-20)
  - Arrange courier pickup for all biweekly triplicate uPCR samples during non-clinic visit weeks
- Physical examination (Visit 16 and 17 only)
- Concomitant medications review (Visit 16 and 17 only)
- Injection Site Assessment (Visit 16 only)
- Antidrug Ab collection
- eGFR assessment
- Urinalysis collection (See schedule of events for details)
- Urine pregnancy test (Visit 16-19 only)
- AE review
- PK Sample collection
- Vital Signs
- Blood tests (See schedule of events for details)
- Triplicate 12-lead ECG
- Dispense uPCR containers for consecutive collection (Visits 16-20):
  - 3 uPCR containers (Visits 16 and 17), 6 uPCR containers (Visit 20), 9 uPCR containers (Visits 18 and 19)
- Dispense 24-hour urine container

### 13.4.1. Exit Visit (Visit 21)

If subjects are not participating in Part B the Long-Term Extension Phase, they will return to the clinical facility for the Exit Visit 24 weeks after the final dose of pegcetacoplan, on Day 504 (or sooner if the subject discontinues prior to the Week 48).

Study participation for each subject will be concluded following completion of the Exit Visit. If a subject withdraws from the study prior to the scheduled Exit Visit, all Exit Visit evaluations should be performed at the subject's final visit to the clinic, including the collection of blood

samples for PK and/or PD assessments, as well as a postdose antigenicity sample if not yet collected.

The Exit Visit procedures are listed in the Schedule of Events in Section 4.

Visit window: ±7 days.

- Arrange courier service to pick up 24-hour urine collection to deliver to site
- Procure 3 previously collected consecutive uPCR samples to site
- Blood tests (see schedule of events for details)
- Concomitant medications
- AE review
- Antidrug Ab assay
- eGFR assessment
- Urinalysis (See schedule of events for details)
- PK Sample
- Vital Signs
- Triplicate 12-lead ECG

### 13.4.2. Unscheduled Follow-up Visits

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

Unscheduled follow-up visits may include (but are not limited to) any of the procedures listed in the Schedule of Events in Section 4.

### 13.4.3. Safety Monitoring Committee

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

The first SMC meeting will be scheduled 3 months after the first subject is dosed, and at further 3 monthly intervals until all subjects complete the Week 48 Visit. An *ad hoc* SMC data review may be recommended by the SMC or requested by the sponsor at any time during the study.

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

## 13.5. Treatment Discontinuation and Study Withdrawal

Subjects will be considered to have completed the study when they have completed the Week 72 exit visit activities described in the Schedule of Assessments in Section 4, when they have enrolled in a subsequent study of pegcetacoplan, or when they have discontinued study treatment and completed any early termination activities.

A subject may withdraw from the study at any time, for any reason, without prejudice to his/her future medical care by the physician or at the institution. If a subject discontinues or is withdrawn from study treatment for any reason, the study site must immediately notify the medical monitor.

Treatment may be discontinued and/or a subject's participation in the study may be discontinued, for any of the following reasons:

1. Any serious adverse event (SAE), clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition (including infections) that indicates to the PI that continued participation is not in the best interest of the subject.
2. Subject's decision to withdraw.
3. Subject's failure to comply with protocol requirements (including pregnancy) or study-related procedures.
4. Termination of the study by the sponsor, US Food and Drug Administration, or other regulatory authorities.
5. Liver Toxicity (please refer to Section 13.5.1 for further details).
6. Sustained and significant reduction in renal function (see more details below).

A sustained and significant reduction in renal function is defined by one of the following: initiation of chronic dialysis, a confirmed and sustained eGFR ≤15 mL/min/1.73 $m^2$ or a confirmed and sustained reduction in eGFR of at least 30% which is drug related in the opinion in the PI. A reduction in eGFR would be considered confirmed if present on 2 separate consecutive measurements and sustained if the 2 measurements are at least 1 week or apart.

The reason for treatment discontinuation and/or withdrawal from the study must be recorded in the subject's source document.

Subjects who discontinue study treatment prior to the end of the treatment period, should undergo all follow-up visits and procedures through study completion (Exit Visit), unless unwilling or unable, or consent has been withdrawn. Subjects who wish to fully withdraw from the study before Visit 15, should be encouraged to complete the Early Termination Exit Visit.

Any subject withdrawn due to an AE (whether serious or nonserious) or clinically significant abnormal laboratory test values will be evaluated by the investigator and should be treated and/or followed at least up until the symptoms or values return to normal or acceptable levels, as judged by the PI.

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

### 13.5.1. Liver Toxicity

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

Drug treatment will be discontinued immediately if either:

- ALT or AST is >3 × the upper limit of normal (ULN) and (total bilirubin is >2× ULN or international normalized ratio [INR] is >1.5)

or

- ALT or AST is >8× ULN

Drug treatment will be withheld if either:

- ALT or AST is >5× ULN

or

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

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

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

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

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

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

### 13.5.2. Lost to Follow-up

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

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

# 14. ASSESSMENTS

## 14.1. Assessments

For Part A, the Core Study Phase, assessments to be performed during the study are described below. Every effort should be made to ensure that the protocol-required assessments are completed as described.

If deemed necessary, additional safety measurements will be performed at the discretion of the PI.

### 14.1.1. Medical History

Medical history, including changes to angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker therapies, will be collected at Screening Visit 3a.

### 14.1.2. Prior and Concomitant Medications

To be eligible for entry into the study, subjects must be on a stable optimized treatment regimen for their disease, in the opinion of the PI, for at least 2 months prior to the first dose of pegcetacoplan (Visit 4), which may include, but is not limited to, use of immunosuppressive agents, antihypertensives and/or antiproteinurics.

All other prior medications administered within 12 Weeks of Screening Visit 3a will be collected.

Use of rituximab, belimumab, and eculizumab during the study (and/or within 6 months prior to the first dose of pegcetacoplan) must be discussed with the sponsor for consideration and approval.

All medications and procedures administered to subjects from the time of informed consent through the End of Study Visit are regarded as concomitant and will be documented.

To the extent possible, baseline treatment regimens (including medications, dietary restrictions, and lifestyle modifications), should not be changed during the study, except as necessary for the well-being of the patient, in the opinion of the PI.

### 14.1.3. Body Height and Weight

Body height (cm) and body weight (kg) will be measured at screening Visit 3a. Body weight will be measured throughout the study as part of the physical examination.

### 14.1.4. Physical Examination

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

Brief physical examinations will include general appearance, heart, lungs, abdomen, extremities, and weight.

The investigator (or designee) at the study site will examine each subject as outlined in the Schedule of Events in Section 4.

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

### 14.1.5. Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure, and heart rate will be measured prior to and 30 minutes after dosing as outlined in the Schedule of Events in Section 4. This will include daily measurements during Days 2 to 7 by the health care professional conducting the self-administration qualification (ie, at-home nurse).

Vital signs may be taken at any other times, if deemed necessary. Blood pressure and heart rate measurements will be performed with subjects in a seated position after resting for 5 minutes, except when they are supine or semireclined because of study procedures and/or AEs (eg, nausea, dizziness) or if deemed necessary by the PI.

Vital signs will be measured before venipuncture and ECG assessment, vital signs collected post dose will be timed from the completion of the study drug administration.

Additional monitoring of vital signs will occur on Day 1 (Visit 4) and Week 48 (Visit 15) at 2 and 4 hours after dosing, with a ±15-minute window of occurrence.

### 14.1.6. Electrocardiogram Monitoring

Triplicate 12-lead ECGs will be measured at the time points outlined in the Schedule of Events in Section 4. There is a ±5-minute window for the start of the triplicate ECGs. Once each triplicate ECG begins, subsequent ECGs should be at least one minute and no more than 2 minutes apart. ECGs will be taken following resting in the supine position for 10 minutes in a quiet environment and prior to any blood sampling procedures, unless specified at time points after timed blood sampling procedures.

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

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

Please see the Study Operations Manual for further details on ECG collection, and reporting.

### 14.1.7. 24 Hour Urine Collection

Subjects will be provided with a container for 24-hour urine collection that can begin at the site or at home. The baseline 24-hour urine collection (during screening at Visit 3a, within the visit window) should be obtained within 2 weeks of the first dose of pegcetacoplan, and final 24-hour urine collection during the treatment period should be obtained within 2 weeks prior to Visit 15. Twenty-four-hour urinary output will be collected in order to determine eligibility for entry into the study by a uPCR on a 24-hour urine collection. Twenty-four-hour urine collection is defined as a total urine collection for the 24-hour period following the (discarded) first urinary output for the day. Urine container will need to be stored at 2-8 °C (ie, in refrigerator). Courier

arrangements will be made by the site to pick up the collection container for the patients and return to it the site. Urinary PCR and ACR on the 24-hour collection will be determined.

### 14.1.8. Consecutive Spot uPCR

Subjects will receive separate spot urine collection containers at the scheduled clinic visits indicated in the schedule of events. Biweekly, subjects will complete urine collection from their first urinary output upon awakening for the day, for 3 consecutive days (see schedule of events for visit window details). On weeks leading up to the scheduled clinic visit subjects will return triplicate uPCR as indicated. On weeks where no clinic visit is scheduled, courier service will be arranged to pick up samples from the patient's home for delivery to the clinic. It is important to have these collections be from the first urinary output upon awakening on each of those days. After collection, the urine samples must be stored at a refrigerated temperature (2-8 °C) until they are returned to the site. Both uPCR and uACR values should be calculated on all spot urine samples.

### 14.1.9. Clinical Laboratory Tests

All tests listed below will be performed as outlined in the Schedule of Events in Section 4. In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the PI or recommended by the SMC. The clinical laboratory tests include (but are not limited to) the following:

#### 14.1.9.1. Hematology

- Hb
- Hematocrit
- RBC count
- Platelet count
- WBC count with differential

#### 14.1.9.2. Coagulation*

- Activated partial thromboplastin time (aPTT)
- Fibrinogen
- INR

*The use of silica reagents in coagulation panels should be avoided in subjects treated with pegcetacoplan.

#### 14.1.9.3. Serum Chemistry

- Blood urea nitrogen (BUN)
- Creatinine
- Estimated Glomerular Filtration Rate (using CKD-EPI formula)
- Bilirubin (total and conjugated)
- Albumin
- Alkaline phosphatase (ALP)
- Lactate dehydrogenase (LDH)
- Gamma-glutamyl transferase (GGT)
- Calcium
- Phosphorus
- Aspartate aminotransferase (AST)
- Alanine Aminotransferase (ALT)
- Uric acid
- Glucose
- Sodium
- Potassium
- Chloride
- Creatinine Kinase (CK)
- Bicarbonate

#### 14.1.9.4. Urinalysis

- pH
- Specific gravity
- Protein
- Glucose
- Ketones
- Albumin-to-creatinine ratio (ACR)
- Protein-to-creatinine ratio (PCR)
- Bilirubin
- Blood
- Nitrite
- Urobilinogen
- Leukocyte esterase
- Urine Sediment

Microscopic examination for protein, blood, nitrite, and/or leukocyte esterase will be performed on all urinalyses.

#### 14.1.9.5. Serum Pregnancy Test and Screening Assays

Serum pregnancy test (beta human chorionic gonadotropin; β-HCG) will be performed for females only. Follicle-stimulating hormone will be performed for postmenopausal females at screening Visit 3a only. Blood tests for HIV, HCV, and HBV will be performed at Screening Visit 3a only.

#### 14.1.9.6. Vaccination Antibody Titer

Serum samples will be collected at Visit 3b and Visit 7 (prior to administration of vaccinations) for analysis of antibody titers to *Neisseria meningitidis* (types A, C, W, Y, and B), Pneumococcal conjugate vaccine or Pneumococcal polysaccharide vaccine 23 (PCV13 or PPSV23,

respectively) and the Haemophilus influenza Type B (Hib) vaccination. The serum samples will only be analyzed in the event that a patient has a positive infection for *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*.

### 14.1.10. Injection/Infusion Site and Pump Safety Assessment

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

Subjects will be instructed to notify the PI or other study personnel in the event that an injection site reaction occurs after self-administration of pegcetacoplan. All CS findings from injection site assessment or related to pump use will be recorded as AEs.

## 14.2. Pharmacokinetic Assessments

### 14.2.1. Blood Sampling and Processing

Blood samples for PK assessment of pegcetacoplan will be collected via direct venipuncture at the time points delineated in the Schedule of Events in Section 4.

PK samples will be taken predose at all other visits.

Instructions for collection, handling, processing, storage, and shipping of samples will be provided in a separate Laboratory Reference Manual prior to study initiation.

### 14.2.2. Analytical Method

Serum sample analysis will be performed using GLP-compliant validated procedures and methods. The methods used and the results obtained will be included in the final report as an appendix.

## 14.3. Pharmacodynamic Assessments

Blood samples will be collected via direct venipuncture at the time points delineated in the Schedule of Events in Section 4. for PD assessment of complement activation through the alternative (ie, AH50) pathways. Blood samples will also be collected to measure CH50, C3, C3a, C4, C5a, and sC5b9 levels. Other relevant PD markers may also be assessed.

Instructions for collection, handling, processing, storage, and shipping of samples will be provided in a separate Laboratory Reference Manual prior to study initiation.

## 14.4. Antidrug Antibody Assessment

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

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

Patients who test positive for ADAs at any time will be followed up with ADA samples being collected every 6 months until the antibody levels are considered to be negative. Antibody levels will be considered to be negative when they revert to baseline or any titer that is less than a 4-fold increase from the baseline titer. Samples that test positive will be characterized by an assay that will determine antibody titer and measure neutralizing capacity.

## 14.5. Blood Volume for Study Assessments

**Table 3: Blood Volume During Part A, the Core Study Phase**

| Sample Type | Number of Visits | Approximate Volume per Visit (mL) | Approximate Volume Over Course of Study (mL) |
|---|---|---|---|
| Screening laboratory safety tests (including hematology, serum chemistry, coagulation serology), FSH (for postmenopausal female patients only) | 1 | 25 | 25 |
| On-study serum chemistry | 20 | 11 | 220 |
| On-study hematology | 20 | 4 | 80 |
| On-study coagulation | 20 | 3 | 60 |
| PK | 19 | 4 | 76 |
| PD (C3, C3a, C4, C5a, and sC5b9) | 16 | 10 | 160 |
| Disease-Specific Biomarkers | 17 | 2 | 34 |
| Immunogenicity (Antidrug antibodies) | 16 | 5 | 80 |
| Vaccination titer sample | 2 | 7 | 14 |
| **Total Approximate Blood Volume for Study:** | | | **749** |

Abbreviations: FSH = follicle-stimulating hormone; sC5b9 = soluble C5b9 complex.
Note: represents the standard collection volume planned over the duration of the study, actual volume may vary.

For subjects who enter the Part B Long-Term Extension Phase, the volumes noted above will continue to be collected as noted in the Study Flow Chart for the Part B Long-Term Extension Phase (Table A1).

## 14.6. Pregnancy Tests

For WOCBP, a serum pregnancy test will be performed at screening (Visit 3a) and during treatment (Visits 4 and 15). Subjects with a positive test will be excluded or discontinued from the study. A urine pregnancy test will also be performed at each site visit during the treatment period (predose). For subjects entering the follow-up period, urine pregnancy tests will be performed at each follow-up visit through 12 weeks after the last dose of pegcetacoplan (Visit 19). Male subjects will be counseled to avoid donating sperm during the time between the first screening and the final Exit Visit.

## 14.7. COVID-19 Assessments

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

# 15. ADVERSE EVENTS

## 15.1. Definitions

### 15.1.1. 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.

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

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

### 15.1.2. 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, according to appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in the above definition.

Examples of important medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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

### 15.1.3. Unexpected Adverse Events

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

## 15.2. Recording and Reporting Adverse Events

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

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

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

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

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

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

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

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

### 15.2.1. 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 4 should be considered when evaluating the relationship of AEs/SAEs to study treatment.

**Table 4: 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. |

### 15.2.2. 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 15.1.2. An AE can be of severe intensity but not be considered serious.

Table 5 presents the severity definitions that should be considered when evaluating the severity of AEs and SAEs.

**Table 5: Severity of Events**

| Severity | Definition |
|---|---|
| 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). |

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

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

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

## 15.3. Pregnancy

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

Any pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Apellis Safety by completing the pregnancy report form within 24 hours of the investigator becoming aware of the event. The completed pregnancy report form must be emailed to PPD

The investigator must follow up the subject until completion of the pregnancy and must report the outcome of the pregnancy (eg, delivery, termination, etc) and neonatal status up to 12 months post delivery. An abnormal outcome is defined as the birth of a child with persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomaly, or birth defects. In the event of an abnormal outcome, an SAE must be reported using the SAE report form, as described in Section 15.2.

## 15.4. Abuse, Misuse, Overdose, and Medication Error

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

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

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

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

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

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

# 16. STATISTICS

## 16.1. Sample Size Justification

Given the exploratory nature of the study no formal statistical hypothesis testing will be performed and so the sample sizes of both parts of the study are not based upon statistical power of the study.

Approximately 48 patients (6-12 per indication) will be enrolled into this study (patients with either IgAN, primary MN, LN, or C3G, enrolled 1:1:1:1). As these complement-mediated glomerulopathies are rare diseases it may be difficult to recruit subjects from 1 or more of the disease types; hence the range of 6-12 subjects per type. The intention is to recruit safety, PK, PD, and efficacy data to support the progress of pegcetacoplan into further clinical studies.

With 6 subjects treated with pegcetacoplan in each disease type there is a 95% chance of an AE being reported if its true incidence is over 40%. Similarly, there is a 47%, 74% and 88% chance if the true incidence is 10%, 20%, or 30% respectively. With 12 subjects treated in each disease type the chance increases to >93% for true incidences over 20% and 72% if the true incidence is 10%.

## 16.2. Statistical Analysis Methodology

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.

All endpoints will be summarized by the diagnosed complement-mediated glomerulopathy (IgAN, LN, primary MN, or C3 glomerulopathy) and visit. Continuous data will be summarized using descriptive statistics (eg, mean and standard deviation) and categorical data will be summarized using frequency tables (counts and percentages).

### 16.2.1. Analysis Populations

#### 16.2.1.1. Screened Population

The screened analysis set will include all patients who signed the ICF, are screened for participation. This set will be used only for the purpose of describing patient disposition.

#### 16.2.1.2. Safety Population/ Intent-to-Treat (ITT) Population

The safety analysis set will include all patients who receive a dose of pegcetacoplan.

#### 16.2.1.3. Per Protocol Population

The PP set will include all subjects 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.

#### 16.2.1.4. Pharmacokinetic (PK) Population

The PK population will include all subjects in the ITT population who receive pegcetacoplan and have at least 1 evaluable post-dose PK measurement.

#### 16.2.1.5. Pharmacodynamic Population

The PD population will include all subjects in the ITT population who have at least 1 evaluable post-dose PD measurement.

#### 16.2.1.6. Data Review for Analysis Populations

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

### 16.2.2. Efficacy Analyses

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

#### 16.2.2.1. Primary Endpoint

Changes from baseline in proteinuria, percentage changes from baseline in proteinuria, and percentage change in mean proteinuria is the primary efficacy endpoint. They will be calculated by using mean of the 3 spot uPCR samples collected for baseline (Day 1) and the subsequent treatment visits. In addition, these calculations will be repeated using the 24-hour urine proteinuria sample which is collected at baseline (Day 1) and Week 48. If additional unscheduled 24-hour urine samples are collected then these will be included as well.

#### 16.2.2.2. Secondary Endpoints

Changes from baseline and percentage changes in baseline eGFR and disease-specific biomarkers are the secondary efficacy endpoints. Changes from baseline and percentage changes from baseline in biomarkers for serum C3, C3a, C4, C5a, and sC5b9, and AH50 levels will be summarized. They will be calculated for each postdose assessment, while the baseline will be taken as the predose assessment on Day 1. Additional disease parameters and/or biomarkers may also be analyzed.

#### 16.2.2.3. Exploratory Endpoints

Changes from baseline and percentage changes from baseline in biomarkers for LN (autoantibodies to double-stranded DNA, C3, and C1q), primary MN (PLA2R autoantibodies), and C3G (C3NeF; Part A only) levels will be summarized. They will be calculated for each postdose assessment, while the baseline will be taken as the predose assessment on Day 1. Additional disease parameters and/or biomarkers may also be analyzed.

### 16.2.3. Safety Analyses

All safety endpoints will be evaluated using the safety population.

#### 16.2.3.1. Adverse Events

TEAEs are defined as those AEs that develop or worsen after the first dose of study medication and up to 8 weeks beyond the last dose of study medication. The current version of MedDRA at the time of analysis will be used to classify all AEs.

TEAEs will be summarized by System Organ Class and Preferred Term, in accordance with the MedDRA coding dictionary. The number of subjects reporting each AE Preferred Term will be tabulated for all TEAEs and separately for those considered as possibly related to study treatment by the investigator. Number of subjects reporting SAEs will also be tabulated. AE summaries will be presented for each period of the study separately within each complement-mediated glomerulopathy group.

#### 16.2.3.2. Clinical Laboratory Tests

Changes from baseline in laboratory will be summarized using descriptive statistics by treatment, visit, and nominal time post dose. Baseline will be taken as the last measurement prior to the first dose of pegcetacoplan.

Out of range values will be flagged in the data listings.

#### 16.2.3.3. Vital Signs and ECGs

Changes from baseline in vital signs and ECG parameters will be summarized using descriptive statistics by treatment, visit, and nominal time post dose. Baseline will be taken as the last measurement prior to the first dose of pegcetacoplan.

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

ECG parameters will be analyzed using concentration effect models.

### 16.2.4. Pharmacokinetic Analyses

The PK concentrations will be evaluated using the PK population.

Concentrations will be summarized using descriptive statistics over time by complement-mediated glomerulopathy.

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

### 16.2.5. Pharmacodynamic Analyses

The PD endpoints will be evaluated using the PD population.

Absolute values, changes from baseline, and % changes from baseline will be summarized using descriptive statistics over time by complement-mediated glomerulopathy.

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

### 16.2.6. Other Data Analyses

Demographic data, baseline characteristics, physical examination, concomitant medication, medical history data, and study medication exposure will be summarized by complement-mediated glomerulopathy.

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

## 16.3. Interim Analyses

No formal interim analyses are planned for the primary endpoint.

# 17. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

## 17.1. Direct Access to Source Data/Documents

The PI must maintain, at all times, the primary records (ie, source documents) of each subject's data for data verification. Examples of source documents are medical records, laboratory reports, study drug records, and eCRFs that are used as the source.

The PI will permit study-related monitoring, audits, and inspections by the sponsor and/or its' designee, IRB/IEC, and the regulatory agencies at any time during the study. The PI will ensure that the auditor is allowed direct access to the source data, medical records, eCRFs, and the site's regulatory file for the study and any other pertinent information.

## 17.2. Quality Control and Quality Assurance

This study is to be performed in full compliance with the protocol, GCP, and applicable regulatory requirements. The PI and sponsor and/or its designee are responsible for ensuring that the study staff receive appropriate training on the protocol, study procedures, and any other relevant information.

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

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

### 17.2.1. Monitoring

On-site monitoring will be performed by the sponsor's designee for the duration of the study. The monitor will ensure that the study is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, GCP, and the applicable regulatory requirements. Monitoring activities will include (but are not limited to):

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that all subject data relating to the study is being recorded on printed or electronic CRFs unless transmitted to the sponsor/designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF
- Ensure that the investigator maintains accurate documentation (source data) that supports the information entered in the CRF
- Confirm that the investigational team is adhering to the protocol and verify the accuracy and completeness of the eCRF entries against source documents

- Confirm that investigational product accountability checks are being performed and documented
- Record and report any protocol deviations not previously sent to the Sponsor
- Confirm that all AEs and SAEs have been properly documented on CRFs and confirm that any SAEs have been forwarded to Apellis and those SAEs that met criteria for reporting have been forwarded to the IRB
- Confirm that suspected unexpected serious adverse reactions are being acknowledged and submitted to the IRB as necessary

The PI will provide direct access to source data/documents for study-related monitoring, as described in Section 17.1. It is important that the PI and the staff are available at these visits. The monitor will record the date of each visit together with a summary of the status and progress of the study. Proposed actions will be documented in writing to the PI.

## 17.3. Ethics

### 17.3.1. Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, applicable regulations, the ethical principles set forth in the Declaration of Helsinki, and the ICH Harmonized Tripartite Guidance for Good Clinical Practice, E6, R2 (ICH GCP).

### 17.3.2. Institutional Review Board or Independent Ethics Committee Review

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

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

### 17.3.3. Subject Information and Consent

The PI is responsible for obtaining an informed consent. A written informed consent, in compliance with ICH Guidance E6, must be obtained from each subject prior to screening and enrollment or performing any study-related procedures.

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the subjects in nontechnical terms. The subject will be given sufficient time to consider the study's implications before deciding to participate in the study. The subject and/or legal guardian will be required to sign and date an ICF and will be assured that they may withdraw from the study at any time without jeopardizing their medical care. The PI shall retain the original, signed informed consent for study participation in the subject's medical record and shall provide the subject and/or legal guardian with a copy of the signed consent.

Patients who live outside the United States or are not proximal to their nearest active site, who may wish to participate in this study for a period of time within the United States will be pre-

consented by the PI and the local physician. The ICF (in local language) will be emailed to the subject's local physician. The ICF will be provided in advance to the patients to ensure adequate time is provided to ask questions and discuss any concerns. This procedure is completed to ensure patients understand the study, procedures, risks, and benefits, etc., before traveling to their activated site for a screening visit. The patient will be consented by the PI over the phone/video with the local physician present on the call/video to aid in the discussion. Additional trained translators will be provided if needed to ensure subjects fully understand the protocol and can ask questions. The ICF will be signed by the patient, local physician, and PI once the patient arrives to the site for the screening visit. The executed ICF will be stored locally at the PI's office. The PI may wish to re-consent the patient again once arriving to the United States.

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

### 17.3.4. Confidentiality

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

### 17.3.5. ClinicalTrials.gov

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

### 17.3.6. Termination of Study

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

## 17.4. Data Handling and Record Keeping

Subject information will be captured and managed by study sites on eCRFs by a web-based EDC tool developed and supported by the Contract Research Organization (CRO) assisting with the conduct of the study and configured by sponsor. It is recommended that data be entered into the EDC system within 5 business days of collection, including batched records and records with source documents.

Data management will be performed by the CRO according to their standard operating procedures. The Data Management Plan will be approved by the sponsor.

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

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

## 17.5. Protocol Amendments

Any amendments to the study protocol deemed necessary as the study progresses will be discussed between sponsor and the PI. The PI will not implement any changes to the protocol without an agreement by the sponsor and prior review and documented approval from the IRB/IEC of an amendment, except where necessary to eliminate immediate hazards to study subject or when the changes involve only logistical or administrative aspects of the study (eg, change in staff, telephone numbers).

Changes resulting in amendments will be made jointly between the sponsor and the PI and must be confirmed in writing. Amendment(s) will be approved and signed off in the same way as the original protocol.

## 17.6. Report Format

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

## 17.7. Finance and Insurance

Finance and insurance will be addressed in a Clinical Trial Agreement between the PI/Institution and the sponsor.

## 17.8. Publication Policy

The data generated for this study are considered confidential information and are the property of the sponsor. All study information provided to the PI and site personnel by the sponsor shall not be published or disclosed to a third party without the prior written consent of the sponsor.

Apellis will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Apellis adheres to external guidelines (eg, Good Publication Practices 2) when forming a publication steering committee, which is done for large, multicenter Phase 2-4 and certain other studies as determined by Apellis. The purpose of the publication steering committee is to act as a noncommercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Apellis products or projects must undergo appropriate technical and intellectual property review, with Apellis agreement to publish prior to release of information. The review is aimed at protecting the sponsor’s proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal investigator will own (or share with other authors) the copyright on his/her publications. To the extent that the principal investigator has such sole, joint, or shared rights, the principal investigator grants the sponsor a perpetual, irrevocable, royalty-free license to make and distribute copies of such publications.

The term “publication” refers to any public disclosure including original research articles, review articles, oral presentations, abstracts, and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral, or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor’s confidential information shall be submitted for publication without the sponsor’s prior written agreement to publish and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by Apellis, the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor’s presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single-site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors current standards. Participation as an investigator does not confer any rights to authorship of publications.

# 18. REFERENCES

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# 19. APPENDICES

# Appendix 1. Long-Term Extension Activities

## A1.1. Part B: Long-Term Extension Phase

This Appendix only contains information that is specific to the design and conduct of Part B, the Long-Term Extension Phase. Any processes, procedure, or information not described in this Appendix is identical to that described through the body of the main protocol.

### A1.1.1. Part B Long-Term Extension Phase: Overview/Rationale

Following Day 336/Week 48 and the completion of Part A (the Core Study Phase), any subject who, in the opinion of the investigator, is experiencing clinical benefit from pegcetacoplan administration will be invited to participate in Part B, the Long-Term Extension Phase, in order to continue to receive treatment with pegcetacoplan until it is commercially available for the disease under treatment.

During Part A Core Study Phase (up to Week 48), an acetate-buffered mannitol formulation of pegcetacoplan (pegcetacoplan 270 mg/day and 360 mg/day) will be used for daily SC dosing. At or after Week 24, at the discretion of the investigator, the subject can be transitioned to pegcetacoplan 1080 mg administered twice weekly by SC infusion using an acetate-buffered sorbitol formulation. At the time of entry into Part B, the Long-Term Extension Phase, subjects will be transitioned to the sorbitol formulation with pegcetacoplan 1080 mg administered twice weekly by SC infusion if they did not make this transition during Part A. In addition, subjects may transition to pegcetacoplan 1080 mg administered every 3 days (ie, a dose on every third day); see Section A1.1.3.2 for more details.

Table A1 provides the schedule of events for visits that will be conducted during the Part B Long-Term Extension Phase.

**Table A1: Part B, Long-Term Extension Phase: Study Flow Chart (Week 48 and Beyond)**

| Study Period | Long-Term Extension Phase: Week 48 and Beyond | | | | | | | ETF & ETE[a] |
|---|---|---|---|---|---|---|---|---|
| | | Dose Transition Visits[b] (Only for those who have not already transitioned to twice-weekly dosing) | | | Continue or Resume Regular Visits | | | |
| Study Week | 48[b] | T+1W | T+2W | T+4W | 60 | 72 | ≥84[c] | |
| Study Day | 336[b] | T+7D | T+14 D | T+28 D | 420 | 504 | 588[c] | |
| Study Visit | 15[b] | T1 | T2 | T3 | E16 | E17 | E≥18[c] | |
| Visit Window (±Days) | 2 | 2 | 2 | 2 | 7 | 7 | 7 | NA |
| Physical examination[d] | X | | | | | X[d] | | X |
| Triplicate 12-lead electrocardiogram[e] | X | | | | X | X | X | X |

## Table A1: Part B, Long-Term Extension Phase: Study Flow Chart (Week 48 and Beyond)

| Study Period | Long-Term Extension Phase: Week 48 and Beyond | | | | | | | ETF & ETE[a] |
|---|---|---|---|---|---|---|---|---|
| | | Dose Transition Visits[b] (Only for those who have not already transitioned to twice-weekly dosing) | | | Continue or Resume Regular Visits | | | |
| **Study Week** | **48[b]** | **T+1W** | **T+2W** | **T+4W** | **60** | **72** | **≥84[c]** | |
| **Study Day** | **336[b]** | **T+7D** | **T+14 D** | **T+28 D** | **420** | **504** | **588[c]** | |
| **Study Visit** | **15[b]** | **T1** | **T2** | **T3** | **E16** | **E17** | **E≥18[c]** | |
| **Visit Window (±Days)** | **2** | **2** | **2** | **2** | **7** | **7** | **7** | **NA** |
| **Pegcetacoplan administration[b,f]** | X | X | X | X | X | X | X | |
| **Injection site assessment[g]** | X | X | X | X | X | X | X | |
| **Concomitant medications** | X | X | X | X | X | X | X | X |
| **Vital sign measurements[h]** | X | X | X | X | X | X | X | X |
| **Urine** | | | | | | | | |
| 24-hour Urine Collection[i] | X | | | | | X[i] | X[i] | X |
| Dispense uPCR containers | X | | X | X | X | X | X | |
| Return uPCR samples[j] | | | X | X | X | X | X | |
| **Urinalysis—microscopic & Dipstick[k]** | X | X | X | X | X | X | X | X |
| **Blood[l]** | | | | | | | | |
| Pharmacokinetic Sample Collection[m] | X | X | X | X | X | X | X | X |
| Antidrug Ab assays[n] | X | | | X | | X | X[n] | X |
| Hematology and chemistry[o,p] | X | X | X | X | X | X | X | X |
| PD for Complement profile | X | X | X | X | X | X | X | X |
| Pregnancy (β-HCG and FSH) | X | | | | | | | |
| Disease-Specific Biomarkers | X | | | | | | | X |
| eGFR[q] | X | | | | | | | X |
| **Urine pregnancy test[r]** | X | | | X | X | X | X | |
| **Adverse events** | X | X | X | X | X | X | X | X |
| **Drug Dispensation for Home Administration** | X | X | X | X | X | X | X | |

Abbreviations: Ab = antibodies; ACR = albumin-to-creatinine ratio; ADA = antidrug antibody; ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = fibrinogen activated partial thromboplastin time; AST = aspartate aminotransferase; β-HCG = beta human chorionic gonadotropin; BUN = blood urea nitrogen; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ETE = Early Termination Exit Visit; ETF = Early Termination Follow-up Visit; FSH = follicle-stimulating hormone; GGT = gamma-glutamyl transferase; INR = international normalized ratio; LDH = lactate dehydrogenase; PCR = protein-to-creatinine ratio; PD = pharmacodynamics; PI = primary investigator; PK = pharmacokinetics; RBC = red blood cell(s); SC = subcutaneous;

uACR = urine albumin-to-creatinine ratio; uPCR = urine protein-to-creatinine ratio; WBC = white blood cell(s); WOCBP = women of childbearing potential.

a Subjects who discontinue treatment early should complete one ETF 6 weeks after discontinuation of treatment and one ETE Visit 6 weeks after the ETF.
b If subjects have not transitioned to twice-weekly dosing before entry into Part B, then transition visits T1, T2, and T3 need to be scheduled. Patients who had transitioned to twice-weekly dosing prior to entry into Part B may omit the Part B dose transition visits.
c Following Extension Visit 18 (Week 84) subjects should continue to schedule visits at 12-week intervals (±7 days) until pegcetacoplan is commercially available for the disease under treatment.
d A full physical examination should be performed at 24-week intervals (ie, at Week 48 and then every other visit starting at Week 72). Additional symptom-driven physical examinations may be performed at unscheduled time points if deemed necessary by the PI.
e Triplicate 12-lead ECGs are to be performed before dosing and before blood sampling procedures.
f Subjects will self-administer SC pegcetacoplan, after receiving appropriate training by a research nurse or other personnel. During site visits subjects will self-administer pegcetacoplan at the site if it occurs on a dosing day.
g Between site visits, subjects will be instructed to report any injection site reaction to the study coordinator.
h On clinic dosing days vital signs will be measured within 2 hours before dosing, venipuncture, and ECG assessments. On clinic dosing days, vital signs will be measured within 30 minutes after dosing.
i 24-hour urine collected for ACR and PCR, defined as collection for a 24-hour period in a urine pooling container following the first urinary output on that day (first urinary output is discarded). Courier arrangements will be made by site personnel to pick up urine containers from patient's home. Urine ACR and PCR will be calculated on 24-hour urine collections for accuracy in estimating 24-hour proteinuria. Starting with the collection at Week 72, 24-hour urine collections will be every other visit (ie, every 24 weeks).
j Urinary PCR samples (first urinary output for the day) should be collected on 3 consecutive days, biweekly, for both uACR/uPCR analysis with a ±3-day window. On weeks of scheduled clinic visits, samples will be brought with patient during the site visit. No biweekly uPCR collection will occur between extension visits, but 1 uPCR collection will occur halfway between each extension visit at the 6-week time point and will be picked up by courier.
k Urinalysis—routine dipstick for protein, glucose, hemoglobin, blood, ketones, ACR, pH, bilirubin, urobilinogen, leukocyte esterase, specific gravity.
l All blood samples will be taken predose.
m All PK collections will be taken predose for treatment visits and following ECGs at all other visits. Predose PK collections to occur within 1 hour before dose. For subject visits falling outside of dosing schedule, PK samples can be taken following ECGs as mentioned for all other visits.
n ADA samples should be collected at approximately 24-week intervals (ie, at Week 48 and then every other visit starting at Week 72). For subjects with positive ADA in last dose samples, additional samples of 6 and 12 months from last dose will be collected for further assessments.
o Hematology consists of Hemoglobin, Hematocrit, RBC count, Platelet count, WBC count with differential (basophils, eosinophils, monocytes, lymphocytes, neutrophils), aPTT, INR. The use of silica reagents in coagulation panels should be avoided in subjects treated with pegcetacoplan.
p Chemistry consists of BUN, Creatinine (b), Bilirubin (total and conjugated), Uric acid, Albumin, ALP, LDH, Creatine kinase, AST, ALT, GGT, Glucose, Sodium, Potassium, Chloride, Bicarbonate.
q CKD-EPI creatinine equation (see https://www.niddk.nih.gov/); the CKD-EPI creatinine-cystatin C equation (if confirmation required).
r Urine pregnancy test should be completed for WOCBP prior to dosing.

### A1.1.2. Part B Long-Term Extension Phase: Study Design and Procedures

Following Visit 15 (Week 48), subjects who elect to continue in Part B, the Long-Term Extension Phase, will return to the site at 12-week intervals until pegcetacoplan is commercially available for the disease under treatment.

Specific procedures for each visit are listed in the Study Flow Chart for the Long-Term Extension Phase in Table A1.

The vaccination history for each subject should be reviewed prior to entry into the Long-Term Extension Phase, and any additional vaccinations or boosters against *N. meningitidis*, *S. pneumoniae*, or *H. influenzae* as recommended in the Advisory Committee on Immunization

Practices (ACIP) guidelines for patients with immunocompromising conditions (available at https://www.cdc.gov/vaccines/schedules/hcp/imz/adult-conditions.html) should be provided. If additional vaccinations or boosters are required, vaccination titer samples should be collected before administration of the vaccination and at the next scheduled visit.

At Visit 15 (Week 48), subjects who are invited to participate in Part B, the Long-Term Extension Phase who have not already transitioned to 1080 mg twice-weekly pegcetacoplan treatment during Part A, will begin a pegcetacoplan dose regimen of pegcetacoplan 1080 mg twice weekly (with potential to escalate to pegcetacoplan 1080 mg every 3 days). Subjects should follow the Dose Transition visits as outlined in Table A1.

If a subject will initiate the pegcetacoplan 1080 mg twice weekly dose regimen at Visit 15, he or she should be instructed to skip their daily Part A Core Study Phase Dose the day prior to Visit 15 (ie, the subject should not self-administer pegcetacoplan on Day 335).

Subjects who discontinue treatment early should complete an Early Termination Follow-up Visit 6 weeks after discontinuation of treatment, and an Early Termination Exit Visit 6 weeks later as outlined in Table A1.

Study Assessments align with those conducted in the Core Study Phase and are described in Section 14.1.

### A1.1.3. Part B Long-Term Extension Phase: Dose Rationale

The rationale for the Part A pegcetacoplan dose regimen is provided in Section 8.2.

#### A1.1.3.1. Target Level of Pegcetacoplan Serum Concentration

The toxicological data accumulated from the animal studies were used to guide dose selection during the Phase 1 single ascending dose and multiple ascending dose studies in healthy volunteers (Study CCI [redacted]). In particular, the highest doses were selected, based on exposure predicted by a PK model and compared with the exposures observed at the NOAEL in cynomolgus monkeys.

The planned twice-weekly dose of pegcetacoplan is 1,080 mg SC twice weekly, equivalent to 308 mg/day. Dose selection is based on past clinical experience with SC pegcetacoplan, coupled with nonclinical toxicological studies. Daily doses up to 360 mg/day have been tested in past and ongoing clinical trials, including this ongoing trial, and have been found to be well tolerated, with exposures that are well below the pegcetacoplan levels associated with the NOAEL in monkeys.

Using a target-mediated drug disposition pharmacokinetic/pharmacodynamic (PK/PD) model (Mager and Jusko, 2001), the relationship between dosing regimen and pegcetacoplan serum concentration is well-understood and well-predicted by the model. Figure A1 is the predicted PK profile for the dose of 1080 mg twice weekly (green line), compared to the NOAEL PK data observed in the pivotal 9-month chronic toxicological study in monkeys (Study 13CATX-004 [black line]). For comparison with previous human exposure, also included is the summary PK data from the ongoing PNH study, Study APL-CP0514 (270 mg/day cohort [blue line]), and healthy volunteer study, Study CCI [redacted], at 360 mg/day (brown line) and 1300 mg biweekly (light blue line). Both studies demonstrated pegcetacoplan to be safe and well tolerated. The figure illustrates that the PK exposure at the dose of 1080 mg twice weekly should derive a PK

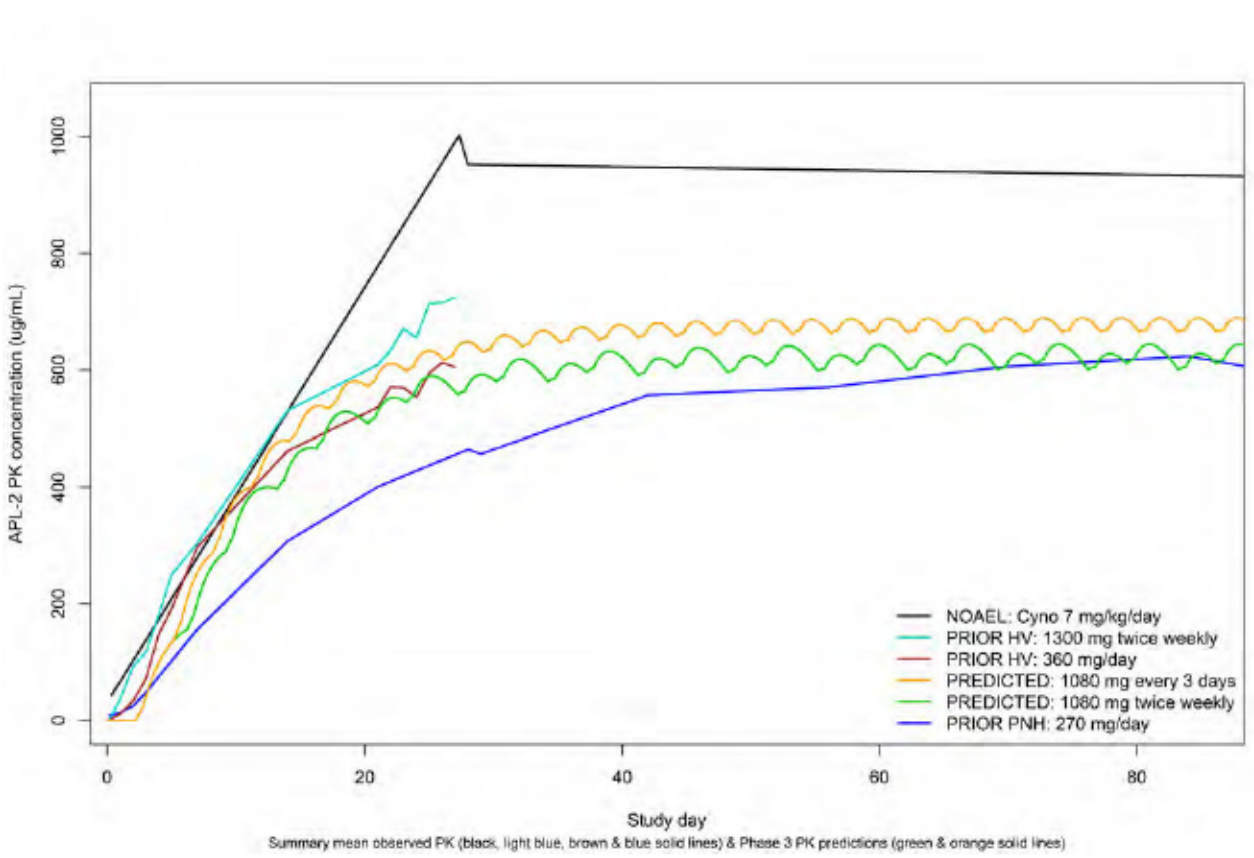
exposure slightly below that of 360 mg daily and should be safely below that observed at the NOAEL.

#### A1.1.3.2. Dosing Adjustment Option

Transition from 360 mg daily to 1080 mg twice weekly may result in a small decrease in exposure. Therefore, if an increase in proteinuria is observed upon transition to twice-weekly dosing, then an increase in dose to 1080 mg every 3 days may be considered, upon agreement with the sponsor. This amended dosing regimen will result in a higher PK exposure than that achieved with twice-weekly dosing. However, as illustrated in Figure A1, this increase in PK exposure ($C_{max}$) will still be lower than that observed in Study CCI [redacted] (1300 mg twice weekly) and will still be safely below that observed at the NOAEL.

Any adjustment in dose will be discussed and confirmed in writing by the sponsor. In the event of a dose adjustment, proteinuria levels will be monitored biweekly (with unscheduled assessments, if necessary) for at least 4 weeks to assess the impact of the dose adjustment. In the event that the dose is adjusted, then a new dosing schedule will be established for that patient.

**Figure A1: Observed and Predicted PK Profiles for Pegcetacoplan**




Abbreviations: cyno = cynomolgus monkey; HV = healthy volunteer; NOAEL = no-observed-adverse-effect-level; PK = pharmacokinetic; PNH = paroxysmal nocturnal hemoglobinuria

Note: Predicted PK profiles for pegcetacoplan (green line) at the planned dose of 1,080 mg twice weekly, compared to the summary PK data at the NOAEL (13CATX-004 [black line]), ongoing PNH study APL-CP0514 270 mg/day cohort (blue line), and healthy volunteer study CCI [redacted] for both the 360 mg/day (brown line) and 1,300 mg twice weekly cohorts (light blue line).

### A1.1.4. Part B Long-Term Extension Phase: Study Treatments

This section contains study treatment information for the Part B Long-Term Extension Phase.

#### A1.1.4.1. Part B Identity of Investigational Product

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

#### A1.1.4.2. Part B Pegcetacoplan Dosing

Starting at Week 48, subjects will receive SC infusions pegcetacoplan at a dosage of 1080 mg twice weekly. During the course of the study, subjects may be switched to an alternate dosing regimen of pegcetacoplan at 1080 mg every 3 days, if warranted, based on clinical response and agreement from the sponsor (see Section A1.1.3.2).

Dosing diaries will be utilized for pegcetacoplan and are to be completed for each dose administered at the study site or outside regular clinic visits. Subjects should not deviate from their pegcetacoplan dosing schedule: Day 1 and Day 4 of each treatment week (eg, Monday/Thursday/Monday) or every 3 days (eg, Monday/Thursday/Sunday).

#### A1.1.4.3. Part B Pegcetacoplan Administration

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

Note: Self-administration may also be conducted by a member of the subject's household or family member, etc. It is not intended to be restricted to the individual subject. Please refer to the Study Operations Manual for further details regarding the self-administration qualification.

### A1.1.5. Part B Long-Term Extension Phase: Labeling, Packaging, Storage, and Handling

#### A1.1.5.1. Part B Labeling

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

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

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

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

- Contradict the clinical study label

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

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

#### A1.1.5.2. Part B Packaging

Investigational product is supplied in 20-mL glass vials.

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

#### A1.1.5.3. Part B Infusion Supplies

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

#### A1.1.5.4. Part B Storage

The investigational product should be stored refrigerated at 2-8 °C.

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented.

A pharmacist or appropriately qualified designated person will be responsible for storing the investigational product at the site appropriately and dispensing the vials of investigational product to the subject. The pharmacist/nominated team member will enter the unique subject identifier on the investigational product bottle/carton labels, as they are distributed.

Temperature monitoring is required at the investigator site (or documented storage location) to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored at the site throughout the duration of the study and that records are maintained.

The investigational product should be transported from the clinic to the subject's residence as described in the pharmacy manual, using the preconditioned phase change material plates and cooler bags. Temperature monitoring will not be required during transport or at the subject's residence, but a log will be kept for every infusion to ensure that all investigational product was kept refrigerated.

With sponsor prior approval, investigational product and/or ancillary supplies may be shipped from the study site to a subject's designated location. Such shipments will only be implemented at sites where this activity is approved by the IRB/EC and health authority (if required). Subject consent will be required prior to any subject information being provided to a courier. The responsibility to return both empty vials and any unused investigational product shall remain unchanged, as described in Section 12.5.