COVER PAGE

Official Title	An Open-label, Nonrandomized, Multicenter Extension Study to Evaluate the Long-term Safety and Efficacy of Pegcetacoplan in the Treatment of Paroxysmal Nocturnal Hemoglobinuria (PNH)
NCT Number	NCT03531255
Document Date	20 July 2022

PROTOCOL NO.: APL2-307

AN OPEN-LABEL, NONRANDOMIZED, MULTICENTER EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND EFFICACY OF PEGCETACOPLAN IN THE TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

Phase:	Phase 3 Extension Study for PNH Patients Who Complete Apellis Clinical Studies
Version:	Amendment 4
Date:	20 July 2022
IND No.:	123087
EudraCT No.:	2019-001106-23

Confidentiality Statement

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SIGNATURE PAGE

Sponsor's Approval

This protocol has been approved by Apellis Pharmaceuticals, Inc.

Sponsor's Representative and Responsible Medical Director:

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 22-Jul-2022 | 09:11 EDT

[redacted]

22-Jul-2022 | 09:11 EDT

Date

[redacted]

Apellis Pharmaceuticals

INVESTIGATOR AGREEMENT

Long Title:	An Open-label, Nonrandomized, Multicenter Extension Study to Evaluate the Long-term Safety and Efficacy of Pegcetacoplan in the Treatment of Paroxysmal Nocturnal Hemoglobinuria (PNH)
Short Title:	Pegcetacoplan Long-term Safety and Efficacy Extension Study
Protocol Number, Version and Date:	APL2-307 Amendment 4, 20 July 2022
Study Phase:	Phase 3 extension study for PNH patients who complete Apellis clinical studies
Sponsor Name and Address:	Apellis Pharmaceuticals, Inc 100 5th Avenue Waltham, MA 02451
Investigational Test Article:	Pegcetacoplan (APL-2)
US IND Number:	123087
EudraCT Number:	2019-001106-23
Indication Studied:	Paroxysmal nocturnal hemoglobinuria (PNH)
Investigator Agreement:	I have read the clinical study 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)

SPONSOR INFORMATION

Sponsor	Apellis Pharmaceuticals, Inc 100 5th Avenue Waltham, MA 02451 USA
Sponsor Representative	[redacted], MD [redacted] Tel.: [redacted] Email: [redacted]

AMENDMENT 4: SUMMARY OF CHANGES FROM THE PREVIOUS VERSION

Protocol Amendment 4 (Approval date 20 July 2022)

Overall Rationale for the Amendment:

The protocol was amended to allow the shipment 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, and to add the ability to receive commercially available pegcetacoplan as a reason for subject discontinuation and withdrawal from the study. Additional revisions were made to clarify study procedures and to align with current company practices.

Non-substantial formatting, editorial, and technical changes that did not impact content of the document have been made for grammar, clarity, and document usability, and any identified typographical errors were corrected; these are not identified individually in the descriptions below.

Summary of Change(s) Since Last Version of Approved Protocol		
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 9.3.4	Align with current company practice permitting direct-to-subject shipments, where permitted.
Added the ability to receive commercially available pegcetacoplan as a reason for subject discontinuation and withdrawal from the study, and a description of the procedures to be followed in this situation.	Section 10.7	Provide flexibility to study participants as pegcetacoplan becomes commercially available and accessible in their countries.
Clarified that efficacy analyses will be performed using the intent-to-treat (ITT) population; amended definition of the population.	Synopsis, Section 13.2.1.2, Section 13.3.2, Section 4.1.11.1.2	Align with current Statistical Analysis Plan.
Added the recording of subject weight at 12-week intervals.	Section 2, Section 10.4, Section 10.5, Section 11.1.3, COVID-19 Schedule of Events, Substudy Schedule of Events	To allow calculation of current BMI through the study.
Amended the COVID-19 response to allow the same procedures to be followed in the case of natural disasters, armed conflicts, or other circumstances beyond the control of Apellis, investigators, or study subjects.	Appendix 3	To provide flexibility to investigative sites in the case of unforeseen disruptions to study activities.

Summary of Change(s) Since Last Version of Approved Protocol		
Description of Change	**Section(s) Affected**	**Rationale for Change**
Clarified the procedures for enrollment of subjects in the acute hemolysis substudy, and the requirements and procedures for enrollment of subject in subsequent treatment courses.	Section 4.1.4	To provide additional guidance for the conduct of the acute hemolysis substudy.
Clarified the timing of dosing in the main study and the acute hemolysis substudy.	Section 9.2.3, Section 4.1.6.2.3	To provide additional guidance for the conduct of the study and the acute hemolysis substudy.
Updated the frequency collection of FACIT Fatigue scores and adverse event assessments in the substudy.	Substudy Schedule of Events	To align Schedule of Events with intended frequency of these activities.

1. SYNOPSIS

Protocol Number:

APL2-307

Protocol Title:

An Open-label, Nonrandomized, Multicenter Extension Study to Evaluate the Long-term Safety and Efficacy of Pegcetacoplan in the Treatment of Paroxysmal Nocturnal Hemoglobinuria (PNH)

Version Number:

Amendment 4, 20 July 2022

Investigational Product, Dose, and Route of Administration:

- Investigational product: Pegcetacoplan (APL-2)
- Doses:
  - 1080 mg twice weekly, or
  - 1080 mg every 3 days (ie, a dose on every third day), or
  - 1080 mg three times weekly
- Route of administration:
  - Subcutaneous (SC) infusion for the treatment of PNH
  - SC infusion or intravenous (IV) infusion for the management of acute hemolysis

For those subjects who enter this extension study receiving pegcetacoplan 270 mg/day, the planned dose of pegcetacoplan is 1080 mg SC twice weekly.

For those subjects who enter this extension study receiving pegcetacoplan 360 mg/day, the planned dose of pegcetacoplan is 1080 mg SC every 3 days.

For those subjects who enter this extension study receiving pegcetacoplan 440 mg/day, the planned dose of pegcetacoplan is 1080 mg SC 3 times weekly.

Those subjects who enter this extension study receiving a dose of either 1080 mg twice weekly or 1080 mg every 3 days will continue to receive that dose and regimen.

Subjects entering this extension study who were previously randomized/allocated to a nonpegcetacoplan treatment arm will start treatment with pegcetacoplan 1080 mg SC twice weekly.

Dose adjustment may be considered based on clinical response (refer to Section 9.2.3.1), or for the management of acute hemolysis (refer to Section 4.1.6.2.3 of Appendix 4).

Study Phase and Type:

This is a multicenter, open-label, nonrandomized extension study with pegcetacoplan in subjects with PNH.

Number of Planned Subjects:

Subjects who have completed an antecedent pegcetacoplan PNH clinical study will be eligible to participate in this trial. Therefore, the number of subjects will not exceed the combined number of PNH subjects who have completed other pegcetacoplan studies in PNH subjects; thus approximately 160 subjects are planned.

Duration of Study Participation:

Duration of participation in this extension study will be 4 years or until pegcetacoplan development in subjects with PNH is terminated.

Study Population:

The study will enroll subjects with PNH who have completed an antecedent pegcetacoplan clinical study and have agreed to participate this extension study.

Rationale for the Study:

This extension study protocol is being developed to continue evaluation of the long-term safety and efficacy of pegcetacoplan in subjects with PNH.

Study Objectives and Endpoints:

Objectives:

The objectives of this study are to:

1. Establish the long-term safety of pegcetacoplan in subjects with PNH
2. Establish the long-term efficacy of pegcetacoplan in subjects with PNH

Endpoints

Safety endpoints:

- Incidence and severity of treatment-emergent adverse events
- Incidence of thromboembolic events
- Laboratory parameters
- Electrocardiogram parameters

Efficacy endpoints:

- Hemoglobin level
- Lactate dehydrogenase level
- Indirect bilirubin level
- Absolute reticulocyte count
- Red blood cell (RBC) transfusions
- Functional Assessment of Chronic Illness Therapy–Fatigue scale score

Pharmacokinetic endpoint:

- Pegcetacoplan pharmacokinetic concentrations

Pharmacodynamic markers:

- Complement (eg, classical pathway hemolytic activity [CH50], alternative pathway hemolytic activity [AH50], and C3) levels
- C3 deposition on RBC cells
- Clonal distribution of PNH RBCs
- Incidence of anti–pegcetacoplan peptide and anti–polyethylene glycol antibodies

Study Design:

This is an open-label, nonrandomized, multicenter extension study with pegcetacoplan in subjects with PNH. Eligible subjects will meet all the inclusion criteria and none of the exclusion criteria. Note: The last study visit of the previous trial must be the first (baseline) study visit of this trial.

Inclusion Criteria:

1. Subjects at least 18 years of age with PNH who have participated in an antecedent pegcetacoplan clinical trial. Subjects who received treatment with pegcetacoplan must have experienced clinical benefit and adequate tolerability in the opinion of the investigator.

   Note: Subjects with PNH who completed an antecedent pegcetacoplan clinical trial without receiving pegcetacoplan (or without receiving pegcetacoplan for long enough to demonstrate clinical benefit) may be enrolled in this study if, in the opinion of the investigator, the subject is expected to demonstrate clinical benefit upon the initiation or continuation of pegcetacoplan therapy.
2. Vaccination against *Neisseria meningitidis* types A, C, W, Y, and B, *Streptococcus pneumoniae,* and *Haemophilus influenzae* type B (Hib) either within 2 years prior to Day 1 dosing of this study, or within 14 days after starting treatment with pegcetacoplan. Vaccination is mandatory unless documented evidence exists that subjects are nonresponders to vaccination as evidenced by titers or display titer levels within acceptable local limits. Immunization status checks will be performed to determine whether subjects require primary or booster vaccinations.
3. Willing and able to give written informed consent.
4. Willing and able to self-administer pegcetacoplan (administration by a caregiver will be allowed).
5. Women of childbearing potential, defined as any females who have experienced menarche and who are NOT permanently sterile or postmenopausal, must have a negative pregnancy test and must agree to continue to use an approved method of contraception for the duration of the study and 90 days after their last dose of study drug. Note: Postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause.

6. Males must agree to continue to use an approved method of contraception and must agree to refrain from donating sperm for the duration of the study and 90 days after their last dose of study drug.

Exclusion Criteria:

1. Subjects who have withdrawn from a pegcetacoplan clinical study and/or subjects who met study drug discontinuation criteria during a pegcetacoplan clinical study.
2. Any condition that could increase the subject's risk by participating in the study.
3. Any comorbidity or condition (such as malignancy) that, in the opinion of the investigator, could put the subject at increased risk or potentially confound the study data.
4. History or presence of hypersensitivity or idiosyncratic reaction to compounds related to the investigational product or SC administration.
5. Acute or active hepatitis B, hepatitis C, or HIV infection.
6. Hereditary complement deficiency.
7. History of bone marrow transplant.
8. Concurrent severe aplastic anemia (defined by bone marrow cellularity <25% [or 25% to 50% if less than 30% of residual cells are hematopoietic] and at least 2 of the following values: peripheral blood absolute neutrophil count <500/μL [$<0.5 \times 10^9$/L], peripheral blood platelet count <20,000/μL, peripheral blood reticulocyte count <20,000/μL).
9. History of meningococcal disease.
10. Concomitant treatment with any complement inhibitor (eg, eculizumab, ravulizumab).
11. Pregnancy, breastfeeding, or positive pregnancy test.

Sample Size:

This study comprises subjects with PNH who have completed an antecedent pegcetacoplan clinical study, approximately 160 subjects.

Statistical Methods:

Populations for Analysis:

Safety Population:

The safety population will include all subjects who receive at least one dose of assigned product.

Intent-to-Treat Population:

The intent-to-treat (ITT) population will include all subjects who enroll and receive at least one dose of pegcetacoplan in this study.

Efficacy:

Efficacy analyses will be performed using the ITT population. Absolute values and changes from baseline will be summarized by visit using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). Changes from baseline will also be summarized categorically by visit. The number and percentage of subjects who have met specific levels

related to the reference range (eg, hemoglobin level ≥ the lower limit of normal) will be tabulated by visit.

Efficacy summaries will be presented by previous study and overall.

Safety:

Medical data coding of the verbatim terms provided by the investigators for adverse events and concomitant medications will be performed using the current versions of the Medical Dictionary for Regulatory Activities and the World Health Organization Drug Dictionary, respectively.

Safety data analyses will be performed using the safety population. Continuous data will be summarized using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) and categorical data will be summarized using counts and percentages.

Interim Analysis:

There is no formal interim analysis planned. The data from this study may be reported at different times for specific reasons, eg, providing data to a regulatory agency.

Analysis of Subjects With Acute Hemolysis:

Analysis of safety and efficacy of pegcetacoplan in subjects with acute hemolysis will be performed as described in Section 4.1.11 of Appendix 4.

2. SCHEDULE OF EVENTS

Study Week	**0**	**2[a]**	**4**	**12**	**24**	**36**	**≥48[b]**	**Exit**
Study Day	**1**	**15**	**29**	**85**	**169**	**253**	**≥337**	**—**
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Exit**
Study Window (± Days)	**—**	**4**	**4**	**7**	**7**	**7**	**7**	**8 weeks from last dose**
Informed consent	X							
Document antecedent study information[c]	X							
Vaccination/vaccination booster[d]	X	X	X	X	X	X	X	
Preventive antibiotic[e]	X	X	X	X	X	X	X	X
Physical examination[f]	X				X		X[f]	X
Medical history	X							
Demographics	X							
Height and weight[g]	X			X	X	X	X	X
12-lead electrocardiogram	X		X	X	X	X	X	X
Pegcetacoplan administration[h]	X	X	X	X	X	X	X	
Injection site assessment	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X
Vital sign measurements[i]	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X
Blood tests:[j]	X	X	X	X	X	X	X	X
Pharmacokinetics	X			X	X	X	X	X
Antidrug antibodies	X			X	X	X	X	X
Lactate dehydrogenase	X	X	X	X	X	X	X	X
Hematology and chemistry	X	X	X	X	X	X	X	X

Study Week	**0**	**2[a]**	**4**	**12**	**24**	**36**	**≥48[b]**	**Exit**
Study Day	**1**	**15**	**29**	**85**	**169**	**253**	**≥337**	**—**
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Exit**
Study Window (± Days)	**—**	**4**	**4**	**7**	**7**	**7**	**7**	**8 weeks from last dose**
Coagulation profile[k]	X	X	X	X	X	X	X	X
Reticulocyte count	X	X	X	X	X	X	X	X
Haptoglobin	X	X	X	X	X	X	X	
C3 profile	X	X	X	X	X	X	X	X
Complement profile (CH50 and AH50)	X			X	X	X	X	X
Flow cytometry for PNH/C3 deposition	X			X	X	X	X	X
Free hemoglobin	X	X	X	X	X	X	X	X
Ferritin, vitamin B_{12}, folic acid	X	X	X	X	X	X	X	X
Urine pregnancy test[l]	X	X	X	X	X	X	X	X
FACIT-Fatigue Scale	X	X	X	X	X	X	X	X
Adverse events[m]	X	X	X	X	X	X	X	X

Abbreviations: AH50 = alternative pathway hemolytic activity; CH50 = classical pathway hemolytic activity; COVID-19 = coronavirus disease 2019; FACIT = Functional Assessment of Chronic Illness Therapy; PNH = paroxysmal nocturnal hemoglobinuria.

a. Please note that a Week 2 study visit is required only for subjects who have started or changed their pegcetacoplan dose or regimen when entering this study. Subjects who have not changed their pegcetacoplan dose or regimen will go from the baseline visit directly to the Week 4 Visit.
b. Subjects will continue to have study visits at 12-week intervals for a duration of 4 years or until pegcetacoplan development in subjects with PNH is terminated.
c. Document antecedent study number, subject identifier, and Day 1 of pegcetacoplan treatment from antecedent study.
d. Immunization status will be monitored to assess whether the subject needs primary vaccinations or boosters per protocol. In order to receive treatment with pegcetacoplan, subjects must have documented evidence of vaccination within 2 years of screening against *Neisseria meningitidis* types A, C, W, Y, and B (administered as 2 separate vaccinations), *Streptococcus pneumoniae* (with a PCV13 or PPSV23 vaccine), and *Haemophilus influenzae* type B (Hib vaccine), unless documented evidence exists that subjects are nonresponders to vaccination (as evidenced by titers or display titer levels within acceptable local limits). For subjects receiving pegcetacoplan before the start of this study who do not have documented evidence of receiving all of the above vaccinations within 2 years prior to screening or who require booster vaccinations, the required missing vaccination(s) will be administered at the baseline visit. Subjects who have not previously received pegcetacoplan treatment will receive prophylactic antibiotics for the first 4 weeks of treatment with pegcetacoplan and will receive any required vaccination(s) 2 weeks after initiation of treatment with pegcetacoplan. If required, the *Neisseria meningitidis* booster (for both ACWY and serotype B vaccinations), and/or PPSV23 vaccination should be administered at least 8 weeks following the initial vaccination(s). For the subjects who are already enrolled in this study, the revaccination schedule should be followed according to the Centers for Disease Control and Prevention guidelines, which can be found on the following website: https://www.cdc.gov/vaccines/schedules/hcp/imz/adult-conditions.html. The principal investigator will discuss with the sponsor regarding individual subject circumstances.

e. Prophylactic antibiotic therapy should be considered in order to minimize potential infection risk. Prophylactic antibiotic therapy should be administered at the discretion of the treating investigator in accordance with local treatment guidelines for subjects with PNH who are receiving treatment with a complement inhibitor. Subjects in receipt of prophylactic antibiotic therapy from their previous study may remain on the treatment they are receiving at the time of entry in this extension study.
f. Following the Week 48 visit, physical examinations should be conducted in 24-week intervals (every other visit).
g. Body height (cm) will be measured at the baseline visit. Body weight (kg) will be measured at 12-week intervals.
h. Subjects who have not changed their pegcetacoplan dose or regimen from the antecedent study must dose with the antecedent study labeled drug at the baseline visit and then commence dosing with APL2-307 labeled drug at their next scheduled dosing.
i. Vital signs will be measured before venipuncture and electrocardiogram. Monitoring of vital signs will occur at Visit 1 (Day 1) before dosing and 2 hours after dosing (±30 minutes). At all other visits, if the subject elects to administer pegcetacoplan during the visit, vital signs should be measured before dosing and again 30-60 minutes after completion of dosing.
j. Blood will be taken before dosing at every scheduled visit.
k. The use of silica reagents in coagulation panels should be avoided in subjects treated with pegcetacoplan where possible as it affects the accuracy of the test results.
l. Urine pregnancy tests will be performed for women of childbearing potential only.
m. Consider testing for COVID-19 if subjects experience symptoms suggestive of COVID-19 and/or acute hemolysis. If performed, the test results must be documented in the electronic case report form.

Note: Baseline visit = the last study visit of the previous trial.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
ADA	antidrug antibodies
AE	adverse event
AH	acute hemolysis
AH50	alternative pathway hemolytic activity
aPTT	activated partial thromboplastin time
ARC	absolute reticulocyte count
CD71+	transferrin receptor
CFB	change from baseline
CH50	classical pathway hemolytic activity
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
FACIT	Functional Assessment of Chronic Illness Therapy
GCP	good clinical practice
Hb	hemoglobin
Hib	*Haemophilus influenzae* type B (vaccine)
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICF	informed consent form
IEC	Institutional Ethics Committee
IRB	Institutional Review Board
IRT	interactive response technology
IV	intravenous
LDH	lactate dehydrogenase
MAC	membrane attack complex
NOAEL	no-observed-adverse-effect level
PCV13	pneumococcal conjugate vaccine
PD	pharmacodynamic(s)
PEG	polyethylene glycol
PI	principal investigator
PK	pharmacokinetic(s)
PNH	paroxysmal nocturnal hemoglobinuria

Term	Definition
PPSV23	pneumococcal polysaccharide vaccine 23
QTc	heart-rate corrected QT interval
QTcF	QT interval corrected for heart rate using the Fridericia formula
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

4. INTRODUCTION

4.1. Background

Pegcetacoplan (APL-2) is being developed for the treatment of paroxysmal nocturnal hemoglobinuria (PNH).

This study is being conducted as part of a series of studies for the clinical development of pegcetacoplan. The study will be conducted in compliance with the protocol, good clinical practice (GCP), and applicable regulatory requirements. The subject population will comprise subjects who previously participated in an antecedent pegcetacoplan study with PNH.

4.1.1. Paroxysmal Nocturnal Hemoglobinuria

PNH is a rare, acquired, clonal, nonmalignant hematologic disease characterized by complement-mediated red blood cell (RBC) hemolysis with or without hemoglobinuria, an increased susceptibility to thrombotic episodes, and/or some degree of bone marrow dysfunction. The onset of PNH is often insidious. Although there have been reports of spontaneous remission, the course of the disease is generally chronic progressive.

It has been known for many years that PNH is caused by complement-mediated lysis of erythrocyte clones lacking functional CD55 and CD59 on their surfaces to protect them against this process. As such, these erythrocytes are particularly susceptible to the membrane attack complex (MAC) and have been shown to lyse readily in the presence of complement activation.

Any therapy that effectively inhibits MAC formation is anticipated to be a plausible candidate-treatment for PNH. Indeed, eculizumab is a monoclonal anti-C5 antibody that inhibits the formation of the MAC, and eculizumab treatment has been approved for the treatment of this serious condition. However, inhibition of MAC formation does not appear to be sufficient to fully control the disease, as many PNH subjects receiving eculizumab treatment still suffer from anemia, with only roughly 13% of subjects being classified as complete responders, ie, achieving transfusion independence and normal hemoglobin (Hb) levels. Most of the subjects (53%) were classified as partial responders with decreased transfusion needs and reduced lactate dehydrogenase (LDH), and 33% of subjects were poor responders, with unchanged transfusion needs and persistent symptoms (DeZern et al. 2013).

Recent studies have suggested that significant opsonization of PNH erythrocytes by C3 fragments is observed in subjects receiving eculizumab treatment. This opsonization is believed to cause the removal of erythrocytes by the spleen and the liver, resulting in extravascular hemolysis. Extravascular hemolysis can be significant in a subset of eculizumab-treated PNH subjects and is considered to be the principal contributor to the lack of complete eculizumab response in most subjects.

4.1.2. Pegcetacoplan

Pegcetacoplan is formed by a pentadecapeptide (combining a bioactive cyclic tridecapeptide C3-inhibiting moiety and a 2-amino acid linker) covalently coupled to each end of a linear 40-kDa polyethylene glycol (PEG) chain, so there are 2 peptide moieties per molecule of pegcetacoplan.

The peptide portion of the drug binds to complement C3 and is a broad inhibitor of the complement cascade, a biological process that is part of innate immunity and is involved in multiple inflammatory processes. The PEGylation of the molecule imparts slower elimination from mammalian systems following administration.

Pegcetacoplan solution for subcutaneous (SC) injection or infusion (drug product) is a solution of pegcetacoplan in acetate-buffered sorbitol. Labels for the 54 mg/mL solution read: Pegcetacoplan Solution for Subcutaneous Injection or Infusion, 1080 mg in 20 mL (54 mg/mL).

Further details can be found in the current pegcetacoplan Investigator's Brochure.

4.1.3. Rationale for Treatment with Pegcetacoplan

Extravascular hemolysis, one of the parameters contributing to the ongoing need for RBC transfusions despite eculizumab therapy, is believed to be mediated by C3b opsonization rather than C5-dependent MAC-mediated intravascular hemolysis (Risitano et al. 2009). While eculizumab is effective in addressing CD59 deficiency by preventing C5-dependent MAC-mediated hemolysis, PNH cells are also deficient in CD55, which normally accelerates the dissociation of C3-convertase enzymes, inhibiting the production of C3 fragments and subsequent opsonization. As a result, in the setting of eculizumab therapy, surviving PNH RBCs become opsonized with C3b, targeting them for clearance through extravascular hemolysis by macrophages bearing complement receptors in the liver and spleen.

Evidence for C3b-mediated extravascular hemolysis was observed in 3 subjects exhibiting a "suboptimal hematologic response [to eculizumab] and massive C3 RBC binding" using 51Cr-labeled RBCs. Although these subjects were still receiving eculizumab and had normal LDH levels, they demonstrated markedly reduced RBC half-lives (10, 11, and 13 days, with a normal range of 25–35 days) and excess counts on images of the spleen and liver (Risitano et al. 2009). In contrast, C3b opsonization of RBCs is not observed in PNH subjects who have not been treated with eculizumab, presumably because RBCs in these subjects are rapidly lysed by MAC (Risitano et al. 2009).

In summary, while C5 inhibition has had a dramatic positive impact on the lives of many PNH subjects, anti-C5 therapy has also led to the emergence of a subpopulation of PNH subjects with persistent extravascular hemolysis and RBC transfusion requirements, despite continuous eculizumab therapy, that appear to result at least in part from C3b opsonization of RBCs. It is reasonable, therefore, to expect that a treatment able to inhibit both MAC formation and C3 opsonization will provide improved therapeutic benefit to PNH subjects compared to eculizumab.

4.1.4. Summary of Clinical Experience

Clinical data from ongoing studies with pegcetacoplan in subjects with PNH indicates that pegcetacoplan is effective in providing broad control of intravascular and extravascular hemolysis, as evidenced by increased and stable Hb levels, along with improvement in Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue Scale score, normalization of LDH, normalization of absolute reticulocyte count (ARC), normalization of total bilirubin levels, along with reduction in C3 fragment opsonization and increased numbers of PNH RBCs. To date, pegcetacoplan at doses of ≥270 mg/day has been generally well tolerated when

administered via SC infusion. No expected serious adverse drug reactions have been identified, and no deaths have occurred that are considered related to treatment with pegcetacoplan.

Results from the Phase 3 study APL2-302, a randomized, multicenter, open-label, active-comparator controlled study in adults with PNH, showed that pegcetacoplan at a dose of 1080 mg SC every 2 weeks controlled the hematologic manifestations of PNH, with superiority for control of anemia, as compared with the C5 inhibitor, eculizumab. Pegcetacoplan was superior to eculizumab with regard to change from baseline (CFB) in Hb level. At Week 16, the pegcetacoplan group (n = 41) had an adjusted mean Hb change of 2.4 g/dL from a baseline of 8.7 g/dL, compared to the eculizumab group (n = 39) who had a change of –1.5 g/dL from a baseline of 8.7 g/dL, resulting in a 3.8 g/dL difference between treatment groups (P<.0001).

Additionally, pegcetacoplan met noninferiority on the key secondary endpoints of transfusion avoidance and ARC. Transfusion avoidance was shown in 85% in the pegcetacoplan group, but only 15.4% in the eculizumab group. The adjusted mean CFB in ARC was -136×10^9/L, in the pegcetacoplan group vs 28×10^9/L in the eculizumab group, resulting in a treatment difference of -164×10^9/L.

Pegcetacoplan did not demonstrate noninferiority to eculizumab in the CFB in LDH. However, the adjusted mean CFB were comparable at Week 16; –15 U/L in the pegcetacoplan group vs –10 U/L in the eculizumab group. Noninferiority for the FACIT-Fatigue score was not assessed due to the prespecified hierarchical testing; however, the adjusted mean CFB was 9.2 points in the pegcetacoplan group vs –2.7 points in the eculizumab group with a difference of 11.9 points between treatment groups. The magnitude of this treatment difference in FACIT-Fatigue score (a 3-point increase is generally accepted as clinically significant), as well as the consistency of results favoring pegcetacoplan across all primary and secondary endpoints, suggests that these improvements in fatigue are meaningful, even though the study was conducted in an open-label fashion.

The safety of pegcetacoplan was comparable to eculizumab in this randomized controlled Phase 3 study, with a similar incidence of adverse events in each study group. The most common adverse events reported during the randomized controlled treatment period were injection site reactions (ISR), hemolysis, abdominal pain, and diarrhea. While some treatment-emergent adverse events (TEAEs) occurred more frequently in the pegcetacoplan group (eg, ISRs and diarrhea), others occurred more frequently in the eculizumab group (eg, hemolysis and headache). TEAEs such as ISRs and diarrhea that occurred more frequently in the pegcetacoplan group did not limit overall tolerability, as none were serious, severe, or led to study drug discontinuation. The incidences of serious adverse events (SAEs) were comparable between the 2 treatment groups. There were 4 serious infections during the study, but none required study drug discontinuation, and none were cases of meningitis. Although there were 3 subjects who discontinued pegcetacoplan due to hemolysis (7.3% in the pegcetacoplan group vs 0 in the eculizumab group), adverse events of hemolysis occurred less frequently in the pegcetacoplan group than in the eculizumab group (9.8% vs 28.2%, respectively). Therefore, discontinuation of pegcetacoplan due to hemolysis does not reflect a safety concern, but rather a return to the currently approved PNH therapy, eculizumab. Overall, pegcetacoplan was generally well tolerated with an acceptable safety profile that can be managed effectively with monitoring.

5. RATIONALE

Clinical data from completed and ongoing studies with pegcetacoplan in patients with PNH (Phase 1b studies APL-CP0514 and APL2-CP-PNH-204 and Phase 2a study APL2-202 [all completed] and Phase 3 studies APL2-302 and APL2-308 [ongoing]) indicate that pegcetacoplan is effective in providing broad control of intravascular and extravascular hemolysis, as evidenced by increased and stable Hb levels, normalization of LDH levels, normalization of ARC, normalization of total bilirubin levels, reduction in C3 fragment opsonization, and increased numbers of RBCs.

To date, pegcetacoplan at a dose of 1080 mg twice weekly has been generally safe and well tolerated when administered via SC infusion. More frequent dosing regimens (daily dosing up to 360 mg/day or 1080 mg every 3 days) have also been well tolerated. No serious adverse drug reactions have been identified, and no deaths have occurred that are considered related to treatment with pegcetacoplan.

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

5.1. Purpose of the Study

The purpose of this study is to continue evaluation of the long-term safety and efficacy of pegcetacoplan in the treatment of PNH.

5.2. Dose Selection

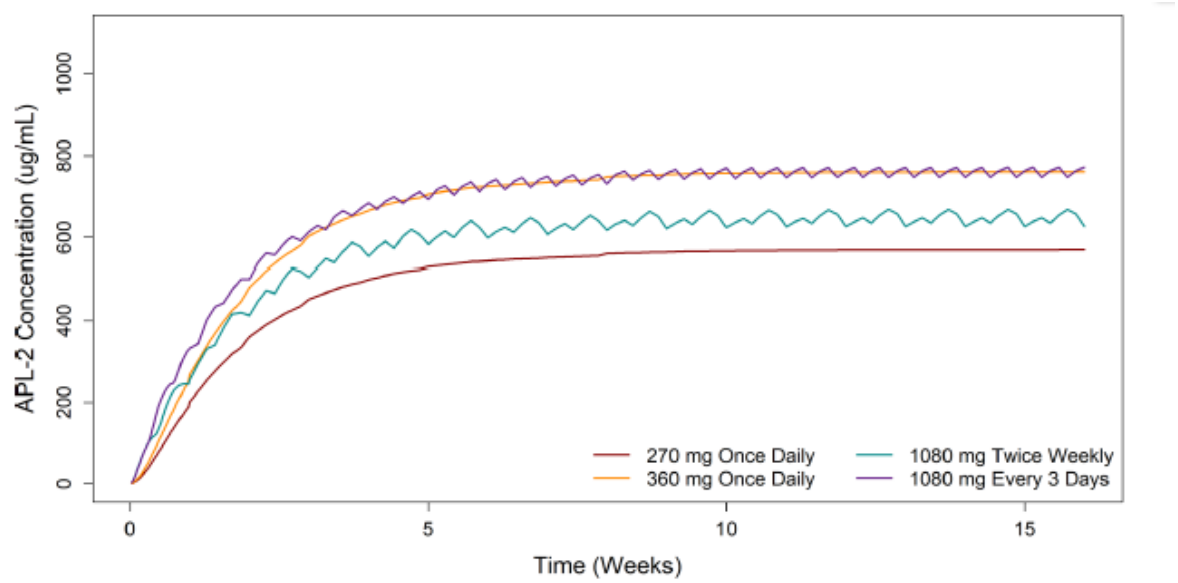
Subjects entering this extension study receiving pegcetacoplan 1080 mg SC twice weekly or pegcetacoplan 1080 mg SC every 3 days will continue with their current dose regimen with no interruptions in dosing.

Subjects entering this extension study who were previously randomized/allocated to a nonpegcetacoplan treatment arm will start treatment with pegcetacoplan 1080 mg SC twice weekly.

For those subjects who enter this extension study receiving pegcetacoplan 270 mg/day, the dose of pegcetacoplan is 1080 mg SC twice weekly. This dose will result in a slightly higher PK exposure compared with daily dosing (Figure 1), but below the established no-observed-adverse-effect-level (NOAEL). The figure also includes a summary of model-predicted concentration-time profiles for PNH subjects treated with various dosing regimens.

Dose adjustment may be considered based on clinical response. Refer to Section 9.2.3.1.

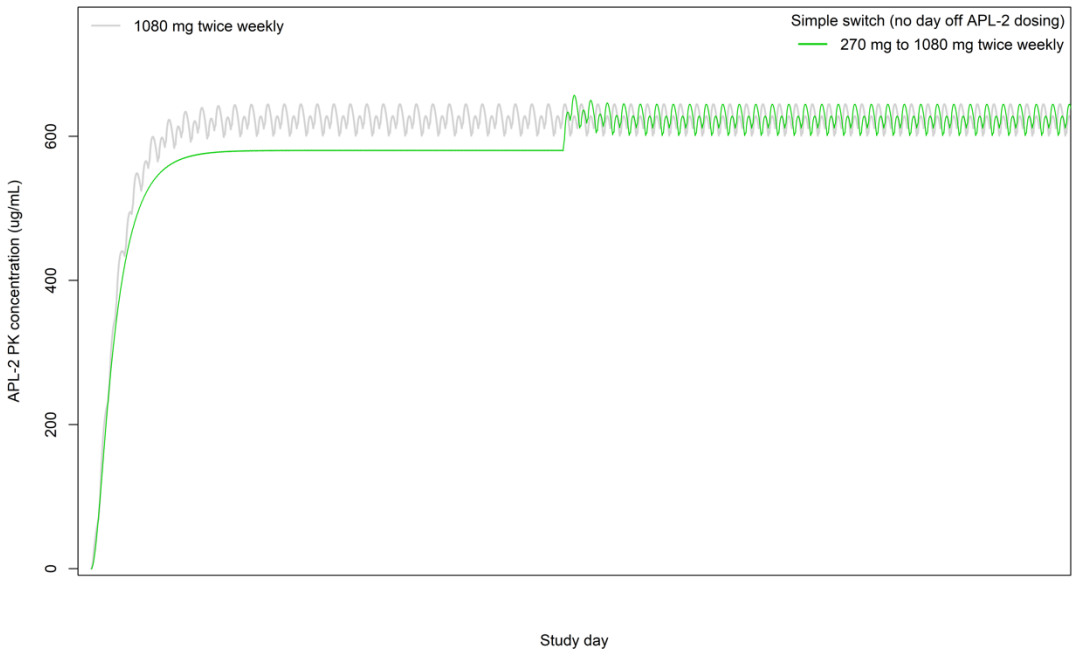
Figure 1: Model-Predicted Typical Pegcetacoplan Concentration-Time Profiles in PNH Patients With Various Dosing Regimens



Abbreviations: APL-2 = pegcetacoplan; PNH = paroxysmal nocturnal hemoglobinuria; ug = micrograms.

To safely manage the switch from a daily lower dose to a higher less frequent dose (1080 mg twice weekly or every 3 days), the expected PK exposure was evaluated. As presented in Figure 2, the impact of switching from 270 mg/day to 1080 mg twice weekly without a break in pegcetacoplan dosing is minimal.

Figure 2: Predicted PK Profiles Following Switching From 270 mg Daily to 1080 mg Twice Weekly Dosing, or Continuous 1080 mg Twice Weekly Dosing

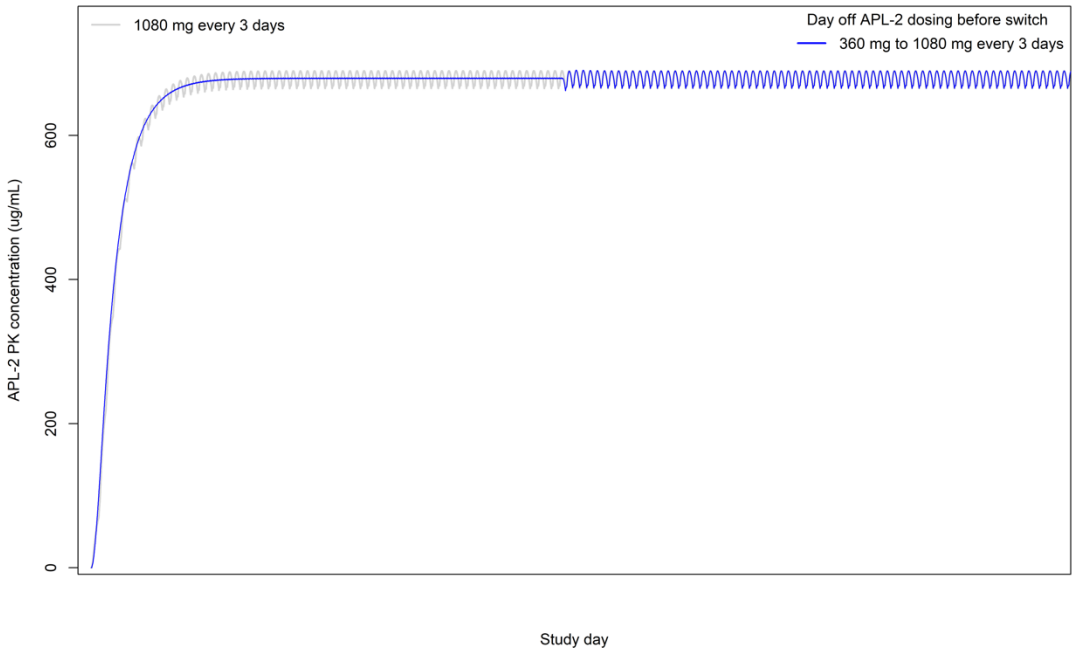


Abbreviations: APL-2 = pegcetacoplan; PK = pharmacokinetic; ug = micrograms.
Note: Profiles represent subjects previously on 270 mg/day simply switching to 1080 mg twice weekly (green line) compared to the predicted PK profile of subjects dosed continuously at 1080 mg twice weekly (gray line).

For those subjects who enter this extension study receiving pegcetacoplan 360 mg/day, the planned dose of pegcetacoplan is 1080 mg SC every 3 days. This dose (1080 mg every 3 days) is predicted to achieve exposure similar to their previous dose of 360 mg/day and, as illustrated in Figure 3, should result in a similar PK exposure (provided subjects have a "day off" from pegcetacoplan dosing before switching). For comparison, the predicted PK profile at the dose of 1080 mg every 3 days is included in Figure 1.

As presented in Figure 3, for subjects switching from 360 mg/day to 1080 mg every 3 days, a "day off" from pegcetacoplan dosing is recommended.

Figure 3: Predicted PK Profiles Following Switching From 360 mg Daily to 1080 mg Every 3 Days, or Continuous Dosing at 1080 mg Every 3 Days



Abbreviations: APL-2 = pegcetacoplan; PK = pharmacokinetic; ug = micrograms.
Note: Profiles represent subjects previously on 360 mg/day switching to 1080 mg every 3 days (blue line), after a day off dosing, compared to the predicted PK profile of subjects dosed continuously at 1080 mg every 3 days (gray line).

A summary of the rationale for the proposed extension study dosing regimens is provided below:

- Maintains an acceptable safety margin based on the PK exposure observed at the NOAEL (13CATX-004)
- For subjects who enter this extension study receiving pegcetacoplan 270 mg/day, a pegcetacoplan dose of 1080 mg SC twice weekly will result in a slightly higher PK exposure, but below the established NOAEL. When switching from 270 mg/day to 1080 mg twice weekly, a simple switch with no gap in dosing is required (eg, 270 mg on Day 300, 1080 mg on Day 301)
- For the 360 mg/day subjects switching to 1080 mg every 3 days there will be little/no impact on the PK exposure provided the subject has a "day off" from pegcetacoplan dosing before switching.

Table 1 in Section 9.2.3 summarizes the extension dosing regimens and any requirement to take a day off dosing before switching.

5.3. Risk/Benefit

5.3.1. Risk Assessment

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, 12-lead electrocardiogram [ECG], hematology, serum chemistry, urinalysis, coagulation, prompt reporting of SAEs and adverse event [AE] collection) in order to ensure the subjects' ongoing safety.

Injection/infusion site and pump use safety will be assessed during clinic visits, and any significant finding from the assessment will be reported as an AE (see Section 11.1.9).

The volume of blood planned for collection from each subject will be minimized in order to limit the impact on the overall health of these subjects.

As systemic complement inhibition might predispose individuals to infections caused by encapsulated organisms, all subjects entering this extension are required to have vaccinations against *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* and may be receiving prophylactic antibiotics to minimize potential infection risk. Subjects in receipt of prophylactic antibiotic therapy may remain on the treatment they are receiving at the time of entry in this extension study, which will be in accordance with local treatment guidelines for PNH subjects who are receiving treatment with a complement inhibitor.

Body temperature and vital signs will be monitored at all clinic visits as well as relevant blood parameters throughout the study to assess for signs of infection. Subjects will be provided with emergency study cards that include a list of symptoms associated with the aforementioned infections. This study card also guides subjects with instructions to contact their study physician or seek emergency medical care in the event they experience any of the listed symptoms. In the event of a suspected infection, the principal investigator (PI) should provide guidance on appropriate action to be taken thereafter.

There may be interference between silica reagents in coagulation panels and PEGylated pegcetacoplan, resulting in artificially prolonged activated partial thromboplastin times (aPTTs). The use of silica reagents in coagulation panels should be avoided. Subjects in clinical studies will be given an emergency card which includes this information and they should be advised to present it to any appropriate health care professional.

If prolonged aPTT or other coagulation abnormalities are observed and reported by laboratories other than the central laboratory investigators should take the following actions:

1. Treat any result with caution until confirmed and check whether the laboratory method uses silica reagents
2. If necessary, perform a repeat coagulation to confirm the results
3. Inform the clinical research associate and/or the medical monitor

Subjects should be instructed to take their pegcetacoplan treatment as prescribed, and to contact the investigator immediately for guidance in the event of any missed doses. If withdrawal of pegcetacoplan treatment is necessary, slow weaning should be considered and subjects should carefully be monitored for at least 8 weeks to detect serious hemolysis or other complications.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in subjects on beta-lactam antibiotic (eg, penicillin, amoxicillin) therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity. Therefore, as the majority of subjects will enter the extension study already receiving prophylactic antibiotic therapy, the risk of this occurring is low as subjects with a known hypersensitivity to penicillin/amoxicillin will already have been prescribed an alternative treatment.

5.3.1.1. 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 on the basis of geographic location, Apellis will continue to evaluate the risk/benefit around study conduct on an ongoing and subject-by-subject basis.

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 3.

5.3.2. Benefit Assessment

There is an anticipated health benefit for participants in this extension study. At the proposed dose levels of pegcetacoplan, a significant decrease in complement-mediated hemolytic activity has been observed in all pegcetacoplan-treated subjects with PNH (both treatment naive and treated previously with eculizumab). Pegcetacoplan is therefore expected to continue to reduce complement-mediated hemolytic activity in PNH subjects. In this context, a careful evaluation of the risk/benefit ratio should be made. Therefore, pegcetacoplan is expected to continue to improve Hb levels and reduce transfusion dependency in these subjects.

5.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with pegcetacoplan are justified by the anticipated benefits that may be afforded to subjects with PNH.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Study Objectives

The objectives of this study are to:

1. Establish the long-term safety of pegcetacoplan in subjects with PNH
2. Establish the long-term efficacy of pegcetacoplan in subjects with PNH

6.2. Study Endpoints

6.2.1. Safety Endpoints

- Incidence and severity of TEAEs
- Incidence of thromboembolic events
- Laboratory parameters
- ECG parameters

6.2.2. Efficacy Endpoints

- Hb level
- LDH level
- Indirect bilirubin level
- ARC
- RBC transfusions
- FACIT-Fatigue scale score

6.2.3. Pharmacokinetic Endpoint

- Pegcetacoplan pharmacokinetic concentrations

6.2.4. Pharmacodynamic Endpoints

- Complement (eg, classical pathway hemolytic activity [CH50], alternative pathway hemolytic activity [AH50], and C3) levels
- C3 deposition on RBC cells
- Clonal distribution of PNH RBCs
- Incidence of anti–pegcetacoplan peptide and anti-PEG antibodies

7. STUDY DESIGN

This is an open-label, nonrandomized, multicenter extension study with pegcetacoplan in subjects with PNH. Eligible subjects will meet all the inclusion criteria and none of the exclusion criteria.

NOTE: The last study visit of the previous trial must be the first (baseline) study visit of this trial.

7.1. Number of Sites and Subjects

Subjects who have completed an antecedent pegcetacoplan PNH clinical trial will be eligible to participate in this trial. Therefore, the number of subjects will not exceed the combined number of PNH subjects who have participated in other pegcetacoplan trials; thus, approximately 160 subjects are planned.

7.2. Estimated Study Duration

Duration of participation in this extension study will be 4 years or until pegcetacoplan development in subjects with PNH is terminated.

8. SUBJECT SELECTION

8.1. Inclusion Criteria

1. Subjects at least 18 years of age with PNH who have participated in an antecedent pegcetacoplan clinical trial. Subjects who received treatment with pegcetacoplan must have experienced clinical benefit and adequate tolerability in the opinion of the investigator.

   Note: Subjects with PNH who completed an antecedent pegcetacoplan clinical trial without receiving pegcetacoplan (or without receiving pegcetacoplan for long enough to demonstrate clinical benefit) may be enrolled in this study if, in the opinion of the investigator, the subject is expected to demonstrate clinical benefit upon the initiation or continuation of pegcetacoplan therapy.

2. Vaccination against *Neisseria meningitidis* types A, C, W, Y, and B, *Streptococcus pneumoniae,* and *Haemophilus influenzae* type B (Hib) either within 2 years prior to Day 1 dosing of this study, or within 14 days after starting treatment with pegcetacoplan. Vaccination is mandatory unless documented evidence exists that subjects are nonresponders to vaccination as evidenced by titers or display titer levels within acceptable local limits. Immunization status checks will be performed to determine whether subjects require primary or booster vaccinations.
3. Willing and able to give written informed consent.
4. Willing and able to self-administer pegcetacoplan (administration by a caregiver will be allowed).
5. Women of childbearing potential, defined as any females who have experienced menarche and who are NOT permanently sterile or postmenopausal, must have a negative pregnancy test and must agree to continue to use an approved method of contraception for the duration of the study and 90 days after their last dose of study drug. Note: Postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause.
6. Males must agree to continue to use an approved method of contraception and must agree to refrain from donating sperm for the duration of the study and 90 days after their last dose of study drug.

8.1.1. Approved Methods of Contraception

Approved methods of contraception include:

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

- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomy (for male subjects) or vasectomized partner (for female subjects of childbearing potential, provided that the vasectomized partner is the sole sexual partner of the study subject) provided that the vasectomized partner has received medical assessment of the surgical success of the procedure
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments)
- Male or female condom with spermicide; cap, diaphragm, or sponge with spermicide; or a combination of male condom with cap, diaphragm, or sponge with spermicide (double barrier method)

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

Subjects must agree to use an approved method of contraception during the study and for 90 days after their last dose of study drug. When possible, subjects should continue to use the method of contraception employed during the antecedent study. Investigators should discuss contraception requirements with subjects at study entry and before any change in method of contraception and should contact the medical monitor if there is any uncertainty regarding the acceptability of a method of contraception.

Pegcetacoplan treatment will be discontinued in subjects no longer using an approved method of contraception.

8.2. Exclusion Criteria

1. Subjects who have withdrawn from a pegcetacoplan clinical study and/or subjects who met study drug discontinuation criteria during a pegcetacoplan clinical study.
2. Any condition that could increase the subject's risk by participating in the study.
3. Any comorbidity or condition (such as malignancy) that, in the opinion of the investigator, could put the subject at increased risk or potentially confound study data.
4. History or presence of hypersensitivity or idiosyncratic reaction to compounds related to the investigational product or SC administration.
5. Acute or active hepatitis B, hepatitis C, or HIV infection.
6. Hereditary complement deficiency.

7. History of bone marrow transplant.
8. Concurrent severe aplastic anemia (defined by bone marrow cellularity <25% [or 25% to 50% if less than 30% of residual cells are hematopoietic] and at least 2 of the following values: peripheral blood absolute neutrophil count <500/μL [$<0.5 \times 10^9$/L], peripheral blood platelet count <20,000/μL, peripheral blood reticulocyte count <20,000/μL).
9. History of meningococcal disease.
10. Concomitant treatment with any complement inhibitor (eg, eculizumab, ravulizumab).
11. Pregnancy, breastfeeding, or positive pregnancy test.

8.3. Inclusion of Subjects Incapable of Informed Consent

Subjects incapable of giving informed consent will not be enrolled in this study; therefore, this section is not applicable.

8.4. Recruitment Methods

Entry into this extension study will be offered to PNH patients who have completed an antecedent pegcetacoplan clinical study.

9. STUDY TREATMENTS

9.1. 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 20-mL glass vials. Additional information is provided in the pegcetacoplan investigator's brochure.

9.1.1. Blinding the Treatment Assignment

Not applicable. This is an open-label study.

9.2. Administration of Investigational Product

9.2.1. Interactive Response Technology for Investigational Product Management

A centralized IRT will be utilized for (but not limited to) the following investigational product management tasks: investigational product supply management, inventory management and supply ordering, expiration tracking and return of investigational product (if applicable). Please refer to the IRT Manual for further information.

9.2.2. Allocation to Treatment

This is an open-label extension study. Subjects will be allocated to their treatment based on the dose received in their previous study (see Table 1).

9.2.3. Dosing

All subjects will receive 1080 mg of pegcetacoplan twice weekly, every 3 days, or 3 times weekly as described in Table 1 and should maintain the prescribed regimen. Weekly dosing regimens (twice or three times weekly) are based on a 7-day period, regardless of the days of the week on which dosing occurs. If the dosing schedule is adjusted, subjects should maintain the revised regimen as prescribed. It is not necessary that dosing align with clinic visits, and subjects should not delay or defer dosing.

Table 1: Study APL2-307 Dosing Regimen and Dosing Instructions at Rollover

Previous study dose and regimen	APL2-307 study dose and regimen	Instructions on switching
270 mg/day	1080 mg twice weekly	No gap in dosing (eg, 270 mg on day prior to baseline then switch to 1080 mg on Day 1)
360 mg/day	1080 mg every 3 days	Day off pegcetacoplan dosing (eg, 360 mg will not take their dose on the day prior to baseline and then switch to 1080 mg on Day 1)
440 mg/day	1080 mg 3 times weekly	Day off pegcetacoplan dosing (eg, 440 mg will not take their dose on the day prior to baseline and then switch to 1080 mg on Day 1)
1080 mg twice weekly or 1080 mg every 3 days	1080 mg twice weekly, 1080 mg every 3 days	Subjects should continue the same dose regimen.
Not allocated to a pegcetacoplan treatment arm	1080 mg twice weekly	Subjects should initiate pegcetacoplan dosing (1080 mg on Day 1)

Subjects should be instructed to take their pegcetacoplan treatment as prescribed, and to contact the investigator immediately for guidance in the event of any missed doses. If withdrawal of pegcetacoplan treatment is necessary, slow weaning should be considered and subjects should carefully be monitored for at least 8 weeks to detect serious hemolysis or other complications. If a subject experiences previously unreported adverse effects associated with a specific antibiotic, their treatment may be switched at the investigator's discretion.

9.2.3.1. Dose Adjustment

Following commencement of monotherapy with pegcetacoplan, LDH will be monitored as part of the scheduled assessments at the planned clinic visits. For any subject receiving pegcetacoplan monotherapy, if LDH is >2 × the upper limit of normal (ULN) on 1 occasion, a pegcetacoplan dose increase to 1080 mg every third day should be considered (see Section 5.2). For any subject already receiving 1080 mg every third day, if LDH is >2 × the ULN on 1 occasion, a pegcetacoplan dose increase to 1080 mg three times weekly should be considered. Any adjustment in dose will be discussed and confirmed, in writing, by Apellis. In the event of a dose increase, LDH will be monitored biweekly (unscheduled assessments, if applicable) for at least 4 weeks to assess the impact of the dose adjustment on LDH levels.

Treatment regimens for subjects in the acute hemolysis substudy, referenced in Section 9.2.4 and described in Appendix 4, including maintenance dosing after completion of intensive pegcetacoplan treatment and adjustments to maintenance dosing regimens, are described in Section 4.1.6.2.3 of Appendix 4.

9.2.4. Management of Acute Hemolysis

Subjects enrolled in Study APL2-307 who experience acute hemolysis (AH) will be offered the opportunity to enter a substudy in which they receive either intensive SC or intravenous pegcetacoplan as an acute treatment for AH. In order to qualify for participation in the substudy, subjects must have LDH >2 × the ULN and the presence of at least one new or worsening sign or symptom of hemolysis (eg, decrease in Hb, hemoglobinuria, fatigue), warranting acute intervention in the opinion of the investigator. The substudy is described in detail in Appendix 4.

Subjects who experience AH but chose not to enter the substudy may continue to participate in the main study, including potential dose adjustment as described in Section 9.2.3.1.

9.2.5. Investigational Product Administration

Pegcetacoplan for the treatment of PNH will be administered as a 20-mL SC infusion.

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. Subjects will have qualified to self-administer injections as a part of their previous study. At the study site subjects may self-administer or pegcetacoplan may be administered by the subject's caregiver or trained study personnel. Self-administration conducted at the clinic will be supervised to ensure that the subject continues to remain compliant with the administration guidelines.

Intensive pegcetacoplan for the management of AH is discussed in Section 4.1.6.2.5 of Appendix 4.

9.3. Labeling, Packaging, Storage, and Handling

9.3.1. 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: 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 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.

9.3.2. Packaging

Investigational product is supplied as a sterile solution of pegcetacoplan, 54 mg/mL, in acetate-buffered sorbitol, supplied in stoppered glass vials.

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

9.3.3. 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.

9.3.4. Storage and Handling

The investigational product should be stored refrigerated at 2 to 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 in the Delegation of Authority Log.

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 study 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 throughout the duration of the study and that records are maintained.

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 any unused investigational product shall remain unchanged.

9.4. Investigational Product Accountability

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

At the conclusion of the study, any unused investigational product will either be destroyed at the study 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.

9.5. Subject Compliance

Compliance will be monitored throughout the study and will be recorded on the drug accountability form by the pharmacist/nominated person.

9.6. Concomitant Medications

9.6.1. Transfusions

If a subject receives a transfusion during the study period, the pretransfusion Hb level and number of packed RBC units transfused must be recorded in the source document. The need for a transfusion will be determined by the PI as standard of care and according to clinical practice and individual subject management.

9.6.2. Prophylactic Antibiotics

Prophylactic antibiotic therapy should be considered in order to minimize potential infection risk. Prophylactic antibiotic therapy should be administered at the discretion of the treating investigator in accordance with local treatment guidelines for subjects with PNH who are receiving treatment with a complement inhibitor.

Subjects may be receiving prophylactic antibiotic therapy from their previous study to minimize potential infection risk, and this may be continued to be administered in concurrence with local guidelines.

Treatment may be switched to another alternative antibiotic, at the discretion of the PI, if a subject experiences tolerability issues (such as nausea and diarrhea).

9.6.3. 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 despite prophylactic antibiotic treatment 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).

9.6.4. QT-Prolonging Medication

While no cardiac safety signal has emerged from preclinical or clinical experience to date, clinical experience is not sufficient to negate any potential unanticipated risks. The use of medications with the potential to prolong the QT interval must be discussed and agreed with the medical monitor. An independently curated list of medications categorized by their potential to cause QT prolongation is available at https://crediblemeds.org/healthcare-providers/drug-list.

9.6.5. Phlebotomy/Venesection for Iron Overload

Phlebotomy/Venesection should only be considered if indicated medically and if the Hb level is with the normal range. If phlebotomy is performed it must be reported in the source document as a concomitant therapy.

10. STUDY PROCEDURES

Please see the Schedule of Events in Section 2 for a summary of the schedule of study participation and procedures. The schedule of visit dates is established 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 rescheduling of visits must be agreed, in advance, with the PI and sponsor.

At each clinic visit, activities should be performed in the following order:

- FACIT-Fatigue Scale questionnaire and any other participant-recorded activity
- Solicited collection of information (eg, review of medical history, concomitant medications, and/or AEs)
- Noninvasive procedures (eg, physical exam, recording of vital signs)
- ECG
- Collection of blood and/or urine samples (eg, for clinical laboratory tests and/or PK or other analyses; samples will not be stored for future exploratory analyses)
- Dosing with prophylactic antibiotics, pegcetacoplan, or other medications
- Evaluation of infusion site and infusion pump safety

Subjects who withdraw from the study will need to be monitored closely according to local practice with respect to any hemolysis that is experienced following withdrawal of pegcetacoplan.

10.1. Baseline Visit (All Subjects)

Specific procedures for each visit are listed in the Schedule of Events (Section 2).

The last study visit of the previous trial must be the first (baseline) study visit of this trial. The baseline visit will occur to confirm that the subject selection criteria for the study have been met. Informed consent for this study will be obtained at baseline prior to any study-related procedures being conducted (see Section 16.3). The subject's previous study and their previous subject identifier will be recorded in the source document. This will allow the tracking of subjects through the studies.

At the baseline visit (Day 1) the SC dose of pegcetacoplan may be administered at the study site. Subsequent doses should maintain the prescribed regimen as described in Table 1 (Section 9.2.3) or, if the dosing schedule is adjusted, should maintain the revised regimen as prescribed.

The following procedures may be performed at the baseline visit:

- Document antecedent study number, subject identifier and pegcetacoplan treatment dose from antecedent study at the time of rollover
- Informed consent
- Medical history
- Vaccination status check

- Demographics
- Height and weight
- Physical examination
- Blood tests (predose)
- Preventive antibiotic (if applicable, see Section 9.6.2)
- 12-lead electrocardiogram
- Pegcetacoplan administration
- Injection site assessment
- Concomitant medications
- Vital sign measurements
- Urinalysis
- Urine pregnancy test
- FACIT-Fatigue Scale
- AEs

10.2. Week 2

Subjects transitioning from daily SC dosing to twice weekly dosing or otherwise changing their dosing regimen and subjects starting treatment with pegcetacoplan will be assessed at Week 2 to ensure adequate safety monitoring through the transition. As discussed in Section 9.2.3, the subject's dosing schedule should be maintained; if dosing aligns with a study visit, subjects may self-administer pegcetacoplan at the study site or pegcetacoplan may be administered by the subject's caregiver or trained study personnel.

Please note that a Week 2 study visit is only required for subjects who have commenced or changed their pegcetacoplan dose or regimen. Subjects who have not changed their pegcetacoplan dose or regimen will go from the baseline visit directly to the Week 4 Visit.

The following procedures will be performed at Week 2:

- Blood tests (predose)
- Vaccination status check
- Preventive antibiotic (if necessary, see Section 9.6.2)
- Pegcetacoplan administration
- Injection site assessment
- Concomitant medications
- Vital sign measurements
- Urinalysis

- Urine pregnancy test
- FACIT-Fatigue Scale
- AEs

10.3. Week 4 (All Subjects)

All subjects will have a Week 4 Visit. As discussed in Section 9.2.3, subjects should maintain the prescribed dosing regimen as described in Table 1 or, if the dosing schedule is adjusted, should maintain the revised regimen as prescribed. It is not necessary that dosing align with clinic visits, and subjects should not delay or defer dosing. If dosing aligns with a study visit, subjects may self-administer pegcetacoplan at the study site or pegcetacoplan may be administered by the subject's caregiver or trained study personnel.

The following procedures will be performed at Week 4:

- Vaccination status check
- Blood tests (predose)
- Preventive antibiotic (if necessary, see Section 9.6.2)
- 12-lead electrocardiogram
- Pegcetacoplan administration
- Injection site assessment
- Concomitant medications
- Vital sign measurements
- Urinalysis
- Urine pregnancy test
- FACIT-Fatigue Scale
- AEs

10.4. Week 12 Through End of Study (All Subjects; 12-Week Intervals Between Study Visits)

Beginning at Week 12, all subjects will begin to have study visits at 12-week intervals in order to continue the long-term assessment of the safety and efficacy of pegcetacoplan in subjects with PNH. As discussed in Section 9.2.3, subjects should maintain the prescribed dosing regimen as described in Table 1 or, if the dosing schedule is adjusted, should maintain the revised regimen as prescribed. It is not necessary that dosing align with clinic visits, and subjects should not delay or defer dosing. If dosing aligns with a study visit subjects may self-administer pegcetacoplan at the study site or pegcetacoplan may be administered by the subject's caregiver or trained study personnel.

Beginning at Week 12 and through the course of the rest of the study, at each site visit the following procedures will be performed:

- Physical examination (at Week 24 and then every other visit [ie, every 24 weeks])
- Blood tests (predose)
- Vaccination status check
- Preventive antibiotic (if necessary, see Section 9.6.2)
- 12-lead electrocardiogram
- Pegcetacoplan administration
- Injection site assessment
- Concomitant medications
- Weight
- Vital sign measurements
- Urinalysis
- Urine pregnancy test
- FACIT-Fatigue Scale
- AEs

10.5. Exit Visit

Any subjects who discontinue or withdraw from the study will be asked to return to the clinical facility for the exit visit 8 weeks after the final dose of pegcetacoplan. Specific procedures for each visit are listed in the Schedule of Events (Section 2).

Study participation for each subject will be concluded following completion of the exit visit.

The following procedures will be performed at the exit visit:

- Physical examination
- Weight
- Blood tests (predose)
- Preventive antibiotic (if necessary, see Section 9.6.2)
- 12-lead electrocardiogram
- Injection site assessment
- Concomitant medications
- Vital sign measurements
- Urinalysis
- Urine pregnancy test

- FACIT-Fatigue Scale
- AEs

10.6. Unscheduled Visits

While a defined site visit schedule exists for all subjects in the pegcetacoplan extension study, an unscheduled visit can occur when the subject determines a need for additional assessment, guidance from the study site, or for the reporting of AEs.

If an unscheduled visit should occur, the study site should document all of the activities and procedures that occurred during this unscheduled visit in the source document.

10.7. Treatment Discontinuation and Study Withdrawal

Subject participation in this study may be discontinued and subjects may be withdrawn from study for any of the following reasons:

- Subject's decision to withdraw.
- Subject does not wish to comply with study procedures.
- Subject is able to receive commercially available pegcetacoplan.

Subjects may be discontinued from study treatment for any of the following reasons:

- Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the PI that continued participation is not in the best interest of the subject.
- Subject’s failure to comply with protocol requirements or study-related procedures.
- Pregnancy

The reason for treatment discontinuation and withdrawal from the study must be recorded in the subject’s source document. Subjects who discontinue treatment may withdraw or may continue to participate in study visits without receiving treatment. Subjects will be encouraged to remain in the study to complete appropriate safety follow-up procedures.

Any subject transitioning to commercially available pegcetacoplan once it is available to them will be asked to return to the clinical study site for an exit visit before starting treatment with alternately sourced pegcetacoplan. Study participation for these subjects will be concluded following completion of the exit visit. Exit visit assessments will be performed as described in the Schedule of Events (Section 2).

If withdrawal of pegcetacoplan treatment is necessary, slow weaning should be considered and subjects should carefully be monitored for at least 8 weeks to detect serious hemolysis or other complications.

If serious hemolysis occurs after pegcetacoplan discontinuation, the following procedures/treatments should be considered: blood transfusion (packed RBCs); anticoagulation; corticosteroids; or reinstitution of a complement inhibitor (other than pegcetacoplan).

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 will be treated and/or followed up until the symptoms or values return to normal or acceptable levels, as judged by the PI.

11. ASSESSMENTS

11.1. Assessments

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.

11.1.1. Medical History

Medical history that has been collected on each participating subject (which includes any AEs reported and any concomitant medication that the subject may now be taking) will be referenced in the extension study medical history documentation. The subject's previous study and their previous subject identifier will be recorded in the source document. This will allow the tracking of subjects through the studies.

11.1.2. Prior and Concomitant Medications

Treatment history of dose and duration of concomitant medications will be collected on each participating subject, which includes prior and current concomitant medication and will be carried forward and become part of the extension study documentation.

Any packed RBC transfusions received during the study will be clearly documented and will include type and date of transfusion.

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

11.1.3. Body Height and Weight

Body height (cm) and body weight (kg) will be measured at baseline as part of the physical examination. Body weight (kg) will be measured at 12-week intervals.

11.1.4. Physical Examination

All 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.

The investigator (or designee) at the study site will examine each subject as outlined in the Schedule of Events in Section 2.

A symptom-driven physical examination may be performed at various unscheduled time points if deemed necessary by the investigator.

11.1.5. Vital Signs

Measurements of body temperature, respiratory rate, blood pressure, and heart rate will be measured as outlined in the Schedule of Events (Section 2). At Visit 1 (Day 1), vital signs will be measured before dosing and 2 hours after dosing (±30 minutes); at all other visits, if the subject

elects to administer pegcetacoplan during the visit, vital signs should be measured before dosing and again 30-60 minutes after completion of dosing.

Vital signs may be taken at any other times, if deemed necessary, such as an unscheduled visit. 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.

11.1.6. ECG Monitoring

12-lead ECGs will be measured at the time points outlined in the Schedule of Events (Section 2). ECGs will be taken following resting in the supine position for 10 minutes in a quiet environment and prior to any blood sampling procedures.

All ECGs will be recorded at the study sites using the site's own equipment.

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 (heart-rate corrected [QTc] and uncorrected) will be reviewed and ongoing safety.

During the study if the QTcF (QT interval corrected for heart rate using the Fridericia formula) at any on treatment ECG is ≥500 milliseconds (mean of QTc replicate values), the investigator should perform 3 additional ECGs over 20-60 minutes; if the mean QTc of the 3 repeat ECGs is ≥500 ms, the site should instruct the subject to return the following day to perform repeat triplicate ECGs. An evaluation will be performed to look for other factors which may have contributed to QTc prolongation (eg, new concomitant medications, hypokalemia).

11.1.7. FACIT-Fatigue Scale

The FACIT-Fatigue Scale is a 13-item Likert scaled instrument which is self-administered by the subjects during clinic visits as outlined in the Schedule of Events in Section 2. Subjects are presented with 13 statements and asked to indicate their responses as it applies to the past 7 days. The 5 possible responses are 'Not at all' (0), 'A little bit' (1), 'Somewhat' (2), 'Quite a bit' (3) and 'Very much' (4). With 13 statements the total score has a range of 0 to 52. Before calculating the total score, some responses are reversed to ensure that the higher score corresponds to a higher quality of life. The FACIT-Fatigue Scale and scoring guidelines are provided in Appendix 1.

11.1.8. Clinical Laboratory Tests

The use of silica reagents in coagulation panels should be avoided. Apellis previously conducted an investigation into prolonged aPTT observed in subjects treated with pegcetacoplan. It was confirmed that false positive aPTT prolongation occurred when coagulation panels were performed using a Stago Analyzer and specifically silica reagents. It was determined that there was interference between the silica reagents and PEGylated pegcetacoplan, resulting in artificially prolonged aPTTs.

All tests listed below will be performed as outlined in the Schedule of Events in Section 2. In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the PI. The clinical laboratory tests include (but are not limited to) the following:

11.1.8.1. Hematology

- Hb
- Hematocrit
- RBC count
- Platelet count
- White blood cell count with differential
- Reticulocytes

11.1.8.2. Coagulation

- Prothrombin time
- Fibrinogen
- Activated partial thromboplastin time
- D-Dimer

NOTE: The use of silica reagents in coagulation panels should be avoided in subjects treated with pegcetacoplan

11.1.8.3. Serum Chemistry

- Blood urea nitrogen
- Creatinine
- Estimated creatinine clearance (using Cockcroft-Gault formula)—baseline visit only
- Bilirubin (total and direct)
- Albumin
- Alkaline phosphatase
- Lactate dehydrogenase
- Haptoglobin
- Gamma-glutamyl transpeptidase
- Creatine kinase
- Aspartate aminotransferase
- Alanine Aminotransferase
- Uric acid
- Glucose
- Sodium
- Potassium
- Chloride
- Ferritin
- B12/folate

11.1.8.4. Urinalysis

- pH
- Specific gravity
- Protein
- Glucose
- Ketones
- Bilirubin
- Blood
- Nitrite
- Urobilinogen
- Leukocyte esterase

If an abnormality is noted for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination will be performed.

11.1.9. Injection/Infusion Site and Pump Safety Assessment

On the days of clinical visits, pump use safety will be performed within 30 minutes after study drug administration. The assessment 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 or issue with the pump occurs after self-administration of pegcetacoplan. All clinically relevant adverse events, as determined by the investigator, from injection site or related to pump use will be recorded as AEs.

11.1.10. COVID-19 Assessments

COVID-19 testing will be conducted in subjects experiencing acute hemolysis (LDH >2 × the ULN and the presence of at least one new or worsening sign or symptom of hemolysis [eg, decrease in Hb, hemoglobinuria, fatigue]) and/or symptoms suggestive of COVID-19 infection (fever or chills, cough, difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, and diarrhea). The test results must be documented in the source document.

11.2. Vaccination and Revaccination

Systemic complement inhibition might predispose individuals to infections caused by encapsulated organisms, including *Streptococcus pneumoniae*, *Neisseria meningitidis* (serogroups A, C, W, Y, and B), and *Haemophilus influenzae* type B. In order to reduce this risk, vaccination against each of these organisms is mandatory, unless documented evidence exists that subjects are nonresponders to vaccination.

11.2.1. Subjects Previously Treated With Pegcetacoplan

Subjects with PNH who participated in an antecedent pegcetacoplan clinical trial were required to have documented evidence of vaccination against each of these organisms within 2 years of screening, or received vaccination upon initiation study treatment, as follows:

- *Neisseria meningitidis* types A, C, W, Y, and B (administered as 2 separate vaccinations)

- *Streptococcus pneumoniae* (with a PCV13 or PPSV23 vaccine)
- *Haemophilus influenzae* type B (Hib vaccine)

Those subjects requiring vaccination received Ciprofloxacin 500 mg twice daily from Week 0 to Week 2, vaccines were administered at Week 2, and antibiotic prophylaxis continued for an additional 14 days after vaccination.

In this study, immunization status will be monitored to assess whether the subject needs primary vaccinations or boosters. In order to receive treatment with pegcetacoplan, subjects must have documented evidence of vaccination against each of the organisms listed above within 2 years of screening. Subjects receiving pegcetacoplan before the start of this study who do not have documented evidence of receiving all of the above vaccinations within 2 years prior to screening will receive the required missing vaccination(s) at the baseline visit. Subjects who require booster vaccinations will receive the required vaccination at the appropriate visit as noted in Section 11.2.1.1.

11.2.1.1. Subjects Who Need Revaccination

For those subjects who are already enrolled in this study, the revaccination schedule should be consistent with the recommendations of the Centers for Disease Control and Prevention (2020) as follows:

- *Neisseria meningitidis* types A, C, W, Y: every 5 years
- *Neisseria meningitidis* type B: every 2-3 years
- *Streptococcus pneumoniae* (PPSV23): 5 years after previous PPSV23 dose
- *Haemophilus influenzae* type B (Hib vaccine): no revaccination needed

11.2.2. Subjects Not Previously Treated With Pegcetacoplan

Subjects who have not previously received pegcetacoplan treatment will receive prophylactic antibiotics for the first 4 weeks of treatment with pegcetacoplan and will receive any required vaccination(s) 2 weeks after initiation of treatment with pegcetacoplan, according to the schedule described above. If required, the *Neisseria meningitidis* booster (for both ACWY and serotype B vaccinations), and/or PPSV23 vaccination should be administered at least 8 weeks following the initial vaccination(s).

The PI will discuss individual subject circumstances with the sponsor.

11.3. Pharmacokinetics Assessments

11.3.1. 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 2.

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

11.3.2. Analytical Method

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

11.4. Flow Cytometry Assessments

Blood samples for flow cytometry assessment will be collected via direct venipuncture at the time points delineated in the Schedule of Events in Section 2. Flow cytometry assessment will include, but not be limited to: PNH clonal distribution of RBCs, PNH clonal distribution of immature reticulocytes (CD71+), monocytes and granulocytes and C3 deposition on RBCs.

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

11.5. Pharmacodynamic Assessments

Blood samples will be collected via direct venipuncture at the time points delineated in the Schedule of Events in Section 2 for PD assessment of complement activation through the classical (ie, CH50) and alternative (eg, AH50) pathways. Blood samples will also be collected to measure C3 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.

11.6. Antidrug Antibody Assessments

The proposed antidrug antibody (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 while minimizing pegcetacoplan level in the sample.

Subjects who test positive for anti–pegcetacoplan peptide antibody or anti-PEG antibody in the last dose samples will be followed with ADA samples being collected every 6 months until the antibody levels revert to baseline. Samples that test positive for anti-pegcetacoplan peptide antibody will be characterized by an assay measuring neutralizing capacity.

ADA samples must be collected at the exit visit.

11.7. Blood Volume for Study Assessments

The long-term extension study will continue for 4 years or until pegcetacoplan development in subjects with PNH is terminated. The approximate total volume of blood to be collected at each study visit is provided in Table 2.

Table 2: Blood Volume During Study

Assay	Approximate volume per time point (mL)
Pharmacokinetics	7.5
Anti–pegcetacoplan peptide antibody and anti-PEG antibody	5
Hematology	3
Chemistry	7.5
Fibrinogen	2.7
C3 profile	2.5
Complement profile (CH50 and AH50)	5
Flow cytometry, PNH clones, and C3 deposition	2
Haptoglobin	2.5
Ferritin	2.5
Total approximate blood volume for each study visit:	40.2

Abbreviations: AH50 = alternative pathway hemolytic activity; CH50 = classical pathway hemolytic activity; PEG = polyethylene glycol; PNH = paroxysmal nocturnal hemoglobinuria.
Note: The use of silica reagents in coagulation panels should be avoided in subjects treated with pegcetacoplan where possible.

11.8. Pregnancy Tests

For women of childbearing potential, a urine pregnancy test will be performed at the study site based on the Schedule of Events (Section 2) predose (a negative urine pregnancy test must be received before dosing with study drug). A final urine pregnancy test will be performed at the final exit visit. Subjects who become pregnant during the study will be discontinued from study treatment.

Male subjects must agree to refrain from donating sperm during the time they are receiving pegcetacoplan and for 90 days after their last dose of study drug.

12. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

12.1. Definitions

12.1.1. Adverse Events

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not 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 a study drug, whether or not considered related to the study drug.

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 source document.

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

TEAEs will be defined as those AEs that occur or worsen in severity after the first dose of pegcetacoplan in this study, for up to 30 days after the last dose of pegcetacoplan.

A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE.

12.1.1.1. Serious Adverse Events

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

Life-threatening is defined as an AE or suspected adverse reaction, which, in the view of either the investigator or sponsor, places the 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.

All SAEs (irrespective of causality) must be reported to Apellis Safety within 24 hours of the investigator or their representative becoming aware of the event, as described in Section 12.3.

12.1.1.2. 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 investigator's brochure that is in effect at the time of event onset.

12.2. Evaluation and Recording of Adverse Events

All AEs and SAEs will be collected from the signing of the informed consent form (ICF) until the exit visit. All identified AEs, including clinically significant laboratory findings, must be recorded and described in the source document. If applicable, the underlying illness or disorder should be recorded rather than its individual symptoms.

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

Any events that occur prior to the start of dosing will be categorized as pretreatment events; events occurring after the start of dosing will be recorded as TEAEs.

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, particularly if the AE was considered by the investigator to be related to the investigational product. AEs resulting in interruption or discontinuation of study drug or that are present at the exit visit should receive follow-up as appropriate.

12.2.1. 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, and outcome (recovered/resolved, recovered/resolved with sequelae, recovering/resolving, not recovered/not resolved, fatal, or unknown) of each event will be noted.

Table 3 should be considered when evaluating the relationship of AEs/SAEs to study treatment.

Table 3: 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

12.2.2. 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 12.1.1.1. An AE can be of severe intensity but not be considered serious.

Table 4 presents the definitions that should be considered when evaluating the severity of AEs and SAEs.

Table 4: Severity of Events

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

12.3. Reporting Adverse Events

All SAEs must be reported to Apellis Safety via eCRF within 24 hours of the investigator or their representative becoming aware of the event, whether or not the event is deemed treatment related. If the electronic data capture system is not operational, the site must complete the paper SAE form and email to [redacted] immediately; the requirement to report all SAEs within 24 hours of becoming aware of the event remains in effect. The reported information submitted as a paper SAE must be entered into the electronic data capture system once it becomes operational.

The sponsor has the responsibility to inform concerned health authorities, ethics committees, 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 ethics committees in compliance with local requirements.

12.4. Pregnancy

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

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

The investigator must follow the subject until completion of the pregnancy and must report the outcome of the pregnancy (eg, delivery, termination) and neonatal status up to 12 months after delivery. An abnormal outcome is defined as any pregnancy that results in the birth of a child with persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies, or birth defects. In the event of an abnormal outcome, an SAE report form will be required, as described in Section 12.3.

12.5. Abuse, Misuse, Overdose, and Medication Errors

Abuse of a medicinal product: Persistent or sporadic, intentional, excessive use of medicinal products which 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: Administration of a quantity of study drug per administration or per day which is above the assigned dose.

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

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

All AEs or SAEs associated with drug abuse, misuse, overdose, or medication error must be reported to Apellis Safety.

12.6. Data Monitoring Committee

A data monitoring committee (DMC) will review cumulative safety/tolerability and efficacy data including but not limited to AEs, physical exams, ECGs, and laboratory tests. The DMC will conduct a thorough safety assessment every 6 months during the course of the study as specified in the DMC charter.

13. STATISTICS

13.1. Sample Size

Only those subjects who completed an antecedent PNH pegcetacoplan study are eligible to enter this extension study. Therefore, the number of subjects in this study will not exceed the total number of subjects who have completed previous PNH pegcetacoplan studies; thus, approximately 160 subjects are planned.

13.2. 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. Continuous data will be summarized using descriptive statistics (eg, n, mean, median, standard deviation, minimum, and maximum) and categorical data will be summarized using counts and percentages.

13.2.1. Analysis Populations

13.2.1.1. Safety Population

The safety population will include all subjects who enroll and receive at least one dose of pegcetacoplan in this study.

13.2.1.2. ITT Population

The intent-to-treat (ITT) population will include all subjects who enroll and receive at least one dose of pegcetacoplan in this study.

13.2.1.3. Pharmacokinetic (PK) Population

The PK population will include all subjects in the ITT population who have at least 1 evaluable postdose PK measurement.

13.2.1.4. Pharmacodynamic (PD) Population

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

13.2.1.5. Data Review for Analysis Populations

Data will be reviewed to identify the subjects included in the analysis populations.

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

13.2.2. Data and Interim Analyses

No formal interim analyses are planned, however, the data from this study may be reported out for specific reasons, eg, providing data to a regulatory agency. In the event that the data will be provided to regulatory agencies for the purpose of supporting marketing authorization, the data will be either frozen or locked depending on the study completion status.

13.2.3. Missing, Unused, and Spurious Data

No imputation of missing data for early terminations will be performed.

Missing dates/times will be reviewed on a case-by-case basis for potential imputations, but the original data will always be presented in data listings.

13.3. Statistical Analyses

13.3.1. Subject Disposition and Demography

The number (percentage) of subjects who are ongoing will be tabulated as well as the number (percentage) of subjects who have discontinued. For those who have discontinued the reasons will also be summarized.

The long-term extension study will continue for 4 years or until pegcetacoplan development in subjects with PNH is terminated.

Demographic data will be summarized and will include a summary of the number of subjects from each antecedent PNH pegcetacoplan study.

13.3.2. Efficacy Analyses

Efficacy analyses will be performed using the ITT population.

Absolute values and changes from baseline will be summarized by visit using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). Changes from baseline will also be summarized categorically by visit.

The number and percentage of subjects who have met specific levels with respect to the reference range (eg, Hb level ≥ the lower limit of normal) will be tabulated by visit.

Efficacy summaries will be presented by previous study enrollment and overall. Baseline will be taken as the last measurement before the start of dosing in this study.

13.3.3. Safety Analyses

Safety data analyses will be performed using the safety population. Continuous data will be summarized using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) and categorical data will be summarized by the number of subjects (n) and the percentage of subjects in each category.

Medical data coding of the verbatim terms provided by the investigators for AEs and concomitant medications will be performed using current versions of the Medical Dictionary for Regulatory Activities and the World Health Organization Drug Dictionary, respectively.

13.3.3.1. Adverse Events

TEAEs will be summarized by System Organ Class and Preferred Term. Tabulations will be produced for all TEAEs and for those considered treatment related. The number of subjects reporting SAEs will also be tabulated.

The by-subject TEAE data listing will include the verbatim term, preferred term, treatment, severity, and investigator judgment of relationship to treatment.

13.3.3.2. Clinical Laboratory Tests

Absolute values and changes from baseline will be summarized using descriptive statistics by visit. Baseline will be taken as the last measurement prior to the first dose of pegcetacoplan in the study.

The by-subject listing will include changes from baseline and values that are outside the laboratory reference range will be flagged.

13.3.3.3. Vital Signs and ECGs

Absolute values and changes from baseline values for vital sign and ECG parameter will be summarized by visit and listed.

Values of potential clinical significance (eg, change in QTcF ≥30 milliseconds from baseline) will be flagged in listings and summarized.

13.3.4. Pharmacokinetic Analyses

The PK concentrations will be evaluated using the PK population.

Concentrations will be summarized by visit.

Population pharmacokinetic and exposure-response modeling of the safety and efficacy data will be described in a pegcetacoplan population pharmacokinetic/pharmacodynamic analysis plan. The methods will be based on the Food and Drug Administration *Guidance for Industry: Exposure-Response Relationships—Study Design, Data Analysis, and Regulatory Applications* (Center for Drug Evaluation and Research, April 2003) and *Guidance for Industry: Population Pharmacokinetics* (Center for Drug Evaluation and Research, February 2019).

13.3.5. Pharmacodynamic Analyses

The PD endpoints will be evaluated using the PD population.

Absolute values and percentage of baseline will be summarized by visit for AH50 and CH50. For C3, absolute values will be summarized by visit.

13.3.6. Analysis of Subjects in the AH Substudy

Analysis of the safety and efficacy of pegcetacoplan in subjects in the AH substudy is described in Section 4.1.11 of Appendix 4.

14. 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, and study drug records 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 and thereafter. The PI will ensure that the auditor is allowed direct access to the source data, medical records, source documents, and the site's regulatory file for the study and any other pertinent information.

14.1. Monitoring

On-site monitoring will be performed by the sponsor and/or the sponsor's designee for the duration of the study and thereafter. The monitor will ensure that the study is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, GCP, and all applicable regulatory requirements. The monitor will verify the accuracy and completeness of the electronic case report form (eCRF) entries, source documents, and other study-related records against each other. The PI will provide direct access to source data/documents for study-related monitoring. 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.

15. QUALITY CONTROL AND QUALITY ASSURANCE

This study is to be performed in full compliance with the protocol, GCP, and all applicable regulatory requirements. The PI, 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.

16. ETHICS

16.1. Ethics Review

The study protocol, any amendments to the protocol, ICF, the current pegcetacoplan investigator's brochure, and other study specific information will be reviewed and approved by the IRB/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 all applicable regulatory requirements.

16.2. 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 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Harmonised Tripartite Guidance for Good Clinical Practice, E6, R1 (GCP).

16.3. Subject Information and Consent

The PI or appropriate designee is responsible for obtaining informed consent. 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.

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.

16.4. Confidentiality

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

16.5. ClinicalTrials.gov

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

16.6. Termination of Study

The sponsor reserves the right to suspend or discontinue this study for administrative and/or safety reasons at any time or if the development program for pegcetacoplan in subjects with PNH is terminated. The PI reserves the right to discontinue dosing subjects at any time for safety reasons.

17. DATA HANDLING AND RECORD KEEPING

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.

17.1. 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 protocol.

17.2. Report Format

According to the ICH Harmonised 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).

17.3. Finance and Insurance

Finance and insurance will be addressed in a clinical trial agreement between the PI/Institution and the sponsor.

18. 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.

After the completion of the study, the data may be reported at a scientific meeting and/or submitted for publication in a scientific journal with the prior written consent of the sponsor. The sponsor must be given at a minimum 30 days to review the materials to be presented at a scientific meeting and/or for publication in a scientific journal.

19. REFERENCES

Centers for Disease Control and Prevention. Table 2. Recommended Adult Immunization Schedule by Medical Condition and Other Indications, United States, 2020. Accessed 30 April 2020. https://www.cdc.gov/vaccines/schedules/hcp/imz/adult-conditions.html

DeZern AE, Dorr D, Brodsky RA. Predictors of hemoglobin response to eculizumab therapy in paroxysmal nocturnal hemoglobinuria. *Eur J Haematol*. 2013; 90(1):16-24. doi: 10.1111/ejh.12021

Risitano AM, Notaro R, Marando L, et al. Complement fraction 3 binding on erythrocytes as additional mechanism of disease in paroxysmal nocturnal hemoglobinuria subjects treated by eculizumab. *Blood*. 2009; 113(17):4094-4100. doi: 10.1182/blood-2008-11-189944

20. APPENDICES

Appendix 1. Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue Scale

FACIT-Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless (“washed out”)	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

FACIT-Fatigue Subscale Scoring Guidelines (Version 4)

Instructions:* 1. Record answers in "item response" column. If missing, mark with an X

2. Perform reversals as indicated, and sum individual items to obtain a score.

3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.

4. The higher the score, the better the QOL.

Subscale	Item Code	Reverse item?	Item response	Item Score
FATIGUE SUBSCALE	HI7	4 -	_____	=_____
	HI12	4 -	_____	=_____
	An1	4 -	_____	=_____
	An2	4 -	_____	=_____
	An3	4 -	_____	=_____
	An4	4 -	_____	=_____
	An5	0 +	_____	=_____
	An7	0 +	_____	=_____
	An8	4 -	_____	=_____
	An12	4 -	_____	=_____
	An14	4 -	_____	=_____
	An15	4 -	_____	=_____
	An16	4 -	_____	=_____

Sum individual item scores:	_____
Multiply by 13:	_____
Divide by number of items answered:	**_____ (Fatigue Subscale Score)**

*For guidelines on handling missing data and scoring options, please refer to the Administration and Scoring Guidelines in the manual or on-line at www.facit.org.

NOTE: The FACIT and all related works are owned and copyrighted by, and the intellectual property of David Cella, Ph.D. Permission for use of the FACIT-FATIGUE questionnaire is obtained by contacting Dr Cella at information@facit.org.

Appendix 2. Protocol Amendment History

DOCUMENT HISTORY	
Document	**Date**
Amendment 4	20 July 2022
Amendment 3	16 December 2020
Amendment 2	04 May 2020
Amendment 1	30 July 2019
Original Protocol	11 April 2018

Amendment 3: Summary of Changes From the Previous Version

Summary of Change(s) Since Last Version of Approved Protocol		
Amendment 3	**Amendment Date** 16 December 2020	**Global**
Description of Change		**Section(s) Affected by Change**
Editorial and technical changes that did not impact content of the document have been made for grammar, clarity, and document usability.		Entire document
Updated the Apellis medical director for the study		Signature Page, Sponsor Information
Added indirect bilirubin level as an efficacy endpoint.		Synopsis, Section 6.2.2
Revised exclusion criterion 5: Previous: Known infection with hepatitis B, C, or HIV. Current: Acute or active hepatitis B, hepatitis C, or HIV infection.		Synopsis, Section 8.2
Clarified definition of severe aplastic anemia in exclusion criterion 8		Synopsis, Section 8.2
Extended Exit Visit to 8 weeks after last dose for consistency with other studies		Schedule of Events, Section 10.5, Appendix 3
Updated study rationale to reflect current status		Section 5
Updated dosing regimens to include 1080 mg three times weekly		Synopsis, Section 9.2.3
Updated dosing selection rationale to reflect current modeling		Section 5.2
Updated risk-benefit assessment to include COVID-19 risk mitigation measures		Section 5.3.1.1
Revised description of approved methods of contraception to reflect the approved methods of contraception in the antecedent studies		Section 8.1.1
Defined a substudy to evaluate intensive therapy with pegcetacoplan for the treatment of acute hemolysis		Section 9.2.4, Section 13.3.6, Appendix 4

Updated wording describing monitoring and reporting of adverse events and serious adverse events to align with current company practices, including: • Updated wording defining terms • Updated description of evaluation and recording of adverse events • Clarified SAE reporting responsibilities and procedures • Clarified pregnancy reporting responsibilities and procedures • Added section defining the reporting of abuse, misuse, overdose, and medication errors	 Section 12.1 Section 12.2 Section 12.3 Section 12.4 Section 12.5
Added definition of efficacy population, and specified that the PK and PD populations will be based on the efficacy population.	Section 13.2.1, Section 13.3.2
Added allowance for remote monitoring activities to the description of changes related to COVID-19 pandemic	Appendix 3

Amendment 2: Summary of Changes From the Previous Version

Summary of Change(s) Since Last Version of Approved Protocol		
Amendment 2	**Amendment Date** 04 May 2020	**Global**
Description of Change		**Section(s) Affected by Change**
Non-substantial editorial and technical changes that did not impact content of the document have been made for grammar, clarity, and document usability.		Entire document
APL-2 was changed to pegcetacoplan, the International Nonproprietary Name.		Entire document
The Apellis address was updated.		Investigator Agreement, Sponsor Information
Updated signatory for the protocol.		Signature page, Sponsor Information
Updated the following in the Schedule of Events • Revised the study day number that corresponds to each study visit such that visits are 2 weeks apart instead of 13 days apart. • Added clarifying information that the Exit Visit should be 7 days from the last dose. • Added Demographics.		Section 3
Added statement that use of silica reagents in coagulation panels should be avoided as there may be interference with PEGylated pegcetacoplan resulting in artificially prolonged aPTTs. Actions laboratories other than the central laboratory investigators should take are provided.		Section 3, Section 6.3, and Section 12.1.8.3 Table 2

Summary of Change(s) Since Last Version of Approved Protocol		
Amendment 2	**Amendment Date** 04 May 2020	**Global**
Description of Change		**Section(s) Affected by Change**
Clarified the approximate number of subjects planned and the duration of the extension study.		Synopsis, Section 3, Section 8.1, Section 8.2, Section 12.7, Section 14.1, Section 14.3.1
The following inclusion criteria were added or revised: • added qualifier that subjects must be at least 18 years of age • new criteria were added for vaccinations against *Neisseria meningitidis* types A, C, W, Y and B, *Streptococcus pneumoniae* and *Haemophilus influenzae* Type B (Hib) • new criteria were added for willingness and ability to self-administer pegcetacoplan (administration by caregiver allowed) • updated inclusion criteria to extend the use of contraception (both males and females) through 90 days after the last dose of study drug and to require males to refrain from donating sperm for the same duration. Definitions of WOCBP and postmenopausal were added.		Synopsis, Section 9.1, criteria #2, #4, #5, #6, Section 12.8, Section 13.7
Updated information in the Summary of Clinical Experience		Section 5.1.4
Clarified what are approved methods of contraception.		Section 9.1.1
Nine new exclusion criteria were added.		Synopsis, Section 9.2
The LDH criterion for dose increase was changed in order to allow consideration of more frequent dosing to occur after 1 instance of an LDH result of >2 × ULN.		Section 10.2.3.1
Defined baseline as the last study visit of the previous trial. Added demographics as a baseline assessment.		Synopsis, Section 3, Section 8, and Section 11.1
Adding the clarification that collected blood and/or urine samples will not be stored for future exploratory analyses		Section 11
Updated reasons for subject withdrawal and treatment discontinuation.		Section 11.7
Added a statement, similar to footnote h in Section 3, of when vital signs are to be measured in relation to dosing on Day 1.		Section 3 and Section 12.1.5
Clarified the revaccination schedule for subjects already enrolled in the study should follow the CDC guidelines.		Section 3 and Section 12.2
Updated the title of the section to more accurately reflect the current terminology regarding anti-pegcetacoplan peptide antibody instead of anti-APL2.		Section 12.6
When describing the relationship between an AE and study drug treatment or study procedures, “unknown” was removed from the list of choices.		Section 13.3

Summary of Change(s) Since Last Version of Approved Protocol		
Amendment 2	**Amendment Date** 04 May 2020	**Global**
Description of Change		**Section(s) Affected by Change**
Clarified the special procedures to follow for serious adverse events. This includes contacting the sponsor (not the medical monitor) via eCRF (not fax or email) immediately and within 24 hours of becoming aware of the event whether or not the SAEs are deemed investigational product-related. SAE reporting contact information will be provided separately and as included in the SAE report/form guidelines.		Section 13.5
Added instructions regarding breastfeeding.		Section 13.7
A new section was added to describe the role of the Data Monitoring Committee.		Section 13.8
Added a statement that in the event data will be provided to regulatory agencies for the purpose of supporting marketing authorization, the data will be either frozen or locked depending on the study completion status.		Section 14.2.2
Deleted the definition of ITT and referred to the safety population when describing all subjects who received at least one dose of pegcetacoplan in this study.		Synopsis, Section 14.2.1.2, Section 14.2.1.3, Section 14.3.2
To align with text in the synopsis the following sentence was revised: Efficacy summaries will be presented by previous study and overall.		Section 14.3.2
To align with text in the synopsis, added a reason for termination of study: If the development program for pegcetacoplan in subjects with PNH is terminated.		Section 17.6
Added Appendix 3 to reflect changes made as a result of the COVID-19 pandemic		Appendix 3
*Of note, in Amendment 1, the following laboratory assessments were removed at Visits 2 and 3 but were not captured in the Summary of Changes: PK, Anti-APL2-Ab Assay, Complement Profile, and Flow Cytometry		Section 3

Amendment 1: Summary of Changes From the Previous Version

The primary purpose of Amendment 1 was to provide for all subjects with PNH who complete an Apellis clinical study with APL-2 to be able to rollover into this long-term safety and efficacy extension study.

Updates to the protocol implemented in Amendment 1 are provided in the table below. Additions to the protocol are marked in **bold**; deletions are marked by ~~strikethrough.~~

Summary of Change(s) Since Last Version of Approved Protocol		
Amendment 1 **Version 1**	**Amendment Date** **30 July 2019**	**Global**
Description of Change		**Section(s) Affected by Change**
Non-substantial changes that did not impact content of the document have been made for grammar and clarity.		Entire document
Reference to study numbers of feeder studies was removed throughout the document to make the extension study available to all Apellis PNH APL-2 studies		Entire document
Instructions for subjects starting APL-2 in the extension study were added. **Subjects entering this extension study who were previously randomized/allocated to a non APL-2 treatment arm will start treatment with APL-2 1080 mg SC twice weekly.**		Synopsis, Section 6.2
Incidence of anti-APL2 and anti-PEG antibodies was added as a pharmacodynamic endpoint to correct previous oversight.		Synopsis, Section 7.2.4, Section 12.6
The requirement for having experienced clinical benefit from APL-2 treatment was revised to accommodate subjects who were on SOC and/or switched to APL-2 near the end of their participation in their original trial and have not yet experienced clinical benefit.		Synopsis, Section 11.1, and throughout the amendment
Schedule of Events and appropriate sections were revised to include regular immunization status checks: **Immunization status will be monitored to assess whether the subject needs primary vaccinations or boosters per protocol. In order to receive treatment with APL-2, subjects must have documented evidence of vaccination against each of the following within 2 years of screening: *Neisseria meningitidis* types A, C, W, Y, and B (administered as 2 separate vaccinations), *Streptococcus*		Section 3, Section 12.2

Summary of Change(s) Since Last Version of Approved Protocol		
Amendment 1 **Version 1**	**Amendment Date** **30 July 2019**	**Global**
Description of Change		**Section(s) Affected by Change**
***pneumoniae* (with a PCV13 or PPSV23 vaccine), and *Haemophilus influenzae* type B (Hib vaccine).** **For subjects receiving APL-2 before the start of this study who do not have documented evidence of receiving all of the above vaccinations within 2 years prior to screening or who require booster vaccinations, the required missing vaccination(s) will be administered at the Baseline visit.** **Subjects who have not previously received APL-2 treatment will receive prophylactic antibiotics for the first 4 weeks of treatment with APL-2 and will receive any required vaccination(s) 2 weeks after initiation of treatment with APL-2. If required, the *Neisseria meningitidis* booster (for both ACWY and serotype B vaccinations), and/or PPSV23 vaccination should be administered at least 8 weeks following the initial vaccination(s).** **Vaccination is mandatory, unless documented evidence exists that subjects are non-responders to vaccination (as evidenced by titers or display titer levels within acceptable local limits). The PI will discuss with the sponsor regarding individual patient circumstances.**		
Section 6 (Non-clinical Data) and Section 7 (Clinical Data) were removed as these data are updated and presented in detail in the APL-2 Investigator's Brochure.		Section 6 and Section 7 (note that for this change only the section numbers refer to the previous version of the protocol)
The following update was added to clarify the use of silica reagents in coagulation panels: **The use of silica reagents in coagulation panels should be avoided. Apellis previously conducted an investigation into prolonged activated partial thromboplastin time (aPTT) observed in subjects treated with APL-2. It was confirmed that false positive aPTT prolongation occurred when coagulation panels were performed using a Stago Analyzer and specifically silica reagents. It was determined that there was interference between the silica reagents and PEGylated APL-2, resulting in artificially prolonged aPTTs.**		Section 12.1.8
Instructions for missed dose and withdrawal from APL-2 treatment were provided: **Subjects should be instructed to take their APL-2 treatment as prescribed, and to contact the investigator immediately for guidance in the event of any missed doses. If withdrawal of APL-2 treatment is necessary, slow weaning**		Section 6.3, Section 10.2.3, and Section 11.7

Summary of Change(s) Since Last Version of Approved Protocol		
Amendment 1 **Version 1**	**Amendment Date** **30 July 2019**	**Global**
Description of Change		**Section(s) Affected by Change**
should be considered and patients should carefully be monitored for at least 8 weeks to detect serious hemolysis or other complications.		
The following section with instructions for vaccination and revaccination was added: **Vaccination and Revaccination:** **Systemic complement inhibition might predispose individuals to infections caused by encapsulated organisms, including *Streptococcus pneumoniae*, *Neisseria meningitidis* (serogroups A, C, W, Y, and B), and *Haemophilus influenzae* type B. In order to reduce this risk, vaccination against each of these organisms is mandatory, unless documented evidence exists that subjects are non-responders to vaccination.** **Subjects with PNH who participated in an APL-2 clinical trial were required to have documented evidence of vaccination against each of these organisms within 2 years of screening, or received vaccination upon initiation study treatment, as follows:** ***Neisseria meningitides* types A, C, W, Y, and B (administered as 2 separate vaccinations)** ***Streptococcus pneumoniae* (with a PCV13 or PPSV23 vaccine)** ***Haemophilus influenzae* type B (Hib vaccine)** **Those subjects requiring vaccination received Ciprofloxacin 500 mg twice daily from Week 0 to Week 2, vaccines were administered at Week 2, and antibiotic prophylaxis continued for an additional 14 days after vaccination.** **In this study, immunization status will be monitored to assess whether the subject needs primary vaccinations or boosters. In order to receive treatment with APL-2, subjects must have documented evidence of vaccination against each of the organisms listed above within 2 years of screening. Subjects receiving APL-2 before the start of this study who do not have documented evidence of receiving all of the above vaccinations within 2 years prior to screening or who require booster vaccinations will receive the required missing vaccination(s) at the Baseline visit. Subjects who have not previously received APL-2 treatment will receive prophylactic antibiotics for the first 4 weeks of treatment with APL-2 and will receive any required vaccination(s) 2 weeks after initiation of treatment with APL-2, according to the schedule described above. If required, the *Neisseria meningitidis* booster (for both**		Section 12.2

Summary of Change(s) Since Last Version of Approved Protocol		
Amendment 1 **Version 1**	**Amendment Date** **30 July 2019**	**Global**
Description of Change		**Section(s) Affected by Change**
ACWY and serotype B vaccinations), and/or PPSV23 vaccination should be administered at least 8 weeks following the initial vaccination(s). **The PI will discuss individual patient circumstances with the sponsor.**		
The definitions for severity of AEs was revised as follows: Mild: ~~Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.~~ **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: ~~Minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL*~~.**Event is sufficiently discomforting so as to limit or interfere with daily activities; may require interventional treatment (eg, febrile illness requiring oral medication).** Severe: ~~Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.Note: An experience may be severe but may not be serious, eg, severe headache).~~**Event results in significant symptoms that prevent normal daily activities; may require hospitalization or invasive intervention (eg, anemia resulting in blood transfusion).**		Section 13.4.2

Appendix 3. Changes Related to COVID-19

COVID-19 Response Overview

As a result of the COVID-19 global pandemic, Apellis issued an urgent safety measure on 26 March 2020 to safeguard the rights, welfare, and safety of Study APL2-307 subjects and investigative site staff. These measures align with current guidance issued by global regulatory health authorities in regards to the impact of COVID-19 on the management of clinical trials.

The urgent safety measures are minimum study requirements and are reflected in the Schedule of Events table below, which supersedes the Schedule of Events table sent in the original urgent safety measure communication.

In the case of natural disasters, armed conflicts, or other circumstances beyond the control of Apellis, investigators, or study subjects, these minimum study requirements may be followed as necessary in order to safeguard the rights, welfare, and safety of Study APL2-307 subjects and investigative site staff.

All assessments missed as a result of COVID-19 or other above mentioned circumstances will be noted in the source document.

Where feasible, sites should continue to follow the full schedule of assessments (based on their treatment group assignment).

Minimum Study Requirements

The following are the minimum study requirements for Study APL2-307 during the COVID-19 pandemic and should be used as guidance when the full protocol requirements cannot be conducted.

1. **Maintain** dosing schedule, considerations for escalation, and management per protocol
2. **Obtain** key safety laboratory assessments
    a. All laboratory assessments should be drawn at the frequency required by the minimized Schedule of Events (provided below).
        i. Includes (at minimum): hematology with differential, reticulocyte count, chemistry, lactate dehydrogenase, coagulation profile, and urine pregnancy test (only for women of child bearing potential)
    b. In the event that the clinical investigative site is closed or subjects are unable/unwilling to travel, subjects should be referred to a certified local laboratory that can perform the required safety testing (see Schedule of Events below). The investigator should collect the local laboratory reports, which must be redacted (eg, name and other local requirements) and added to the study records.
3. **Perform** minimal medical safety assessments
    a. If the subject is unable to have an in-person assessment, the investigator (or delegated site staff) should have a telephone and/or video contact at a frequency noted in the protocol (at minimum) to solicit adverse events (including SAEs),

transfusion requirements and concomitant medications. The appropriate forms in the electronic case report form should be completed.

b. All serious adverse events are still required to be reported to Apellis immediately and within 24 hours of the investigator becoming aware.

4. **Document** appropriate contact with the subject
    a. Earnest and reasonable attempts must be made to solicit adverse events and concomitant medications. The CRA/medical monitor must be notified of any subjects lost to follow-up.
    b. All communication with the subject (including failed attempts at contact) must be documented in the study records.
5. Remote monitoring measures may be implemented with subjects' consent, in accordance with local and institutional guidelines. On-site monitoring should resume when it is practical to do so.

COVID-19 Schedule Of Events

Sites are encouraged to complete the full assessment schedule to whatever extent possible, per the protocol, if it is safe to do so.

Study Week	**0**	**2[a]**	**4**	**12**	**24**	**36**	**≥48[b]**	**Exit**
Study Day	**1**	**15**	**29**	**85**	**169**	**253**	**≥337**	**--**
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Exit**
Study Window (± Days)	**—**	**4**	**4**	**7**	**7**	**7**	**7**	**8 weeks from last dose**
Informed consent	X							
Document antecedent study information[c]	X							
Vaccination/vaccination booster[d]	X	~~X~~	X	~~X~~	X	~~X~~	X	
Preventive antibiotic[e]	X	~~X~~	X	~~X~~	X	~~X~~	X	X
Physical examination[f]	X				X		X[f]	X
Medical history	X							
Demographics	X							
Height and weight[g]	X			~~X~~	~~X~~	~~X~~	~~X~~	~~X~~
12-lead electrocardiogram	X		X	~~X~~	X	~~X~~	X	X
Pegcetacoplan administration[h]	X	X	X	X	X	X	X	
Injection site assessment	X	~~X~~	X	~~X~~	X	~~X~~	X	~~X~~
Concomitant medications	X	X	X	X	X	X	X	X
Vital sign measurements[i]	X	~~X~~	X	~~X~~	X	~~X~~	X	X
Urinalysis	X	~~X~~	X	~~X~~	X	~~X~~	X	X
Blood tests:[j]	X	X	X	X	X	X	X	X
Pharmacokinetics	X			~~X~~	~~X~~	~~X~~	~~X~~	~~X~~
Antidrug antibodies	X			~~X~~	~~X~~	~~X~~	~~X~~	~~X~~
Lactate dehydrogenase	X	X	X	X	X	X	X	X

Study Week	**0**	**2[a]**	**4**	**12**	**24**	**36**	**≥48[b]**	**Exit**
Study Day	**1**	**15**	**29**	**85**	**169**	**253**	**≥337**	**--**
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Exit**
Study Window (± Days)	**—**	**4**	**4**	**7**	**7**	**7**	**7**	**8 weeks from last dose**
Hematology and chemistry	X	X	X	X	X	X	X	X
Coagulation profile[k]	X	X	X	X	X	X	X	X
Reticulocyte count	X	X	X	X	X	X	X	X
Haptoglobin	X	~~X~~	X	~~X~~	X	~~X~~	X	
C3 profile	X	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~
Complement profile (CH50 and AH50)	X			~~X~~	~~X~~	~~X~~	~~X~~	~~X~~
Flow cytometry for PNH/C3 deposition	X			~~X~~	~~X~~	~~X~~	~~X~~	~~X~~
Free hemoglobin	X	~~X~~	X	~~X~~	X	~~X~~	X	X
Ferritin, vitamin B_{12}, folate	X	~~X~~	X	~~X~~	X	~~X~~	X	X
Urine pregnancy test[l]	X	X	X	X	X	X	X	X
FACIT-Fatigue Scale	X	~~X~~	X	~~X~~	X	~~X~~	X	X
Adverse events	X	X	X	X	X	X	X	X

Abbreviations: AH50 = alternative pathway hemolytic activity; CH50 = classical pathway hemolytic activity; FACIT = Functional Assessment of Chronic Illness Therapy; PNH = paroxysmal nocturnal hemoglobinuria.

a. Please note that a Week 2 study visit is required only for subjects who have started or changed their pegcetacoplan dose or regimen when entering this study. Subjects who have not changed their pegcetacoplan dose or regimen will go from the baseline visit directly to the Week 4 Visit.
b. Subjects will continue to have study visits at 12-week intervals for a duration of 4 years or until pegcetacoplan development in subjects with PNH is terminated.
c. Document antecedent study number, subject identifier, and Day 1 of pegcetacoplan treatment from antecedent study.
d. Immunization status will be monitored to assess whether the subject needs primary vaccinations or boosters per protocol. In order to receive treatment with pegcetacoplan, subjects must have documented evidence of vaccination within 2 years of screening against *Neisseria meningitidis* types A, C, W, Y, and B (administered as 2 separate vaccinations), *Streptococcus pneumoniae* (with a PCV13 or PPSV23 vaccine), and *Haemophilus influenzae* type B (Hib vaccine), unless documented evidence exists that subjects are nonresponders to vaccination (as evidenced by titers or display titer levels within acceptable local limits). For subjects receiving pegcetacoplan before the start of this study who do not have documented evidence of receiving all of the above vaccinations within 2 years prior to screening or who require booster vaccinations, the required missing vaccination(s) will be administered at the baseline visit. Subjects who have not previously received pegcetacoplan treatment will receive prophylactic antibiotics for the first 4 weeks of treatment with pegcetacoplan and will receive any required vaccination(s) 2 weeks after initiation of treatment with pegcetacoplan. If required, the *Neisseria meningitidis* booster (for both ACWY and serotype B vaccinations), and/or PPSV23 vaccination should be administered at least 8 weeks following the initial vaccination(s). For the subjects who are already enrolled in this study, the revaccination schedule should be followed according to the Centers for Disease Control and

Prevention guidelines, which can be found on the following website: https://www.cdc.gov/vaccines/schedules/hcp/imz/adult-conditions.html. The principal investigator will discuss with the sponsor regarding individual subject circumstances.

e. Prophylactic antibiotic therapy should be considered in order to minimize potential infection risk. Prophylactic antibiotic therapy should be administered at the discretion of the treating investigator in accordance with local treatment guidelines for subjects with PNH who are receiving treatment with a complement inhibitor. Subjects in receipt of prophylactic antibiotic therapy from their previous study may remain on the treatment they are receiving at the time of entry in this extension study.
f. Following the Week 48 visit, physical examinations should be conducted in 24-week intervals (every other visit).
g. Body height (cm) will be measured at the baseline visit. Body weight (kg) will be measured at 12-week intervals.
h. Subjects who have not changed their pegcetacoplan dose or regimen from the antecedent study must dose with the antecedent study labeled drug at the baseline visit and then commence dosing with APL2-307 labeled drug at their next scheduled dosing.
i. Vital signs will be measured before venipuncture and electrocardiogram. Monitoring of vital signs will occur at Visit 1 (Day 1) before dosing and 2 hours after dosing (±30 minutes). At all other visits, if the subject elects to administer pegcetacoplan during the visit, vital signs should be measured before dosing and again 30-60 minutes after completion of dosing.
j. Blood will be taken before dosing at every scheduled visit.
k. The use of silica reagents in coagulation panels should be avoided in subjects treated with pegcetacoplan where possible as it affects the accuracy of the test results.
l. Urine pregnancy tests will be performed for women of childbearing potential only.

Note: Baseline visit = the last study visit of the previous trial.

Appendix 4. Acute Hemolysis Substudy

4.1 Acute Hemolysis Substudy

4.1.1 Rationale for the Substudy

In completed paroxysmal nocturnal hemoglobinuria (PNH) studies in the pegcetacoplan program, there have been a total of 8 subjects with events of acute hemolysis (AH). Of these, at the time of AH, 7 subjects had pegcetacoplan serum concentrations that were in the lower half of the expected range, according to modeling and simulation. The hypothesis, therefore, is that increasing pegcetacoplan exposures to a higher range will help in the immediate management of the acute AH event and that maintaining higher drug exposures will reduce future events of AH.

4.1.1.1 Substudy Dose Selection

To identify dosing regimens that could achieve an immediate increase in pegcetacoplan concentrations, simulations were performed to predict pegcetacoplan exposure following various loading dose strategies with a subsequent increase in maintenance dosing.

Dosing interventions that rapidly increase exposure among subjects in the lower exposure quartiles without exceeding safety thresholds are desired. The target for loading dose regimens is to increase exposure for subjects in the lowest 2 preintervention exposure quartiles to approximate the preintervention exposures in the next highest quartile during the intervention week (ie, postintervention exposure in subjects in Quartile 1 approximating preintervention exposure in subjects in Quartile 2, and postintervention exposure in subjects in Quartile 2 approximating preintervention exposure in subjects in Quartile 3). The simulation results demonstrated the following:

- In adult subjects at steady state on a pegcetacoplan dose of 1080 mg subcutaneously (SC) twice weekly, loading doses of 1080 mg intravenously (IV) once or 1080 mg SC every 24 hours for 3 doses followed by an increase in maintenance dose to 1080 mg SC every 3 days, rapidly increase and sustain average weekly pegcetacoplan exposure to values approximating the next highest preintervention exposure quartile.
- In adult subjects at steady state on a pegcetacoplan dose of 1080 mg SC every 3 days, loading doses of 1080 mg IV once or 1080 mg SC every 24 hours for 3 doses followed by an increase in maintenance dose to 1080 mg SC 3 times weekly rapidly increase and sustain average weekly pegcetacoplan exposure to values approximating the next highest preintervention exposure quartile.

It was confirmed that safety data of PNH subjects at the highest exposure quartile (ie, Quartile 4, the quartile with highest median trough concentration at steady state) was acceptable by reviewing the treatment-emergent adverse event (TEAE) profile for subjects in Study APL2-302 (through Week 16). The observed pegcetacoplan serum concentrations in the highest exposure quartile of Study APL2-302 (through Week 16) are similar to those of Quartile 4 of the simulated population. The overall TEAE profile of the Study APL2-302 subjects with the highest PK exposures was similar to that of the remainder of the subjects.

IV administration of pegcetacoplan will use the same acetate-buffered sorbitol formulation used for SC administration (10 mM acetate buffer, pH 5.0, containing 4.1% w/v sorbitol). In a study in healthy volunteers (Study APL2-CP-HV-401), single IV doses of pegcetacoplan up to 2300 mg were demonstrated to be safe and generally well tolerated. As for SC dosing, exposure metrics were dose proportional in the range evaluated. Median $t_{½}$, ranging from 201 to 285 hours (8.4 to 11.9 days), was similar across doses and in line with values found with SC dosing. Variability between subjects across all PK parameters was low with coefficients of variation ≤30.3% and analogous to that of SC dosing. Although the healthy volunteer study evaluated a different formulation (10 mM acetate buffer, pH 5.0, 0.9% NaCl) for IV administration than will be used in this study, the overall elimination properties of pegcetacoplan following IV administration in Study APL2-CP-HV-401 were comparable to those found following SC dosing of pegcetacoplan in sorbitol formulation. Moreover, sorbitol is an inactive ingredient in many approved marketed drugs, with a highest formula percentage of 30% w/v for intravenously administered drugs.

4.1.2 Benefit/Risk Assessment of the Substudy

4.1.2.1 Risk Assessment

The safety monitoring practices and risk assessments employed in the main protocol of this study (see Section 5.3.1) will also be closely followed in this substudy in order to ensure subjects' ongoing safety. Assessment of additional risks associated with participation in the substudy will be as follows:

During the intensive therapy portion of this substudy, SC infusions of pegcetacoplan may be administered more frequently or pegcetacoplan may be administered IV rather than via the typical SC route. Particular attention will therefore be given to assessment of IV/SC infusion/injection site and pump use safety during clinic visits, and any significant finding from the assessment will be reported as an AE (see Section 11.1.9).

Subjects should be instructed to take their pegcetacoplan treatments as prescribed and to contact the investigator immediately for guidance in the event of any missed doses.

Discontinuation of pegcetacoplan or noncompliance with the prescribed dose regimen may lead to the potential for an increased risk for serious hemolysis. Subjects entering this substudy will have had an AH event and may be continuing to experience symptoms. If withdrawal of pegcetacoplan treatment is necessary, slow weaning should be considered and subjects should carefully be monitored for at least 8 weeks to detect serious hemolysis or other complications. The sponsor's medical monitor should be contacted before interrupting or discontinuing treatment with pegcetacoplan.

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

4.1.2.2 Benefit Assessment

There is an anticipated health benefit for participants in this substudy. Increasing pegcetacoplan exposures to a higher range in this specific population may help with the immediate management of the acute hemolytic event, and maintaining higher exposures may reduce future similar events.

At the proposed intensive SC/IV and maintenance dose levels, according to performed modeling and simulation, pegcetacoplan is expected to alleviate the acute complement-mediated hemolysis, resulting in improved hemoglobin levels and reduced transfusion dependency in these subjects.

Through the control of the hemolytic condition, long-term additional benefits are expected, such as the reduction of the thromboembolitic episodes, renal dysfunction, and pulmonary hypertension associated risks.

4.1.2.3 Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to participants in this substudy, the potential risks identified in association with pegcetacoplan are justified by the anticipated benefits that may be afforded to subjects with AH.

4.1.3 Substudy Objectives and Endpoints

4.1.3.1 Substudy Objectives

The objectives of this substudy are to:

1. Evaluate the safety of intensive SC or IV pegcetacoplan dosing in subjects with PNH
2. Evaluate the effectiveness of intensive SC or IV pegcetacoplan dosing for the management of AH in subjects with PNH treated with pegcetacoplan

4.1.3.2 Substudy Endpoints

4.1.3.2.1 Safety Endpoints

- Incidence and severity of TEAEs
- Incidence of repeated acute hemolysis episodes
- Incidence of thromboembolic events
- Laboratory parameters
- Electrocardiogram (ECG) parameters

4.1.3.2.2 Efficacy Endpoints

- Absolute change from baseline (CFB) and percent CFB in lactate dehydrogenase (LDH) level from Day 1′ to Day 21′
- Absolute CFB and percentage CFB in hemoglobin level from Day 1′ to Day 21′
- Number of transfusions and number of packed red blood cell (RBC) units transfused

- Hemoglobin level during maintenance dosing
- LDH level during maintenance dosing
- Indirect bilirubin
- Absolute reticulocyte count
- Incidence of repeated AH episodes
- RBC transfusions
- Functional Assessment of Chronic Illness Therapy–Fatigue Scale score

4.1.3.2.3 Pharmacokinetic Endpoint

- Pegcetacoplan pharmacokinetic concentrations

4.1.3.2.4 Pharmacodynamic Endpoints

- Complement (eg, classical pathway hemolytic activity [CH50], alternative pathway hemolytic activity [AH50], and C3) levels
- C3 deposition on RBC cells
- Clonal distribution of PNH RBCs
- Incidence of anti–pegcetacoplan peptide and anti–polyethylene glycol antibodies

4.1.4 Substudy Design

This is an open-label, nonrandomized, multicenter substudy to evaluate the safety and efficacy of intensive pegcetacoplan dosing for the treatment of AH in subjects with PNH treated with pegcetacoplan. Eligible subjects will meet all the inclusion criteria and none of the exclusion criteria.

Subjects enrolled in Study APL2-307 who experience AH that, in the opinion of the investigator, warrants an acute intervention will be offered the opportunity to enter this substudy. The investigator should confirm subject eligibility with the medical monitor prior to enrollment in the substudy. To qualify for participation in the substudy, subjects must have LDH >2 × the upper limit of normal (ULN) and the presence of at least one new or worsening sign or symptom of hemolysis (eg, decrease in hemoglobin, hemoglobinuria, fatigue).

The first day of the substudy will be considered Day 1′. On this day, after informed consent has been obtained and predose assessments have been completed, the investigator may opt to treat the subject with either intensive SC or IV pegcetacoplan, but not both. IV pegcetacoplan will be administered in the clinic. Intensive SC doses of pegcetacoplan may be administered in clinic or self-administered by the subject (or administered by a caregiver) at home, depending on the primary investigator's assessment of the subject's clinical condition and local logistical circumstances.

Once a subject enters the substudy, they remain in the substudy, following the substudy schedule, rather than the main study. A subject may receive subsequent treatment courses for AH, as long as they meet substudy inclusion criteria prior to the start of each course and the

courses are separated by at least 14 days (starting from the day of the IV dose or the day of the last dose of the 3 intensive SC doses). Additional informed consent is not required for subsequent treatment courses after Week 16′ but subject eligibility should be confirmed with the medical monitor prior to enrollment in each treatment course. Subsequent treatment courses for AH may be either intensive SC or IV pegcetacoplan, regardless of which was used for a prior course.

After the Day 28′ visit, subjects will resume visits every 3 months, with the same assessments as planned for visits in the main APL2-307 study.

4.1.4.1 Estimated Duration of Substudy

Duration of participation in this substudy will be the remainder of the subject's 4-year participation in Study APL2-307, or until pegcetacoplan development in subjects with PNH is terminated.

4.1.5 Subject Selection

4.1.5.1 Inclusion Criteria

1. Subjects with PNH enrolled in Study APL2-307 who experience acute AH accompanied by LDH >2 × the ULN and the presence of at least one new or worsening sign or symptom of hemolysis (eg, decrease in hemoglobin, hemoglobinuria, fatigue) that, in the opinion of the investigator, warrants an acute intervention
2. Willing and able to give written informed consent
3. Willing and able to self-administer SC pegcetacoplan (administration by caregiver will be allowed)
4. Women of childbearing potential, defined as any women who have experienced menarche and who are NOT permanently sterile or postmenopausal, must have a negative pregnancy test and must agree to continue to use an approved method of contraception for the duration of the study and 90 days after their last dose of study drug. Note: *Postmenopausal* is defined as 12 consecutive months with no menses without an alternative medical cause.
5. Men must agree to continue to use an approved method of contraception and must agree to refrain from donating sperm for the duration of the study and 90 days after their last dose of study drug.

4.1.5.2 Exclusion Criteria

1. Subjects who withdrew from and/or met study drug discontinuation criteria during Study APL2-307
2. Any comorbidity or condition that, in the opinion of the investigator, could put the subject at increased risk by participating in the substudy or potentially confound the substudy data

4.1.6 Substudy Treatments

4.1.6.1 Identity of Investigational Product

The test product is pegcetacoplan, which will be provided as a sterile solution of pegcetacoplan, 54 mg/mL, in acetate buffer containing sorbitol, supplied in stoppered 20-mL glass vials. Additional information is provided in the systemic pegcetacoplan investigator's brochure.

4.1.6.2 Administration of Investigational Product

4.1.6.2.1 Interactive Response Technology (IRT) for Investigational Product Management

A centralized IRT will be utilized for (but not limited to) the following investigational product management tasks: investigational product supply management, inventory management and supply ordering, expiration tracking and return of investigational product (if applicable). Please refer to the IRT Manual for further information.

4.1.6.2.2 Allocation to Treatment

This is an open-label substudy. The investigator may opt to treat the subject with either intensive SC or IV pegcetacoplan, but not both simultaneously. A subject may receive subsequent intensive treatment courses for AH, as long as the courses are separated by at least 14 days. Subsequent treatment courses for AH may be either intensive SC or IV pegcetacoplan, regardless of which was used for a prior course.

4.1.6.2.3 Dosing

Subjects will receive pegcetacoplan according to 1 of 2 loading regimens:

- 1080 mg SC daily for 3 days (intensive SC dosing)
- One 1080 mg IV dose (administered as a bolus over approximately 30 minutes)

Intensive SC doses of pegcetacoplan may be administered in clinic or self-administered by the subject (or administered by a caregiver) at home, depending on the primary investigator's assessment of the subject's clinical condition and local logistical circumstances. Following an SC intensive therapy regimen, maintenance dosing will resume, with the timing of the first maintenance dose determined relative to the last dose of the 3 intensive SC doses. Intravenous pegcetacoplan will be administered in the clinic. Maintenance dosing will continue uninterrupted for subjects receiving an IV intensive therapy regimen, with the timing of the first maintenance dose determined relative to the previous SC dose.

Maintenance dosing after either regimen will be at the next higher dosing frequency as before the episode of AH (ie, subjects receiving 1080 mg twice weekly prior to entry into the substudy will receive maintenance dosing at 1080 mg every 3 days, and subjects receiving 1080 mg every 3 days prior to entry into the substudy will receive maintenance dosing at 1080 mg three times weekly). Maintenance dosing will not exceed 1080 mg three times weekly. On resumption of maintenance dosing, subjects should be instructed to take their pegcetacoplan treatment as prescribed and to contact the investigator immediately for guidance in the event of any missed doses. It is not necessary that dosing align with clinic visits, and subjects should not delay or

defer dosing. If withdrawal of pegcetacoplan treatment is necessary, slow weaning should be considered and subjects should carefully be monitored for at least 8 weeks to detect serious hemolysis or other complications.

4.1.6.2.4 Maintenance Dose Adjustment

Following resumption of maintenance dosing with pegcetacoplan, LDH will be monitored as part of the scheduled assessments at the planned clinic visits. If LDH is >2 × the ULN on 1 occasion, an increase in the frequency of pegcetacoplan dosing should be considered. Any adjustment in dose will be discussed and confirmed, in writing, by Apellis. In the event of a dose increase, LDH will be monitored biweekly (unscheduled assessments, if applicable) for at least 4 weeks to assess the impact of the dose adjustment on LDH levels.

4.1.6.2.5 Investigational Product Administration

Pegcetacoplan will be administered as a 20 mL infusion. During the intensive therapy regimen, the infusion will be either SC or IV; once maintenance dosing has resumed, the infusion will be SC.

IV dosing will be administered as an infusion over ~30 minutes.

The preferred site of SC infusions will be the abdomen; however, if a subject does not tolerate administration into the abdomen, alternative appropriate sites may be considered. Subjects will have qualified to self-administer injections as a part of Study APL2-307. At the study site, subjects may self-administer or pegcetacoplan may be administered by the subject's caregiver or trained study personnel. Self-administration conducted at the clinic will be supervised to ensure that the subject continues to remain compliant with the administration guidelines.

4.1.6.3 Labeling, Packaging, Storage, and Handling

Labeling, packaging, storage, and handling of clinical supplies for the substudy will follow the practices described in Section 9.3.

4.1.6.4 Investigational Product Accountability

Investigational product accountability for the substudy will follow the practices described in Section 9.4.

4.1.6.5 Subject Compliance

Compliance will be monitored throughout the substudy and will be recorded on the drug accountability form by the pharmacist/nominated person, as described in Section 9.5.

4.1.6.6 Concomitant Medications

The use of concomitant medications by subjects in the substudy will follow the restrictions and guidance described in Section 9.6.

4.1.7 Substudy Procedures

Please see the Schedule of Events in Section 4.1.13 for a summary of the schedule of substudy activities and procedures.

At each clinic visit, activities should be performed in the following order:

- Functional Assessment of Chronic Illness Therapy–Fatigue Scale questionnaire and any other participant-recorded activity
- Solicited collection of information (eg, review of medical history, concomitant medications, and/or adverse events)
- Noninvasive procedures (eg, physical exam, recording of vital signs)
- ECG
- Collection of blood and/or urine samples (eg, for clinical laboratory tests and/or PK or other analyses; samples will not be stored for future exploratory analyses)
- Dosing with prophylactic antibiotics, pegcetacoplan, or other medications
- Evaluation of infusion site and infusion pump safety

Subjects who withdraw from the substudy will need to be monitored closely according to local practice with respect to any hemolysis that is experienced following withdrawal of pegcetacoplan.

Following Visit 6, visits will continue at 12-week intervals and should follow the procedures described in Section 10.4.

4.1.8 Treatment Discontinuation and Withdrawal from the Substudy

Subject participation in this substudy may be discontinued and subjects may be withdrawn from the substudy as described in Section 10.7.

4.1.9 Assessments

Assessments to be performed during the substudy will follow the procedures described in Section 11.

4.1.10 Safety Data Collection, Recording, and Reporting

Safety data collection, recording, and reporting for the substudy will follow the practices outlined in Section 12.

4.1.11 Statistics

Statistical analyses for this AH substudy will be similar to those shown in Section 13 of the main protocol (where applicable) except that the summary will be presented by the route of administration and overall.

Upon receipt of either intensive SC or IV pegcetacoplan therapy (Day 1′), a subject enters the substudy, and all data for that subject from that point forward will be analyzed only within the substudy, rather than the core APL2-307 study. Data for that subject prior to Day 1′ will remain within the core APL2-307 study.

4.1.11.1 Populations for Analysis

4.1.11.1.1 Safety Population

The safety population will include all subjects who enroll and receive at least one dose of pegcetacoplan.

4.1.11.1.2 Efficacy

Efficacy analyses will be performed using the ITT population. Absolute values and changes from baseline will be summarized by visit using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). Changes from baseline will also be summarized categorically by visit. The number and percentage of subjects who have met specific levels related to the reference range (eg, hemoglobin level ≥ the lower limit of normal) will be tabulated by visit. In addition, percent CFB will be summarized, and the number and percentage of subjects with transfusion avoidance will also be summarized and presented in table along with the number of units transfused.

4.1.11.1.3 Safety

Medical data coding of the verbatim terms provided by the investigators for AEs and concomitant medications will be performed using the Medical Dictionary for Regulatory Activities and the World Health Organization Drug Dictionary, respectively.

Safety data analyses (laboratory test, ECG, and vital signs) will be performed using the safety population. Continuous data will be summarized using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum), and categorical data will be summarized using counts and percentages.

4.1.11.1.4 Pharmacokinetic Analyses

The PK concentrations will be evaluated using the PK population.

Concentrations will be summarized by visit.

Population pharmacokinetic and exposure-response modeling of the safety and efficacy data will be described in a pegcetacoplan population pharmacokinetic/pharmacodynamic analysis plan. The methods will be based on the Food and Drug Administration *Guidance for Industry: Exposure-Response Relationships—Study Design, Data Analysis, and Regulatory Applications* (Center for Drug Evaluation and Research, April 2003) and *Guidance for Industry: Population Pharmacokinetics* (Center for Drug Evaluation and Research, February 2019).

4.1.11.1.5 Pharmacodynamic Analyses

The PD endpoints will be evaluated using the PD population.

Absolute values and percentage of baseline will be summarized by visit for AH50 and CH50. For C3, absolute values will be summarized by visit.

4.1.11.1.6 Interim Analysis

No formal interim analyses are planned. The data from this substudy may be reported at different times for specific reasons; eg, providing data to a regulatory agency.

4.1.12 Ethical and Administrative Considerations

Ethical and administrative considerations for the substudy will follow the practices outlined in Section 14, Section 15, Section 16, Section 17, and Section 18.

4.1.13 Substudy Schedule of Events

Substudy Week	**1′**	**1′**	**1′**	**2′**	**3′**	**4′**	**≥16′[a]**	**Exit**
Substudy Day	**1′**	**2′**	**7′**	**14′**	**21′**	**28′**	**≥112′**	**--**
Substudy Visit	**1′**	**2′**	**3′**	**4′**	**5′**	**6′**	**≥7′**	**Exit**
Visit Window (± Days)	**0**	**0**	**4**	**4**	**4**	**4**	**7**	**8 weeks from last dose**
Informed consent	X							
Document vaccination/vaccination booster[b]	X						X	
Preventive antibiotic[c]	X	X	X	X	X	X	X	X
Physical examination[d]	X						X[d]	X
Medical history	X							
Demographics	X							
Height and weight[e]	X					X	X	X
12-lead electrocardiogram	X	X	X	X			X	X
Pegcetacoplan administration	X	X	X	X	X	X	X	
Injection site assessment	X	X	X	X	X	X	X	X
Concomitant medications	X	X					X	X
Vital sign measurements[f]	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X
Blood tests:[g]								
Pharmacokinetics	X	X	X	X	X	X	X	X
Antidrug antibodies	X						X	X
Lactate dehydrogenase	X	X	X	X	X	X	X	X
Hematology and chemistry	X	X	X	X	X	X	X	X
Coagulation profile[h]	X	X	X	X	X	X	X	X
Reticulocyte count	X	X	X	X	X	X	X	X
Haptoglobin	X	X	X	X	X	X	X	

Substudy Week	**1′**	**1′**	**1′**	**2′**	**3′**	**4′**	**≥16′[a]**	**Exit**
Substudy Day	**1′**	**2′**	**7′**	**14′**	**21′**	**28′**	**≥112′**	**--**
Substudy Visit	**1′**	**2′**	**3′**	**4′**	**5′**	**6′**	**≥7′**	**Exit**
Visit Window (± Days)	**0**	**0**	**4**	**4**	**4**	**4**	**7**	**8 weeks from last dose**
C3 profile	X	X	X	X	X	X	X	X
Complement profile (CH50 and AH50)	X	X	X	X	X	X	X	X
Flow cytometry for PNH/C3 deposition	X						X	X
Free hemoglobin	X						X	X
Ferritin, vitamin B_{12}, folate	X						X	X
Urine pregnancy test[i]	X	X	X	X	X	X	X	X
FACIT-Fatigue Scale	X			X		X	X	X
Adverse events[j]	X	X	X	X	X	X	X	X

Abbreviations: AH50 = alternative pathway hemolytic activity; CH50 = classical pathway hemolytic activity; COVID-19 = coronavirus disease 2019; FACIT = Functional Assessment of Chronic Illness Therapy; PNH = paroxysmal nocturnal hemoglobinuria.

a. Subjects will continue to have visits at 12-week intervals for a total duration of 4 years in Study APL2-307 and this substudy, or until pegcetacoplan development in subjects with PNH is terminated.
b. Immunization status against *Neisseria meningitidis* types A, C, W, Y, and B, *Streptococcus pneumoniae*, and *Haemophilus influenzae* type B will be monitored to assess whether the subject needs primary vaccinations or boosters per protocol. Documented evidence of vaccination against these organisms within 2 years of screening is a requirement for participation in Study APL2-307, unless documented evidence exists that subjects are nonresponders to vaccination; immunization status will be reviewed on entry into the acute hemolysis substudy and subjects will receive any required booster vaccinations, according to the Centers for Disease Control and Prevention guidelines (found at https://www.cdc.gov/vaccines/schedules/hcp/imz/adult-conditions.html). The investigator will discuss with the sponsor regarding individual subject circumstances.
c. Prophylactic antibiotic therapy should be considered in order to minimize potential infection risk. Prophylactic antibiotic therapy should be administered at the discretion of the treating investigator in accordance with local treatment guidelines for subjects with PNH who are receiving treatment with a complement inhibitor. Subjects in receipt of prophylactic antibiotic therapy from their previous study may remain on the treatment they are receiving at the time of entry in this substudy.
d. Following the Week 16′ visit, physical examinations should be conducted at 24-week intervals (every other visit).
e. Body height (cm) will be measured at the first substudy visit. Following the Week 16′ visit, body weight should be recorded at 12-week intervals.
f. Vital signs will be measured before venipuncture and electrocardiogram. Monitoring of vital signs will occur at Visit 1 (Day 1) before dosing and 2 hours after dosing (±30 minutes). At all other visits, if the subject elects to administer pegcetacoplan during the visit, vital signs should be measured before dosing and again 30-60 minutes after completion of dosing.
g. Blood will be taken before dosing at every scheduled visit.
h. The use of silica reagents in coagulation panels should be avoided in subjects treated with pegcetacoplan as it affects the accuracy of the test results.
i. Urine pregnancy tests will be performed for women of childbearing potential only.
j. Consider testing for COVID-19 if subjects experience symptoms suggestive of COVID-19 and/or acute hemolysis. If performed, the test results must be documented in the electronic case report form.