COVER PAGE

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STATISTICAL ANALYSIS PLAN

PEGCETACOPLAN (APL-2)
PHASE 3 EXTENSION

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

PROTOCOL IDENTIFIER: APL2-307

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REVISION HISTORY

Version	Issue Date	Summary of Changes
1.0	16Jul2021	New Document
2.0	20Oct2021	• Clarified calculation of total number of expected infusions for Measurements of Treatment Compliance (Section 5.7) • Updated summary of transfusion section; Added transfusion avoidance analysis, transfusion free overtime analysis; updated acute hemolysis definition; added breakthrough hemolysis analysis per 302/308; added acute hemolysis based on AE events; Added APPENDICES 17.4: AE Reporting Terms for Acute Hemolysis (Section 6.1) • Added summary items of exposure adjusted incidence rate of AE, and AE related and SAE related to study drug; Defined calculation of exposure adjusted incidence rate; Updated summary of AEs and TEAE definition (Section 7.1) • Added APPENDICES17.3: Algorithm for Standardizing Local Lab Values with Different Normal Ranges (Section 7.2) • Corrected calculation formulation of C3d deposition on RBC cells (percent Type II + III) (Section 9) • Added ADA data analysis section (Section 10) • Added necessary abbreviations; Corrected wordings, typos across whole documentation
3.0	October 7 2025	• Removed substudy-related content from each section and added a section dedicated to the substudy; Updated analysis for PK, PD, ADA sections. • Added Section 14. Database Lock Strategy for CSR

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ABBREVIATIONS

ADA	Anti-drug Antibodies
AE	Adverse event
AH	Acute hemolysis
AH50	Alternative pathway hemolytic activity
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
ARC	Absolute reticulocyte count
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Class
BLQ	Below the limit of Quantitation
C3	Complement Component 3
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
FDA	Unites States Foods and Drug Administration
GGT	Gamma Glutamyl Transferase
Hb	Hemoglobin
Hib	Haemophilus influenzae Type B (vaccine)
ITT	Intent-to-Treat
IV	Intravenous
Kg	Kilogram(s)
LDH	Lactate dehydrogenase
LDPRC	Leukocyte-depleted red blood cell
LLN	Lower Limit of Normal
MedDRA®	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
mL	Milliliter(s)
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PNH	Paroxysmal Nocturnal Hemoglobinuria
PRBCs	Transfusions of Packed Red Blood Cells
QTc	Heart-rate corrected QT interval
QTcF	QT interval corrected for heart rate using the Fridericia formula
RBC	Red blood cell
SAP	Statistical Analysis Plan
SE	Standard Error
SC	Subcutaneous
SI	International System of Units
SMQ	Standardized MedDRA Queries
TEAE	Treatment-emergent adverse event
ULN	Upper Limit of Normal

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1. INTRODUCTION

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of efficacy, safety and pharmacokinetic (PK)/pharmacodynamic (PD) data as described in the final study protocol version 1.0 dated 11 Apr 2018 incorporating most recent amendment # 3 (16 Dec 2020) and amendment #4 (20 July 2022).

This SAP includes the main study, with the substudy presented separately in Section 12, as outlined in Appendix 4 of the protocol.

Specifications for tables, figures, and listings are contained in a separate document. Details in this SAP take precedence over those provided in the statistical section of the protocol.

2. OBJECTIVES AND ENDPOINTS FOR MAIN STUDY

2.1 Objectives

The objectives are to:

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

2.2 Endpoints

2.2.1 Safety Endpoints

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

2.2.2 Efficacy Endpoints

- Hemoglobin level
- Lactate dehydrogenase (LDH) level
- Absolute reticulocyte count (ARC)
- Indirect bilirubin level
- Packed red blood cell (PRBC) transfusions
- Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue scale score

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2.2.3 Pharmacokinetic Endpoints

- Pegcetacoplan pharmacokinetic concentrations

2.2.4 Pharmacodynamics Endpoints

- Complement (e.g., 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

3. STUDY DESIGN FOR MAIN STUDY

3.1 General Description

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 trials must be the first (baseline) study visit of this trial. Antecedent studies include Phase 1b studies APL-CP0514 and APL2-CP-PNH-204 and Phase 2a study APL2-202 and Phase 3 studies APL2-302 and APL2-308. All studies are completed.

3.2 Randomization and Blinding

This is an open-label, single-arm study. All participants will receive pegcetacoplan; no randomization or blinding is used.

3.3 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.

4. STATISTICAL ANALYSIS SETS FOR MAIN STUDY

4.1 Screened Set

The Screened Set will include all subjects who have signed informed consent.

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4.2 Safety Set/Intent-to-Treat Set

The Safety Set will include all subjects who receive at least 1 dose of pegcetacoplan. The intent-to-treat (ITT) set will be identical to the Safety Set for main study.

4.3 Pharmacokinetic Set

The Pharmacokinetic (PK) Set will include all subjects in the ITT set who have at least 1 evaluable PK measurement after the first dose. Participants will be analyzed according to the treatment received.

4.4 Pharmacodynamic Set

The Pharmacodynamic (PD) Set will include all subjects in the ITT set who have at least 1 evaluable PD measurement after the first dose. Participants will be analyzed according to the treatment received.

5. STUDY SUBJECTS FOR MAIN STUDY

5.1 Disposition of Subjects

For the Safety Set, the following will be presented overall:

- Number and percentage of subjects who received at least one dose of treatment
- Number and percentage of subjects who completed study
- Number and percentage of subjects who discontinued study

For those subjects who have discontinued, the reason for discontinuation will be summarized.

Subjects who have finished all visits in the main study and also did not participate in the substudy are considered as completed the main study. If the subject still needs treatment after the study, it will be counted as 'Changed to Commercial Product' in the discontinued category.

For those who have completed the study will be summarized as number and percentage of subjects.

Subject data listings with disposition will be provided as well as a listing of subjects who did not satisfy the inclusion/exclusion criteria.

The number of subjects in each analysis set will be tabulated by antecedent study and overall and by country or region (North America, Europe, Asia Pacific, Latin America) and will be presented in a listing.

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5.2 Demographic and Other Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics for the main study will be presented overall for the Safety Set.

Demographic and other baseline characteristics are collected at the Day 1 assessment of Study 307. If Day 1 assessments are missing, non-missing assessments from the most recent visit in the antecedent study, conducted within 60 days prior to Day 1, will be used.

Demographic variables to be presented include age (years), age category (<65 years, >=65 - <75 years, >=75 - <85 years, and ≥85 years), sex, race, ethnicity, country, weight (kg), weight category (<70 kg, ≥70 - ≤90 kg, >90 kg), height (cm), BMI (kg/m^2), and BMI category (<18.5, ≥18.5 - <25, ≥25 - <30, ≥30 - < 35, ≥ 35 kg/m^2).

As date of birth may not be recorded for all subjects, the age recorded on the eCRF will be used for analyses. The following formula will be used if the date of birth was reported, and the age was not recorded on the eCRF:

Age (years) = (date of informed consent – date of birth + 1)/365.25.

Baseline characteristics to be presented include the following:

- Time since diagnosis of PNH (years) to Day 1
- Hemoglobin level (Hb) at baseline
- Absolute Reticulocyte count (ARC) at baseline
- LDH level at baseline
- FACIT-Fatigue score at baseline
- Indirect bilirubin level at baseline
- Complement profile (C3, CH50, and AH50) at baseline
- C3 Deposition on RBC cells at baseline
- PNH granulocytes at baseline
- PNH monocytes at baseline
- Vaccination status (including *Streptococcus pneumoniae*, *Neisseria meningitidis* (serogroups A, C, W, Y, and B), and *Haemophilus influenzae* type B).

5.3 Medical History

Medical history will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA®). The medical history will be summarized by System Organ Class (SOC) and Preferred Term (PT) with numbers and percentages for the Safety Set. Each subject will be counted only once in each SOC or SOC/PT summary.

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All medical history and AEs including ongoing AEs from the antecedent study will be mapped into APL2-307 medical history in main study.

In the summary table, medical history will be presented by decreasing frequency of subjects overall within each SOC and then similarly by decreasing frequency of subjects overall within each PT. In cases of SOCs or PTs with equal frequencies, medical history will be sorted alphabetically.

5.4 Prior Therapies, Procedures and Medication

WHO Drug Dictionary (version March 2021) will be used to classify prior medications by preferred term or therapeutic class. Prior medication is defined as any medication with the start date prior to the date of the first dose of investigational product. All concomitant therapies, procedures and medications started from the antecedent study and ended before APL2-307 first dose will be mapped into APL2-307 as prior therapies, procedures, and medication in main study.

Medication will be presented by ATC level 2 (therapeutic main group) and preferred name (active ingredient) with numbers and percentages for the Safety Set. A subject who takes more than one medication will be counted only once if these medications belong to the same extended ATC classification.

In the summary tables, prior medication and concomitant medications will be presented by decreasing frequency of subjects overall within each ATC level 2 class and then similarly by decreasing frequency of subjects overall within each preferred name. In cases of ATC level 2 classes or preferred names with equal frequencies, medications will be sorted alphabetically.

Prior therapies and procedures will be presented like those of prior medications detailed above.

All prior therapies, procedures and medications will be listed for the Safety Set.

5.5 Concomitant Therapies, Procedures and Medications

The WHO Drug Dictionary version (March 2021) will be used to classify concomitant medications by preferred term or therapeutic class. Concomitant medication is defined as any medication with a start date prior to the date of the first dose of investigational product in this study and continuing after the first dose of investigational product or with a start date between the dates of the first and last doses of investigational product, inclusive. Any medication with a start date after the date of the last dose of investigational product will not be considered a concomitant medication.

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The concomitant medication usage will be summarized by the number and proportion of subjects receiving each medication within each preferred term for the Safety Set. Multiple medication usage by a subject in the same category will be counted only once.

Concomitant therapies and procedures will be presented similarly to those of concomitant medications detailed above.

All concomitant therapies, procedures and medications will be listed for the Safety Set.

5.6 Exposure to Investigational Product

Study drug exposure is calculated from first dose in 307 for main study. The following parameters will be calculated and presented:

- Last dose frequency at antecedent study
- First dose frequency in main study
- Subjects who received infusions
- Number of infusions for each subject
- Total dose administered (mg)
- Maximum dose frequency
- Duration of Treatment (days)
- Number and percentage of subjects who received at least one infusion
    - Number and percentage of subjects with all infusions completed
    - Number and percentage of subjects with incomplete dosing due to infusion interruption
    - Number and percentage of subjects with incomplete dosing not due to infusion interruption
    - Number and percentage of subjects with any infusions interrupted
    - Number and percentage of subjects with any missed doses
    - Number and percentage of subjects who received study drug by infusion period
        - Number and percentage of subjects who received study drug infusion <16 weeks
        - Number and percentage of subjects who received study drug infusion ≥16 - ≤26 weeks
        - Number and percentage of subjects who received study drug infusion >26 - ≤48 weeks
        - Number and percentage of subjects who received study drug infusion >48 - ≤96 weeks

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- Number and percentage of subjects who received study drug infusion >96 -≤144 weeks
- Number and percentage of subjects who received study drug infusion >144 weeks

- Total number of infusions
  - Number and percentage of infusions completed
  - Number and percentage of infusions incompleted
  - Number and percentage of infusions interrupted

A comparison will be made between subjects' initial dosing regimen and their highest dosing frequency during the study.

Listings of change of dose frequency as well as start date of the highest dose frequency will also be provided.

The number of injections or infusions for each subject will be summarized using descriptive statistics in the main study.

5.7 Measurements of Treatment Compliance

Percent compliance will be calculated for the Safety Set of the main study as follows:

> Percent compliance = total number of study injections taken from Day 1 to end of the main study / total number of expected injections to end of the main study.

The end of the main study is defined as the day prior to the first substudy drug infusion or, for subjects who are not enrolled in the substudy, as the last dose date of the main study. The total number of expected infusions will be based on the subject's actual planned dosing frequency during the main study treatment period.

Subjects enrolled in this study will receive pegcetacoplan 1080 mg subcutaneously (SC) either twice weekly or every 3 days. During the study, subjects may increase their dosing frequency to either 1080 mg SC every 3 days or 1080 mg SC three times weekly.

For the calculation of percent compliance, the actual planned dosing frequency during the treatment period will be used to determine the total number of expected injections up to the end of the study. Since dosing frequency may vary, different formulas will be applied as follows:

- **Twice-weekly dosing:**
  Percent compliance = Actual number of doses divided by {[(last dose date-first dose date +3.5)/7] x 2}

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- **Every 3 days dosing:**
  Percent compliance = Actual number of doses divided by [(last dose date-first dose date)/3 +1]

- **Three times weekly dosing:**
  Percent compliance = Actual number of doses divided by [(last dose date-first dose date +2.3)/7] x 3}

The number and percentage of subjects who had a percentage of drug compliance (< 80%, ≥ 80% - 120%, and > 120%) will then be presented in a table.

Listening by subjects will be produced for treatment compliance and exposure.

5.8 Protocol Deviations

All protocol deviations will be reviewed and documented before the database lock. Protocol deviations are being captured in accordance with the Protocol Deviation Plan.

Major protocol deviations include any enrollment not in adherence with inclusion and exclusion criteria and on-study violations which may have an impact on subject safety, or the data interpretation, such as taking prohibited medication.

The CRO assigned by Apellis will classify major and minor protocol deviations per the agreed protocol deviation management plan. The Apellis study team will review the protocol deviations and their classification throughout the study and before data cut/database lock.

6. EFFICACY ANALYSES FOR MAIN STUDY

Efficacy analysis will be performed using the ITT set. Absolute values and changes from baseline (CFB) for treatment period will be summarized by visit using descriptive statistics (e.g., n, mean, standard deviation, median, Q1, Q3, minimum and maximum). The number and percentages of categorical endpoints for the treatment period will also be summarized in tables by visit. In addition, percent CFB will also be summarized, and the number and percentage of subjects with transfusion avoidance (TA) will also be summarized and presented in table along with the number of units transfused. Efficacy summaries for the main study will be presented overall.

6.1 Analyses of Efficacy Endpoints

The absolute values and changes from baseline for each of the following efficacy endpoints will be listed and summarized by study visit.

- Hemoglobin level (Hb)

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- Lactate dehydrogenase level (LDH)
- Indirect bilirubin level
- Total bilirubin level (Bili)
- Absolute reticulocyte count (ARC)
- Platelet Count
- FACIT-Fatigue scale score.

The number and percentage of subjects meeting the following criteria in absence of on-study transfusion will be tabulated (Yes/No) for each visit. Subjects who have a transfusion will be considered as not meeting the following criteria for the following visits until the end of study.

- Hb normalization (≥ 1 x Lower Limit of Normal (LLN)) per gender specified criteria
- Hb normalization defined as >12 g/dL
- ARC normalization (< 1 x Upper Limit of Normal (ULN))
- LDH normalization (≤ 1 x ULN)
- Total bilirubin normalization (≤ 1 x ULN)

Hemoglobin (Hb) level will also be categorized as increase from baseline (<0 g/dL, >=0 - < 1.0 g/dL, ≥1.0 - < 2.0 g/dL and ≥ 2 g/dL) and the number and percentages will be presented and summarized in a table.

Transfusions from antecedent studies and 6 months before enrollment of 307 will be mapped into APL2-307 as transfusions history.

Number of PRBC transfusions, number of PBRC transfusion units and the number and percentage of subjects who receive at least one transfusion will be presented by study periods (such as 0-3 months, 3-6 months, and every 6 months later on until data cutoff date or end of study). The number of PRBC is reported in units and mL in the database, therefore, the mL will be converted to units using the following formula:

Number of PRBC units = round((PRBC (mL) / 300), 1).

Where PRBC transfusion consists of PRBCs, LDPRC and all types of RBC transfusions.

The number and percentage of subjects who have transfusion avoidance (Yes) and who do not have transfusion avoidance (No) will be summarized.

Transfusion avoidance (Yes) is defined as subjects who do not require a transfusion during treatment period up to data cutoff date or end of study.

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Transfusion avoidance (No) is defined as subjects who require transfusion or prematurely withdraw study. Subjects transferred to commercial study drug use are not considered as prematurely withdraw study and will not be counted into transfusion avoidance (No). Number of PRBC units transfused and number of PRBC transfusions occurred will also be summarized for those who require transfusion.

The percentage of transfusion-free subjects over time will be summarized for each prespecified study period: 0–3 months, 3–6 months, and every 6-month interval thereafter up to 42 months. Transfusion-free subjects are those who have no transfusion in each study period. Percentage is based on the number of subjects who stay in the study for at least the lower bound of the time interval defined in study periods.

The number and percentage of subjects with incidence of acute hemolysis (AH), which is defined as subjects with LDH >2 × ULN and the presence of at least one new or worsening sign or symptom of hemolysis (such as fatigue; hemoglobinuria; abdominal pain; shortness of breath [dyspnea]; anemia [Hb <10 g/dL]; major adverse vascular events (MAVE), including thrombosis; dysphagia; or erectile dysfunction), warranting acute intervention in the opinion of the investigator, will be summarized.

The number and percentage of subjects with breakthrough hemolysis (BTH) will be summarized. BTH is defined as at least 1 new or worsening symptom or sign of intravascular hemolysis (fatigue; hemoglobinuria; abdominal pain; shortness of breath [dyspnea]; anemia [Hb <10 g/dL]; major adverse vascular events (MAVE), including thrombosis; dysphagia; or erectile dysfunction) in the presence of elevated LDH ≥2 x ULN, after prior LDH reduction to <1.5 x ULN on therapy.

For subjects who received a transfusion, all collected data will be included in the other efficacy summaries.

The presence of acute hemolysis/breakthrough hemolysis/acute hemolysis based on AE reporting terms will also be summarized. Detail AE reporting terms are in APPENDICES 17.4.

6. SAFETY ANALYSIS FOR MAIN STUDY

The safety analysis will be conducted using the Safety Set. Safety variables include AEs, clinical laboratory variables, vital signs, ECG variables, and physical exam. For blood tests defined in protocol amendment 3, value collected at day 1 of pegcetacoplan dose will be used as baseline, for other safety values if there is no pre-dose assessment at day 1, the value collected in the last study visit of the previous trial within 60 days of day 1 will be used as baseline for all analyses of that safety variable.

All safety analyses for the main study will be presented overall.

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7.1 Adverse Events

Adverse events will be coded using the most recent version of MedDRA®.

An AE (classified by preferred term) that occurs during the study will be considered a TEAE if it has a start date on or after the first dose of investigational product or if it has a start date before the date of the first dose of investigational product but increases in severity on or after the date of the first dose of investigational product. If more than 1 AE with the same preferred term is reported before the date of the first dose, then the AE with the greatest severity will be used as the benchmark for comparison to the AEs occurring during the study under the preferred term. An AE that occurs more than 8 weeks after the last dose of study will not be counted as a TEAE.

An overall summary with the number and percentage of subjects, total events, and total unique events who have the following will be tabulated:

- Overall summary of AEs:
  - Any AE
  - Any AE considered related to study medication
  - Any AE considered related to injection site
  - Any AE considered severe
  - Any Serious AE
  - Any Serious AE considered related to study medication
  - Any AE leading to study drug dosing interruption
  - Any AE leading to study drug discontinuation
  - Any AE leading to study drug dose change
  - Any AE leading to study discontinuation
  - Any AE leading to death
  - Any treatment emergent infections
  - Any treatment emergent infections related to study medication
  - Any serious treatment emergent infections
  - Any serious treatment emergent infections related to study medication
  - Any AEs of special search category (Hemolytic Disorders, Hypersensitivity, Sepsis, Infections, Thrombosis)
  - Any AEs and SAEs related to injection site reaction
- Summary of Exposure Adjusted incidence rate of AEs and SAEs by System Organ Class (SOC) and Preferred Term (PT)
- Summary of Exposure Adjusted incidence rate of AEs and SAE related to study drug by System Organ Class (SOC) and Preferred Term (PT)
- Summary of AEs by System Organ Class (SOC) and Preferred Term (PT)
- Summary of AEs by Preferred Term
- Summary of AEs Reported by 5% or More Subjects by SOC and PT
- Summary of AEs Related to Study Medication by SOC and PT

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- Summary of Serious AEs by SOC and PT
- Summary of Serious AEs by PT
- Summary of Serious AEs Related to Study Medication by SOC and PT
- Summary of AEs leading to study drug dosing interruption by SOC and PT
- Summary of AEs leading to study drug discontinuation by SOC and PT
- Summary of AEs leading to study drug dose change by SOC and PT
- Summary of AEs leading to study discontinuation by SOC and PT
- Summary of AEs leading to death by SOC and PT. AEs leading to death are those events with outcome recorded as "Fatal" on the Adverse Events page of the eCRF.
- Summary of AEs by Maximum Severity, SOC and PT. Severity is classified as mild/moderate/severe. AEs starting after the first dose of study medication with a missing severity will be classified as severe. If a subject reports an AE more than once within an SOC/PT, the AE with the worst-case severity will be used in the corresponding severity summaries.
- Summary of AEs Related to Study Medication by Maximum Severity, SOC and PT
- Summary AEs and SAEs related to injection site reaction
- Summary AEs of special search category (Hemolytic Disorders, Hypersensitivity, Sepsis, Infections, Thrombosis)

  Special search category:
  - Hemolytic Disorders: SMQ (narrow)- Haemolytic disorders
  - Hypersensitivity: SMQ (narrow)- Hypersensitivity
  - Sepsis: SMQ (narrow)-Sepsis
  - Infections: SOC-infections and infestations
  - Thrombosis: HLGT- Embolism and thrombosis

The number and percentage of subjects reporting AEs will be tabulated by system organ class (SOC) and preferred term, by SOC, preferred term, and maximum severity. AEs considered related to investigational product will also be summarized by SOC and preferred term. If more than 1 AE occurs with the same preferred term for the same subject, then the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to investigational product.

All summaries will be ordered by descending frequency of subjects within each SOC and then similarly by decreasing frequency of subjects within each PT, in the overall column. In cases of SOCs or PTs with equal frequencies, AEs will be sorted alphabetically.

Exposure-adjusted incidence rate of an AE event is defined as the number of events divided by the total duration of exposure of the subjects at risk during treatment, which is computed as follows:

Exposure Adjusted incidence rate (e) = n*100/EY

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where n is the number of subjects impacted; the exposure year (EY) = (sum of time to onset of the event)/365.25, where time to onset of the event = date of onset of event – date of the first study drug dose +1.

For subjects without the event, time to onset is censored as follows:

> Time to onset of the event = (last dose date + 56 days) – first study drug dose date +1.

For subjects who experienced the same event on multiple occasions:

> Time to onset of the event = date of onset at the first occasion–first study drug dose date +1.

A separate listing of serious AEs will also be generated. If there are any deaths, a listing will include the date of death and primary cause of death.

7.2 Clinical Laboratory Data

Descriptive statistics for clinical laboratory values (in SI units) and changes from baseline at each assessment time point, as well as shift tables from baseline to each visit for quantitative variables will be presented. If lab data for baseline from APL2-307 is missing, the lab data for the last study visit from antecedent study will be mapped into the APL2-307 study.

The laboratory values will be compared to their normal ranges (N-Rs) at every visit and the following categories will be derived for the shift tables (below normal range (N-R), normal, above normal range (N-R), and undetermined).

In cases where a certified local laboratory is used instead of a central laboratory (e.g., due to the COVID-19 pandemic), the units and normal reference ranges may differ. Therefore, it may be necessary to convert all values to SI units, and the normalization method developed by Stein (Stein, 1992; 2001) may be applied to standardize laboratory data for analysis purposes. However, if the normal ranges across all laboratories are sufficiently similar, global normal ranges may be established for each laboratory parameter and used in the analyses.

The following formula will be used to convert local lab value at observation level to central lab value:

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$$CCCCCCCCCCCCC\ vvCCCCvvCC = NNNNNNNN(CCNN) + \frac{CCllllCCCC\ vvCCCCvvCC - NNNNNNNN}{NNNNNNNN - NNNNNNNN} \times (NNNNNNNN(CCNN) - NNNNNNNN(CCNN))$$

Where,

NRLO: Low normal range for local lab

NRHI: High normal range for local lab

NRLO(CL): Low normal range for central lab

NRHI(CL): High normal range for central lab.

Detailed algorithm for standardizing local lab value with different local normal ranges and lab outliers will be applied as shown in APPENDICES 17.3.

Clinical laboratory test values are potentially clinically significant (PCS) if they meet either the low or high PCS criteria listed in Table 1. The number and percentage of subjects with post-baseline PCS values will be tabulated by visit. The percentages will be calculated relative to the number of subjects with available baseline values and at least 1 post-baseline assessment. The numerator is the total number of subjects by-visit with at least 1 post-baseline PCS value. A supportive listing of subjects with post-baseline PCS values will be provided including the subject number, baseline, and post-baseline values.

Clinical laboratory test values are potentially clinically significant (PCS) if they meet either the low or high PCS criteria listed in the table below:

Table 1: Criteria for Potentially Clinically Significant Laboratory Tests

Parameter	Criteria
Hematology	
WBC (total) (x10^9/L)	<3.0 > 16
Lymphocyte (x10^9/L)	< 0.5 < 0.8 > 12
Neutrophils (x10^9/L)	< 1.0 < 1.5 > 12
RBC (x10^12/L)	< 3.3 > 6.8
Hemoglobin (g/dL)	< 10

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Platelet count (x10^9/L)	< 100 > 600
Serum Chemistry	
ALT	> 1.5xULN > 3.0xULN
AST	> 1.5xULN > 3.0xULN
Total Serum Bilirubin	> 1.5
GGT	> 1xULN
ALT or AST > 3xULN and concurrent elevated total bilirubin defined as	> 1.5xULN > 2.0xULN

For the following serum chemistry parameters, Creatinine, Estimated creatinine clearance (using Cockcroft-Gault formula) – screening only; Albumin; ALP; LDH; Haptoglobin; LDH isoenzymes; Creatine kinase (CK); Uric acid; Glucose; Sodium; Potassium; Chloride; Ferritin; and Erythropoietin (EPO), abnormal values will be used as potentially clinically significant.

Similarly, for Urinalysis parameters, PH, Specific gravity; Protein; Glucose; Ketones; Bilirubin; Blood; Nitrite; Urobilinogen; and Leukocyte esterase, abnormal values will be used as potentially clinically significant.

The number and percentage of subjects with post-baseline PCS laboratory values will be tabulated overall for main study. The percentages will be calculated relative to the number of subjects with available baseline values and at least 1 post-baseline assessment. The numerator is the total number of subjects by-visit with at least 1 post-baseline PCS value. A listing of subject data with at least one post-baseline PCS value will be provided.

All laboratory data will be listed for the Safety Set. The listing will include change from baseline values and values outside the laboratory reference range will be flagged.

Any urine microscopy data collected will be listed.

For all applicable lab parameters, the mean plot (+/- SE) will be presented over time.

7.3 Vital Signs

Descriptive statistics for vital signs (e.g., body temperature, respiratory rate, blood pressure, and heart rate) and their changes from baseline will be presented by visit. All

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vital signs from clinic visits will only be listed for the Safety Set. The listing will include change from baseline values.

Vital signs are potentially clinically significant (PCS) if they meet the PCS criteria listed in the table below:

Table 2: Criteria for Potentially Clinically Significant Vital Signs

Parameter	Criteria
Temperature	> 38°C with ≥ 1°C increase from baseline
Heart Rate (BPM)	(>120 post-baseline if <=120 at baseline) or (>20 increase from baseline) >120 post-baseline if <=120 at baseline >20 increase from baseline (<50 post-baseline if >=50 at baseline) or (>20 decrease from baseline) <50 post-baseline if >=50 at baseline >20 decrease from baseline
Systolic Blood Pressure (mmHg)	(>180 post-baseline if <=180 at baseline) or (>40 increase from baseline) >180 post-baseline if <=180 at baseline >40 increase from baseline (<90 post-baseline if >=90 at baseline) or (>30 decrease from baseline) <90 post-baseline if >=90 at baseline >30 decrease from baseline
Diastolic Blood Pressure (mmHg)	(>105 post-baseline if <=105 at baseline) or (>30 increase from baseline) >105 post-baseline if <=105 at baseline >30 increase from baseline (<50 post-baseline if >=50 at baseline) or (>20 decrease from baseline) <50 post-baseline if >=50 at baseline >20 decrease from baseline

The number and percentage of subjects with post-baseline PCS vital sign values will be tabulated overall for main study. The percentages will be calculated relative to the number of subjects with available baseline values and at least 1 post-baseline assessment. The numerator is the total number of subjects by-visit with at least 1 post-baseline PCS value. A listing of subject data with at least one post-baseline PCS value will be provided.

7.4 Electrocardiogram (ECG)

Descriptive statistics for ECG variables (e.g., heart rate, PR interval, QRS interval, QT interval, and QTc interval) and their changes from baseline will be presented by visit (day) and scheduled time. QTc interval will be calculated using both Bazett ($QTcB=QT/(RR)^{1/2}$) and Fridericia ($QTcF=QT/(RR)^{1/3}$) corrections; and if RR is not available, it will be replaced with 60/hr in the correction formula.

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ECG interpretation will be summarized by visit. The "worst" clinical assessment of the ECGs (order of abnormal clinically significant, abnormal not clinically significant and normal) will be used if multiple assessments exist.

A shift table from baseline to each visit for qualitative ECG results will be presented.

The number of subjects with at least one value post baseline satisfying the PCS criteria will be tabulated. All replicates (i.e., individual values for triplicates) and all scheduled and unscheduled values will be assessed. The following categories will be used:

Table 3: Criteria for Potentially Clinically Significant Abnormal ECG Parameters

Parameter	**Criteria**
Heart Rate	All values within 50 -100 bpm At least one value ≤ 50 bpm* and no values ≥ 100 bpm At least one value ≥ 100 bpm* and no values ≤ 50 bpm At least one value ≥ 100 bpm* and one value ≤ 50 bpm*
PR Interval	< 200 msec ≥ 200 msec*
QT Interval	< 480 msec ≥ 480 msec*
QRS Interval	< 120 msec ≥ 120 msec*
QTcB, QTcF	<450 msec ≥ 450 msec and <480 msec ≥ 480 msec and <500 msec* ≥ 500 msec*
QT, QTcF, QTcB increase from baseline	< 30 msec ≥ 30 msec and < 60 msec* ≥ 60 msec*

* Values of PCS.

All ECG data will be listed for the Safety Set. Separate listings will be provided for the replicate data and the means of triplicate measurements. Changes from baseline values will be included in the listings, and in both listings, PCS values will be flagged.

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7.5 Other Safety Data

Physical examination, and pregnancy test data will be listed for the Safety Set. In addition, COVID-19 test results (if available) will be listed in subjects experiencing acute hemolysis.

8. PHARMACOKINETIC ANALYSIS FOR MAIN STUDY

All summaries and analyses of the pharmacokinetic data will be based on the PK Set.

8.1 Drug Concentration

The pegcetacoplan concentrations will be evaluated using the PK set. Pegcetacoplan concentrations will be summarized by dosing regimen at each scheduled time point using descriptive statistics over Treatment Period for subjects without dose modification (original 307 regimen).

Separately, for subjects who underwent dose modifications during the study, Pegcetacoplan concentrations will be summarized by dosing regimen at each scheduled time point using descriptive statistics over Treatment Period.

If a subject discontinues pegcetacoplan dosing, then concentrations from samples collected more than 1 day after the last dose will be excluded from calculations.

The number of subjects with a value > BLQ will also be tabulated.

Linear and semi-logarithmic mean (± SE) concentration profile plots against nominal time will be produced.

A mean (± SE) concentration-time profile plot (Linear and semi-logarithmic) by nominal time will be generated by dosing regimen for subjects without dose modification (original 307 regimen) throughout the study.

A separate mean (± SE) concentration-time profile plot (Linear and semi-logarithmic) by nominal time will be generated by dosing frequency for dose-modified subjects.

8.2 Handling BLQ Values

8.2.1 Handling of BLQ Pegcetacoplan Concentrations in Summary Tables

BLQ concentrations prior to first dosing (day 1): Pre-treatment pegcetacoplan concentrations reported as below the limit of quantification (BLQ) will be taken as zero for the computation of descriptive statistics, except geometric mean. Geometric mean cannot be calculated and will be reported as “N/A” or “-”.

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BLQ concentrations occurring at any time after first dosing: Pegcetacoplan concentrations reported as below the limit of quantification (BLQ) will be taken as half the lower limit of quantification (LLOQ/2).

8.2.2 Handling of BLQ Pegcetacoplan Concentrations in Figures

BLQ concentrations prior to first dosing (day 1): Pre-treatment pegcetacoplan concentrations reported as below the limit of quantification (BLQ) will be taken as zero for linear plots, and equal to half the lower limit of quantification (LLOQ/2) for semilogarithmic plots.

BLQ concentrations occur at any time after first dosing: Pegcetacoplan concentrations reported as BLQ will be taken as half the lower limit of quantification (LLOQ/2) for both linear and semilogarithmic plots.

8.2.3 Handling of BLQ Pharmacodynamic Parameters

8.2.3.1 C3

C3 levels reported as BLQ any time after first dosing will be taken as half the lower limit of quantification (LLOQ/2).

8.2.3.2 AH50 and CH50

AH50 and CH50 levels reported as BLQ any time after first dosing will be taken as zero (if available).

8.2.4 Handling of QNS (Quantity Not Sufficient) Values

Values reported as QNS will be taken as missing

8.3 Statistical Analysis

Descriptive statistics will include number of observations (N), arithmetic mean, standard deviation (SD), coefficient of variation (CV), geometric mean, CV (%) of geometric mean, median, minimum value, and maximum value. Missing values will be omitted from the calculation of descriptive statistics.

A summary table of pegcetacoplan concentrations by treatment group (dosing regimen) at each scheduled time point will be generated for subjects who received the original dosing frequency (original 307 regimen) without any dose modification.

A separate summary table of pegcetacoplan concentration by dosing frequency at each scheduled time point will be generated for subjects who underwent dose modifications during the study.

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A listing of all concentration data will be presented by dose regimen including dosage and dose frequency. The actual time (sample collected date), nominal time (schedule day), relative time (actual time -first dose date), deviation from scheduled day, and antecedent study information will also be listed.

9. PHARMACODYNAMIC ANALYSIS FOR MAIN STUDY

All summaries and analyses of the pharmacodynamic data will be based on the Pharmacodynamic set.

Observed values, changes from baseline, and percentage changes from baseline will be summarized at each visit by treatment group (dosing regimen) for subjects without dose modification (original 307 regimen) using descriptive statistics for the following parameters:

- Change from Baseline in percentage of PNH Type II+III RBC cells opsonized with C3.
- Change from Baseline in percentage of PNH Type II+III RBC cells.
- Change from Baseline in complement (e.g., CH50, AH50, and C3) levels.
- Changes from baseline and percentage changes from baseline for C3 deposition on RBC cells (percent C3d CD59 Type I, II and III), clonal distribution of PNH RBCs (percent CD59 Type I, II and III), PNH granulocytes (percent FLAER) and PNH monocytes (percent FLAER).

The first two endpoints, percentage of PNH Type II+III RBC cells opsonized with C3 and percentage of PNH Type II+III RBC cells, will be derived as following if data permits:

- C3d deposition on RBC cells (percent Type II + III); this is the sum of the numbers of events for C3d deposition on RBC cells (Type II) and RBC cells (Type III) divided by number of events for PNH CD59 Type II and III expressed as a percent.
- Clonal distribution of PNH RBCs (percent Type II + III); this is simply the sum of the clonal distribution of PNH RBCs Type II and Type III.

Separately, for subjects who underwent dose modifications during the study, observed values, changes from baseline, and percentage changes from baseline of the pharmacodynamic parameters will also be summarized at each visit by dosing frequency using descriptive statistics.

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Mean (±SE) profile plots will also be presented graphically for the observed values, change from baseline, and percentage changes from baseline. The nominal sampling time will be used on the x-axis. Plots will be presented for the full profile.

In addition to the analyses outlined above, all PK and complement biomarker concentration data may be used to develop the population PK and exposure-response models in conjunction with other clinical study data. The methods and procedures will be described in a separate Analysis Plan if needed. The results from population modeling will be reported separately.

10. ANTI-DRUG ANTIBODIES (ADAs) FOR MAIN STUDY

Immunogenicity data will be listed and summarized using safety set separately for anti-pegcetacoplan peptide antibody and anti-PEG antibody results. A sample and subject level summary table will be presented by the treatment group (dosing regimen) over the treatment period for subjects without dose modification (original 307 regimen) as described below.

Separately, for subjects who underwent dose modifications during the study, a sample and subject level summary table will be presented by the treatment group (dosing frequency) over the treatment period for dose-modified subjects.

Sample Level Summary

The number of evaluable (ADA-positive, ADA-negative, and ADA-inconclusive) and unevaluable samples will be summarized by treatment group and overall. The number and percentage of each ADA sample classification will be summarized by treatment group and overall, in the evaluable samples. In addition, the number and percentage of baseline and post-dose ADA positive samples along with the titer range for each will also be summarized by treatment group and overall, in samples that are ADA positive.

ADA samples will be classified as follows:

• ADA-Positive Sample – when the sample is positive in the confirmatory assay

• ADA-Negative Sample – when the sample is negative in the screening assay or the confirmatory assay, and drug is at a level that does not interfere with the ADA method.

• ADA-Inconclusive Sample – when the sample is negative in the screening assay or the confirmatory assay, and drug is at a level that interferes with the ADA method, then the sample is considered inconclusive. Note that the drug is considered at a level that interferes with the ADA method if the corresponding visit's PK concentration is greater than or equal to: (a)1000 ug/mL for anti-pegcetacoplan peptide antibody; or (b) 5000 ug/mL for anti-PEG antibody.

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• Unevaluable Sample – when a sample could not be tested for ADA status due to inadequate sample volume, mishandling, or errors in sample collection, processing, storage, etc.

Subject Level Summary

The number and percentage of subjects with pre-existing ADAs will be summarized by dosing regimen group and overall, in the subjects with a baseline sample result. In addition, the number and percentage of subjects with an ADA positive response, ADA negative response, and ADA inconclusive response, as well as the type and kinetics of the positive ADA response, will be summarized by dosing regimen group and overall, in the evaluable subjects. The subject summary table will include a summary by doing regimen group and overall, for the ADA population parameters. For subjects with a positive ADA response, association with changes in PK, efficacy, and safety may be explored.

Pre-existing ADA will be defined as follows: any subject with an ADA positive baseline sample from the total subjects with a baseline sample result.

Evaluable subjects will be defined as follows: a subject with at least one sample taken with a reportable result after first dosing during the treatment or follow-up period.

Evaluable subjects will be classified as follows for ADA response:

• ADA-Positive Subject – An evaluable subject with at least one pre-dose sample and one treatment-emergent or treatment-boosted ADA-positive sample at any time after dosing

• ADA-Negative Subject – An evaluable subject without a treatment-emergent or treatment-boosted ADA-positive sample during the treatment or follow-up period

• ADA-Inconclusive Subject – An evaluable subject who cannot be classified as either ADA-positive or ADA-negative (eg, assay drug tolerance issues, post-dose positive without a baseline sample, positive baseline and positive post-dose sample without a titer value, etc.)

ADA positive responses will be classified as follows:

• Treatment-Boosted ADA Response – An evaluable subject with a baseline ADA positive sample and a post-dose ADA positive sample that is ≥ 4x the baseline titer (eg, baseline titer of 10 vs. post-dose titer of 40)

• Treatment-Emergent ADA Response – An evaluable subject with a baseline ADA negative sample and an ADA positive sample after treatment, ADA developed de novo

The kinetics of ADA positive responses will be classified as follows:

• Transient ADA Response

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− Treatment-emergent positive subjects are classified as having a transient response if they have only a single ADA positive sample (that was not the last assessment), or more than 1 ADA positive sample where the first and last ADA positive samples are separated by a period of less than 112 days (16 weeks), irrespective of any negative and positive samples in between.

− Treatment-boosted ADA positive subjects are classified as having a transient response if they have only a single ADA boosted sample (that was not the last assessment), or more than 1 positive boosted sample where the first and last ADA positive samples are separated by a period of less than 112 days (16 weeks), irrespective of any negative and positive samples in between.

• Persistent ADA Response

− Treatment-emergent positive subjects are classified as having a persistent response if they have more than 1 positive ADA sample ≥ 112 days (16 weeks) apart, or a positive ADA sample at the last timepoint with no further results available

− Treatment-boosted ADA positive subjects were classified as having a persistent response if they have more than 1 positive boosted sample ≥ 112 days (16 weeks) apart, or a positive boosted sample at the last timepoint with no further results available

• Unclassified Response

− Any ADA positive subject that cannot be defined as having a transient or persistent ADA response

ADA population parameters are derived as follows:

• ADA Prevalence – The proportion of all ADA positive subjects, including pre-existing ADA, computed as a percentage of the total number of evaluable and unevaluable subjects

• ADA Incidence – The sum of all ADA positive treatment-emergent and treatment-boosted subjects computed as a percentage of the total number of evaluable subjects

Note: This population parameter is the same as the percentage of subjects with an ADA positive response.

10.1 Assessment of Incidence of ADAs on Safety

Subgroup analyses of AEs will be performed by those with positive/negative ADA. Descriptive summary (number and percent) will be presented overall.

Detail analysis for ADA data will be in additional data analysis specification.

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11. DATA HANDLING CONVENTIONS

11.1 Data Reporting Conventions

Continuous variables will be summarized using the following descriptive statistics: n, mean, median, standard deviation, minimum, maximum. Categorical and count variables will be summarized by the number of subjects (n) and the percentage of subjects in each category.

All subjects in the analysis set being used will be accounted for in summary tables.

Unless otherwise specified, the mean, median should be printed out to 1 more decimal place than the original values, and standard deviations should be printed out to 2 more decimal places than the original values. The minimum and maximum should report the same number of decimal places as the original values. Percentages will be displayed with 1 decimal place; except percentages will not be presented when the count is zero and 100% will be presented as an integer. Unless stated otherwise, for all percentages, the number of subjects in the analysis population will be the denominator.

11.2 Definition of Baseline

For the main study, baseline is defined as assessment on day 1. If assessments are missing on day 1, non-missing assessments of previous visit from antecedent study, which is within 60 days of day 1, will be used as baseline.

11.3 Definition of Visit Windows

Data will be summarized and analysed based on the list of visits specified in table below. The relative day of each assessment [(date of assessment) – (date of first dose) +1] will be calculated. The relative day will be used to assign analysis visit following the table below. All the records post-baseline will be assigned to an appropriate analysis visit using the following:

For the post-baseline visits, the lower and the upper bound for the analysis visit windows are defined as the midpoints of the target date of the scheduled visits. If the date of assessment falls in between the lower bound and the upper bound for a visit as specified in the schedule of assessments of the protocol, then it will be assigned to that visit. If more than 1 record is within the same analysis visit window, the record closest to the midpoint of the interval will be used in the analysis. If 2 records are tied before and after the middle of the interval, the earlier record will be used in the analysis. If more than one assessment (including the early termination or unscheduled assessments) falls within the same defined window, the assessment closest to the target day with non-missing data will be considered for analysis.

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See the table below for details on visit windows for main study:

Visit	Target Day	Analysis Window (days)	Interval
Baseline	1	1	-
Week 2	15	2 - 24	23
Week 4	29	25 - 42	18
Week 12	85	43 - 126	84
Week 24	169	127 – 210	84
Week 36	253	211 – 294	84
Week 48	337	295 – 378	84
Repeat for visits every 84 days	Previous target day + 84	(target day-42) – (target day+41)	84

11.4 Derived Efficacy Endpoints

FACIT-fatigue scale score

The FACIT Fatigue Scale is a 13 item Likert scaled instrument which is self-administered by the subjects during clinic visits. The 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, most responses (all except Item Codes 5 and 7 of the FACIT Fatigue Scale Version 4) are reversed to ensure that the higher score corresponds to a higher quality of life.

11.5 Repeated or Unscheduled Assessments of Safety Parameters

If the end of study assessments are repeated or unscheduled, the last post-baseline assessment will be used as the end of study assessment for generating descriptive statistics. However, all post-baseline assessments will be used for PCS value determination and all assessments will be presented in the data listings.

11.6 Handling of 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.

11.6.1 Missing Date of Investigational Product

When the date of the last dose of the investigational product is missing for a subject in the Safety Set, all efforts should be made to obtain the date from the investigator. If it is

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still missing after all efforts, then the last visit date when investigational product was returned will be used in the calculation of treatment duration.

11.6.2 Missing Date Information for Prior or Concomitant Medications

For prior or concomitant medications, including rescue medications, incomplete (i.e., partially missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a subject, impute the start date first.

11.6.2.1 Incomplete Start Date

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

11.6.2.1.1 Missing Day and Month

- If the year of the incomplete start date is the same as the year of the date of the first dose of investigational product, then the day and month of the date of the first dose of investigational product will be assigned to the missing fields.

- If the year of the incomplete start date is before the year of the date of the first dose of investigational product, then December 31 will be assigned to the missing fields.

- If the year of the incomplete start date is after the year of the date of the first dose of investigational product, then 01 January will be assigned to the missing fields.

11.6.2.1.2 Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

11.6.2.1.3 Missing Day Only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of investigational product, then the day of the date of the first dose of investigational product will be assigned to the missing day.

- If either the year is before the date of the first dose of the investigational product or if both years are the same, but the month is before the month of the date of the

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first dose of investigational product, then the last day of the month will be assigned to the missing day.

- If either the year is after the year of the date of the first dose of investigational product or if both years are the same, but the month is after the month of the date of the first dose of investigation product, then the first day of the month will be assigned to the missing day.

11.6.2.2 Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the date of the last dose of the investigational product is missing, then replace it with the last visit date. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

11.6.2.2.1 Missing Day and Month

- If the year of the incomplete stop date is the same as the year as of the date of the last dose of investigational product, then the day and month of the date of the last dose of investigational product will be assigned to the missing fields.

- If the year of the incomplete stop date is before the year of the date of the last dose of investigational product, then 31 December will be assigned to the missing fields.

- If the year of the incomplete stop date is after the year of the date of the last dose of investigational product, then 01 January will be assigned to the missing fields.

11.6.2.2.2 Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

11.6.2.2.3 Missing Day Only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of investigational product, then the day of the date of the last dose of investigational product will be assigned to the missing day.

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- If either the year is before the year of the date of the last dose of the investigational product or if both years are the same, but the month is before the month of the date of the last dose of investigational product, then the last day of the month will be assigned to the missing day.

- If either the year is after the year of the last dose of investigational product or if both years are the same, but the month is after the month of the date of the last dose of investigational product, then the first day of the month will be assigned to the missing day.

11.6.3 Missing Date Information for Adverse Events

For AEs with partial start dates, non-missing date parts will be used to determine if the AE is treatment-emergent or not. If a determination cannot be made using the non-missing date parts as to when the AE occurred relative to study drug administration, e.g., AE start year and month are the same as the year and month of the first dose of investigational product, then the AE will be classified as treatment-emergent.

To facilitate categorization of AEs as treatment emergent, imputation of dates can be used. For AEs, the default is to only impute incomplete (i.e., partially missing) start dates. Incomplete stop dates may also be imputed when calculation of the duration of an AE is required per the protocol. If imputation of an incomplete stop date is required, and both the start date and the stop date are incomplete for a subject, impute the start date first.

11.6.3.1 Incomplete Start Date

[Follow the same rules as in Section 14.6.2.1]

11.6.3.2 Incomplete Stop Date

[Follow the same rules as in Section 14.6.2.2]

11.6.4 Missing Severity Assessment for Adverse Events

If severity is missing for an AE starting prior to the date of the first dose of investigational product, then a severity of "Mild" will be assigned. If the severity is missing for an AE starting on or after the date of the first dose of investigational product, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summaries, while the actual values will be used in data listings.

11.6.5 Missing Relationship to Investigational Product for Adverse Events

If the relationship to investigational product is missing for an AE starting on or after the date of the first dose of investigational product, a causality of "Related" will be assigned. The imputed values for relationship to investigational product will be used for incidence

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summaries, while both the actual and the imputed values will be presented in data listings.

11.6.6 Character Values of Clinical Laboratory Variables

If the reported value of a clinical laboratory variable cannot be used in a statistical analysis due to, for example, that a character string is reported for a numerical variable, the appropriately determined coded value will be used in the statistical analysis. If the laboratory results are collected as < or > a numeric value, 0.0000000001 will be subtracted or added, respectively to the value. However, the actual values as reported in the database will be presented in data listings.

12. STATISTICAL ANALYSIS PLAN FOR SUBSTUDY

This section outlines the analysis plan for the substudy. Unless otherwise stated, definitions or rules will remain consistent with those used in the main study.

12.1 Objectives And Endpoints for Substudy

12.1.1 Objectives

The objectives of the substudy are to:

- Evaluate the safety of intensive SC or IV pegcetacoplan dosing in subjects with PNH
- Evaluate the effectiveness of intensive SC or IV pegcetacoplan dosing for the management of acute hemolysis (AH) in subjects with PNH treated with pegcetacoplan

12.1.2 Endpoints

12.1.2.1 Safety Endpoints

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

12.1.2.2 Efficacy Endpoints

- Absolute change from baseline (CFB) and percent CFB in lactate dehydrogenase (LDH) level from Day 1′ to Day 21′

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- Absolute CFB and percentage CFB in hemoglobin level from Day 1′ to Day 21′
- Number of transfusions and number of packed red blood cell (PRBC) units transfused from Day 1′ to Day 21′
- Hemoglobin level during maintenance dosing
- LDH level during maintenance dosing
- Absolute reticulocyte count
- Indirect bilirubin
- FACIT–Fatigue Scale score
- Time (Days) to resolution of AH
- LDH normalization (<2x Upper limit of normal (ULN))

12.1.2.3 Pharmacokinetic Endpoints

- Pegcetacoplan pharmacokinetic concentrations

12.1.2.4 Pharmacodynamics Endpoints

- Complement (e.g., 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

12.2 Study Design For Substudy

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.

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.

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 (multiple rounds of intensive dosing) 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.

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

This substudy will have intensive treatment dose regimen and maintenance dose. When subjects enter the intensive treatment, they 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 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. IV 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.

12.3 Sample Size for Substudy

Only those 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 (e.g., decrease in hemoglobin, hemoglobinuria, fatigue).

12.4 Statistical Analysis Sets for Substudy

Substudy analysis sets are defined as the following:

12.4.1 Safety Set/Intent-to-Treat Set

The Safety Set will include all subjects who enroll and receive at least 1 dose of pegcetacoplan in substudy. The intent-to-treat (ITT) set will be identical to the Safety Set for the substudy.

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12.4.2 Pharmacokinetic Set

The Pharmacokinetic (PK) Set will include all subjects in the ITT set who have at least 1 evaluable PK measurement after the first dose.

12.4.3 Pharmacodynamic Set

The Pharmacodynamic (PD) Set will include all subjects in the ITT set who have at least 1 evaluable PD measurement after the first dose.

12.5 Study Subjects for Substudy

12.5.1 Disposition of Subjects

For the Safety Set in substudy, the following will be presented overall in each round:

- Number and percentage of subjects
- Number and percentage of subjects who completed the substudy
- Number and percentage of subjects who discontinued the substudy and reasons for discontinuation

12.5.2 Demographic and Other Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics for the substudy will be presented overall for the Safety set.

Demographic variables to be presented include age (years), age category (<65 years, >=65 - <75 years, >=75 - <85 years, and ≥85 years), sex, ethnicity, race, country, weight (kg), weight category (<70 kg, ≥70 - ≤90 kg, >90 kg), height (cm), BMI (kg/m^2), and BMI category (<18.5, ≥18.5 - <25, ≥25 - <30, ≥30 - < 35, ≥ 35 kg/m^2).

The following formula will be used if the date of birth was reported, and the age was not recorded on the eCRF:

Age (years) = (date of informed consent at main study – date of birth + 1)/365.25.

Baseline characteristics at APL2-307 study entry will be presented for substudy subjects overall. Baseline characteristics refer to data collected on the first day a subject was enrolled in APL2-307 include:

- Time since diagnosis of PNH (years) to Day 1’

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- Hemoglobin level (Hb) at baseline
- Absolute Reticulocyte count (ARC) at baseline
- LDH level at baseline
- Indirect bilirubin level at baseline
- Total FACIT-fatigue score
- Complement profile (C3, CH50, and AH50) at baseline
- PNH Type II+III RBC
- PNH Type II RBC
- PHN Type III RBC
- PNH granulocytes at baseline
- PNH monocytes at baseline
- Vaccination status (including *Streptococcus pneumoniae*, *Neisseria meningitidis* (serogroups A, C, W, Y, and B), and *Haemophilus influenzae* type B).

12.5.3 Medical History

Medical history will be coded using the most recent version of MedDRA. The medical history will be summarized by System Organ Class (SOC) and Preferred Term (PT) with numbers and percentages for the Safety Set. Each subject will be counted only once in each SOC or SOC/PT summary. All medical history and AEs including ongoing AEs from the antecedent study and APL-2 307 main study will be mapped into APL2-307 substudy medical history.

In the summary table, medical history will be presented by decreasing frequency of subjects overall within each SOC and then similarly by decreasing frequency of subjects overall within each PT. In cases of SOCs or PTs with equal frequencies, medical history will be sorted alphabetically overall.

12.5.4 Prior Therapies, Procedures and Medication

WHO Drug Dictionary (version March 2021) will be used to classify prior medications by preferred term or therapeutic class. Prior medication is defined as any medication with the start date prior to the date of the first dose of pegcetacoplan. All concomitant therapies, procedures and medications started from the antecedent study, APL2-307 main study and ended before first dose in APL2-307 substudy will be mapped into APL2-307 substudy as prior therapies, procedures, and medication.

Medication will be presented by ATC level 2 (therapeutic main group) and preferred name (active ingredient) with numbers and percentages for the Safety Set. A subject who takes more than one medication will be counted only once if these medications belong to the same extended ATC classification.

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In the summary tables, prior medication and concomitant medications will be presented by decreasing frequency of subjects overall within each ATC level 2 class and then similarly by decreasing frequency of subjects overall within each preferred name. In cases of ATC level 2 classes or preferred names with equal frequencies, medications will be sorted alphabetically overall.

Prior therapies and procedures will be presented like those of prior medications detailed above.

All prior therapies, procedures and medications will be listed for the Safety Set.

12.5.5 Concomitant Therapies, Procedures and Medications

The WHO Drug Dictionary version (March 2021) will be used to classify concomitant medications by preferred term or therapeutic class. Concomitant medication is defined as any medication with a start date prior to the date of the first dose of pegcetacoplan in substudy and continuing after the first dose of pegcetacoplan or with a start date between the dates of the first and last doses of pegcetacoplan, inclusive. Any medication with a start date after the date of the last dose of pegcetacoplan will not be considered a concomitant medication.

The concomitant medication usage will be summarized by the number and proportion of subjects receiving each medication within each preferred term overall for the entire substudy period. Multiple medication usage by a subject in the same category will be counted only once.

Concomitant therapies and procedures will be presented similarly to those of concomitant medications detailed above.

All concomitant therapies, procedures and medications will be listed for the Safety Set.

12.5.6 Exposure to Investigational Product

The following parameters will be calculated and presented overall in each round of substudy:

- Total Dose administered (mg)
  - Since Day 1 of APL2-307 main study entry
  - Since Day 1’ of APL2-307 substudy entry
- Duration of Treatment (days)
  - Since Day 1 of APL2-307 main study entry
  - Since Day 1 of APL2-307 substudy entry
- Total number of infusions
  - Since Day 1 of APL2-307 main study entry

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- Since Day 1 of APL2-307 substudy entry

- Number and percentage of subjects who received infusion
  - Number and percentage of subjects with all infusions completed
  - Number and percentage of subjects with incomplete dosing due to infusion interruption
  - Number and percentage of subjects with incomplete dosing not due to infusion interruption
  - Number and percentage of subjects with any infusions interrupted
  - Number and percentage of subjects with any missed doses

By-subjects listing will be produced with dosing frequency change as well as start change date will be provided.

12.5.7 Measurements of Treatment Compliance

Percent compliance will be calculated overall for the Safety Set for the entire period of the substudy. Details in algorithms for different dosing regimen can be found in Section 5.7.

> Percent compliance = total number of study infusions taken from first dose to end of dose in the round of substudy for maintenance dose / total number of expected infusions to end of the round of substudy for maintenance dose.

The number and percentage of subjects who had a percentage of drug compliance (< 80%, ≥ 80% - <=100%, >100%- <=120%, and > 120%) will then be presented in a table.

By-subjects listing will be produced for treatment compliance and exposure.

12.6 Efficacy Analyses for Substudy

Efficacy analyses will be performed using the ITT set. Absolute values, changes from baseline (CFB) and percent CFB for treatment period will be summarized by visit using descriptive statistics (e.g., n, mean, median, standard deviation, 1st and 3rd quartile (Q1 and Q3), minimum and maximum). Efficacy summaries will be presented overall, for each round of treatment.

The efficacy analysis will be conducted using the substudy ITT Set. Efficacy variables will be presented overall, for each round of treatment in the same format as for the main study.

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12.7 Safety Analysis for Substudy

The safety analysis will be conducted using the substudy Safety Set. Safety variables include TEAEs, clinical laboratory variables, vital signs, ECG variables, and physical exam will be presented overall, for each round of treatment in the same format as for the main study.

12.8 Pharmacokinetic Analysis for Substudy

Statistical summary tables like those used in the main study will be provided for the substudy by round and, within each round, by loading dosing regimens (IV single dose or SC once daily for three doses) and maintenance dosing regimens (two times per week, every 3 days or three times per week) at each scheduled time point during the treatment period using descriptive statistics.

A mean (± SE) concentration-time profile plot (Linear and semi-logarithmic) by nominal time will be generated by round and, within each round, by loading dosing regimens (IV x1 dose or SC QD x3 doses) and maintenance dosing regimens (two times per week, every 3 days or three times a week) throughout the treatment period.

A listing of all concentration data will be presented by round and, within each round, by loading dosing regimens (IV x1 dose or SC QD x3 doses) and maintenance dosing regimens (two times per week, every 3 days or three times a week) at each scheduled time point using descriptive statistics over Treatment Period. The actual time (sample collected date), nominal time (schedule day), relative time (actual time -first dose date), deviation from scheduled day, and antecedent study information will also be listed.

12.9 Pharmacodynamic Analysis for Substudy

Statistical summary tables similar to those used in the main study will be provided for the substudy. Observed values, changes from baseline and percentage changes from baseline will be summarized at each visit by round and, within each round, by loading dosing regimens (IV x1 dose or SC QD x3 doses) and maintenance dosing regimens (two times per week, every 3 days or three times a week) using descriptive statistics.

12.10 Anti-Drug Antibodies (ADAs) For Substudy

Statistical summary tables like those used in the main study will be provided for the substudy. A sample and subject level summary table will be presented by round and, within each round, by loading dosing regimens (IV x1 dose or SC QD x3 doses) and maintenance dosing regimens (two times per week, every 3 days or three times a week) over the treatment period.

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12.11 Data Handling Conventions for Substudy

The following definitions apply specifically to the substudy.

12.11.1 Definition of Baseline

Baseline of each round is defined as the assessment conducted on substudy Day 1' prior to the loading dose. If no assessment is available on Day 1', the most recent assessment prior to the loading dose will be used as the baseline.

12.11.2 Definition of Visit Windows

Data will be summarized and analysed based on the list of visits specified in tables below separately for analysis by rounds and by AH episodes. The relative day of each assessment [(date of assessment) – (date of first dose) +1]
will be calculated. The relative day will be used to assign analysis visit following the table below. All the records post-baseline will be assigned to an appropriate analysis visit using the following:

For the post-baseline visits, the lower and the upper bound for the analysis visit windows are defined as the midpoints of the target date of the scheduled visits. If the date of assessment falls in between the lower bound and the upper bound for a visit as specified in the schedule of assessments of the protocol, then it will be assigned to that visit. If more than 1 record is within the same analysis visit window, the record closest to the midpoint of the interval will be used in the analysis. If 2 records are tied before and after the middle of the interval, the earlier record will be used in the analysis. If more than one assessment (including the early termination or unscheduled assessments) falls within the same defined window, the assessment closest to the target day with non-missing data will be considered for analysis.

See the table below for details on visit windows for each round of substudy:

Visit	Target Day	Analysis Window (days)	Interval
Round 1 Baseline	1	1	-
Round 1 Day 2	2	2	-
Round 1 Week 1	7	3 - 10	8
Round 1 Week 2	14	11 - 17	7
Round 1 Week 3	21	18 – 24	7
Round 1 Week 4	28	25 – 31	7
Repeat for visits every 84 days	Previous target day + 84	(target day-42) – (target day+41)	84

Note: Relative days in each round is based on Day 1 of that round (First intensive dose). Analysis visits in each round will be mapped based on relative days. Analysis window for each round follows the same mapping strategy as Round 1.

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See the table below for details on visit windows for each AH of substudy:

Visit	Target Day	Analysis Window (days)	Interval
1st AH Baseline	1	1	-
1st AH Day 2	2	2	-
1st AH Week 1	7	3 - 10	8
1st AH Week 2	14	11 - 17	7
1st AH Week 3	21	18 - 24	7
1st AH Week 4	28	25 - 31	7
1st AH Week 5	35	32 - 38	7
1st AH Week 6	42	39 - 45	7
1st AH Week 7	49	46 - 52	7
1st AH Week 8	56	53 - 59	7
Repeat for visits every 84 days	Previous target day + 84	(target day-42) – (target day+41)	84

Note: Relative days in each AH is based on the date of onset of that AH. Analysis visits in each AH will be mapped based on relative days. Analysis window for each AH follows the same mapping strategy as the first AH. If an AH is resolved after one round of treatment, then the analysis visit follows visits every 84 days after Week 4. If an AH requires more than 2 rounds of treatment, then visits will be mapped weekly after week 8 until resolution. After resolution, analysis visit will be mapped every 84 days as maintenance dosing.

13. DATA MONITORING COMMITTEE/REVIEW 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 approximately every 6 months during the course of the study as specified in the DMC charter.

14. DATABASE LOCK STRATEGY FOR CSR

The post marketing requirement (PMR) requires completion of Study 307 and submission of the CSR by February 2026. Country-specific amendments (CSA) are needed to allow patients to remain in the study until transition into the PTA; however, the Peru site will not obtain approval in time to meet the PMR deadline.

To address this, two database locks (DBLs) will be conducted:

- DBL1 (23 October 2025): Data up to this cutoff (12 September 2025) will be analyzed and used for the primary CSR submission.
- DBL2 (~November 2025, post-LPLV in Peru): The Peru site data will be included in the updated final datasets, and selected TLFs will be generated for a CSR

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addendum. If any clinically significant findings emerge from the additional data, further TLFs will be performed as part of a post-hoc analysis.

Analyses and outputs based on DBL1 will support the CSR. Following DBL2, final datasets will be updated and the CSR addendum prepared.

15. INTERIM ANALYSIS

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

16. ANALYSIS SOFTWARE

Statistical analyses will be performed using Version 9.4 (or newer) of SAS® on a suitably qualified environment.

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17. APPENDICES

17.1 Schedule of Assessments

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 & Weight	X							
12-lead electrocardiogram	X		X	X	X	X	X	X
Pegcetacoplan administration[g]	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[h]	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X
Blood Tests:[i]	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
Coagulation profile[j]	X	X	X	X	X	X	X	X
Reticulocyte count	X	X	X	X	X	X	X	X

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Statistical Analysis Plan: 3.0
Protocol Number: APL2-307

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**
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 B12, folic acid	X	X	X	X	X	X	X	X
Urine pregnancy test[k]	X	X	X	X	X	X	X	X
FACIT Fatigue Scale	X	X	X	X	X	X	X	X
Adverse events[l]	X	X	X	X	X	X	X	X

FOOTNOTES:

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

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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 acomplement 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. 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.

h. 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 minutes post dose.

i. Blood will be taken before dosing at every scheduled visit.

j. 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.

k. Urine pregnancy tests will be performed for women of childbearing potential only.

l. 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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17.2 Substudy Schedule of Assessments

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**
Study Window (+/- Days)	**0**	**0**	**4**	**4**	**4**	**4**	**7**	**8 weeks from last dose**
Informed Consent	X							
Document vaccination/vaccination booster [b]	X							
Preventive antibiotic[c]	X	X	X	X	X	X	X	X
Physical examination[d]	X				X		X[f]	X
Medical History	X							
Demographics	X							
Height and Weight	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[e]	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X
Blood Tests:[f]	X	X	X	X	X	X	X	X
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[g]	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

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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**
Study Window (+/- Days)	**0**	**0**	**4**	**4**	**4**	**4**	**7**	**8 weeks from last dose**
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 B12, folic acid	X						X	X
Urine pregnancy test[h]	X	X	X	X	X	X	X	X
FACIT Fatigue Scale	X						X	X
Adverse events[i]	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.

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d. Following the Week 16′ visit, physical examinations should be conducted at 24-week intervals (every other visit).

e. 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 minutes post dose.

f. Blood will be taken before dosing at every scheduled visit.

g. 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.

h. Urine pregnancy tests will be performed for women of childbearing potential only.

i. 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.

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17.3 Algorithm for Standardizing Local Lab Values with Different Normal Ranges

1. Convert all parameters' units from different local lab units to SI units.
2. Impute the local normal ranges as shown below.
3. Assume there is one central Lab (Medpace) and all NRLO(CL) and NRHI(CL)

   i. If the NRLO is missing and NRHI is not missing, then do the following:

   NRLO=NRHI * NRLO(CL) / NRHI(CL).

   ii. If the NRHI is missing and NRLO is not missing, then do the following:

   NRHI=NRLO * NRHI(CL) / NRLO(CL).

   iii. If both NRLO and NRHI are missing prior to the imputations above, do the following:

   NRLO=min (all NRLO including CL) and NRHI=max (all NRHI including CL). (Use gender or age specific NRs when applicable.)

4. Use the following formula (Location-Scale) to convert local lab value at observation level to central lab value:

   $CCCCCCCCCCCCC\ vvCCCCvvCC = NNNNNNNN(CCNN) + (CCllllCCCC\ vvCCCCvvCC - NNNNNNNN)/(NNNNNNNN - NNNNNNNN) \times (NNNNNNNN(CCNN) - NNNNNNNN(CCNN))$

   Where $z = (CCllllCCCC\ vvCCCCvvCC - NNNNNNNN)/(NNNNNNNN - NNNNNNNN)$ give Lab values (0,1).

5. Check for negative Lab values after the normalization. If so, do the following:
   a. Set negative value to Zero, or

   b. Use Upper Scale Formula: Central Value = Local value * NRHI (CL)/ NRHI, or

   c. Use Lower Scale Formula: Central Value = Local value * NRLO (CL)/ NRLO

   (Use a, or b or c as appropriate).
6. Perform the analyses (e.g., CFB) as usual.

Where:

NRLO: Low normal range for local lab

NRHI: High normal range for local lab

NRLO (CL): Low normal range for central lab

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NRHI (CL): High normal range for central lab

CL: Central Lab

NR: Normal Range

CFB: Change from Baseline

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17.4 AE Reporting Terms for Acute Hemolysis

Verbatim term	PT (MedDRA 23.0)
Acute hemolysis	Haemolysis
Acute hemolysis probable related to infection*	Haemolysis
Break-through hemolysis, all spellings	Haemolysis
Exacerbation of PNH	Paroxysmal nocturnal haemoglobinuria
Hemolithic activity	Haemolysis
Hemolysis, haemolysis	Haemolysis
Hemolytic anemia	Haemolytic anaemia
Hemolytic crisis	Haemolysis
Intermittent hemolysis	Haemolysis
Intravascular haemolysis	Intravascular haemolysis
Intravascular hemolysis	Intravascular haemolysis
PNH flair ****	Paroxysmal nocturnal haemoglobinuria
Severe***** hemolysis	Haemolysis
Worsening PNH, or of PNH	Paroxysmal nocturnal haemoglobinuria

*Compound term-per MedDRA points to consider should have been coded separately (haemolysis and infection)

** In general, MedDRA does not include comparative or grading PTs (worsening, worse, aggravated, exacerbated etc); there is no “worsening” PT available for hemolytic events

***See above, no qualifying PTs for hematuria

****No “flare” PT available in MedDRA for PNH

*****Same here, no “severe” PT available

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Number of Documents:	1
Document page count:	56
Number of supporting files:	0
Supporting files page count:	0

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